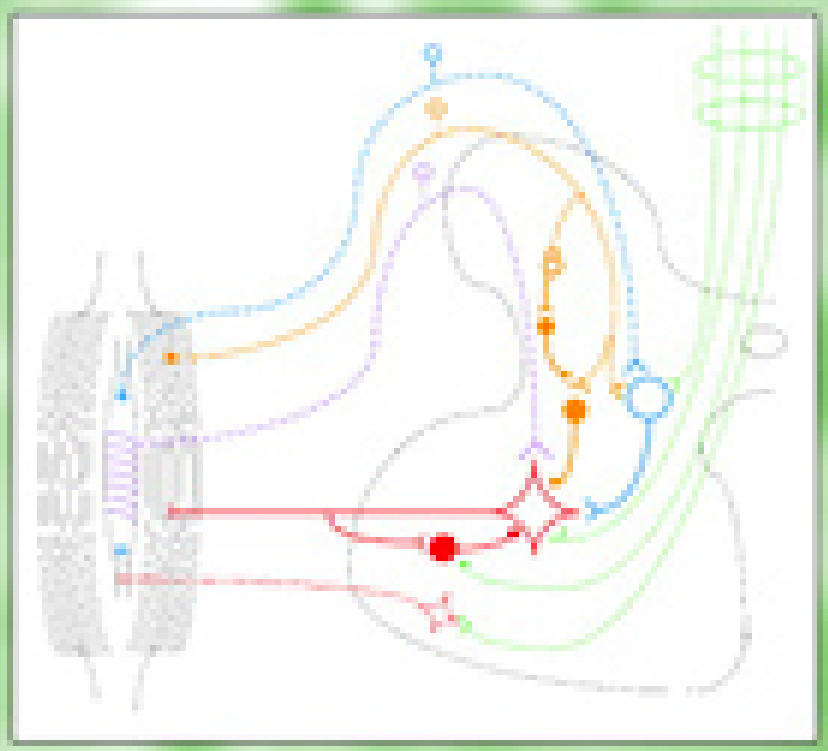
The Circuitry of the Human Spinal Cord

Its Role in Motor Control and Movement Disorders



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and David Burke

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THE CIRCUITRY OF THE HUMAN SPINAL CORD

Studies of human movement have proliferated in recent years, and there have been many studies of spinal pathways in humans, their role in movement, and their dysfunction in neurological disorders. This comprehensive reference surveys the literature related to the control of spinal cord circuits in human subjects, showing how they can be studied, their role in normal movement, and how they malfunction in disease states. The distinguished authors each bring to the book a lifetime's research and practice in neuroscience, motor control neurobiology, clinical neurology and rehabilitation. Chapters are highly illustrated and consistently organised, reviewing, for each pathway, the experimental background, methodology, organisation and control, role during motor tasks, and changes in patients with CNS lesions. Each chapter concludes with a helpful résumé that can be used independently of the main text to provide practical guidance for clinical studies. This is therefore the last word on the role of the spinal cord in human motor control. It will be essential reading for research workers and clinicians involved in the study, treatment and rehabilitation of movement disorders.

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CAMBRIDGE
UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo

Cambridge University Press
The Edinburgh Building, Cambridge CB2 2RU, UK

Published in the United States of America by Cambridge University Press, New York

www.cambridge.org
Information on this title: www.cambridge.org/9780521825818

First published in print format 2005

ISBN-13 978-0-511-12416-7 eBook (Adobe Reader)
ISBN-10 0-511-12416-3 eBook (Adobe Reader)

ISBN-13 978-0-521-82581-8 hardback
ISBN-10 0-521-82581-4 hardback

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Preface

Spinal mechanisms in the control of movement. In the 1910–1920s Paul Hoffmann demonstrated that percutaneous electrical stimulation of the posterior tibial nerve in human subjects produced a synchronised response in the soleus muscle with the same central delay as the Achilles tendon jerk. This landmark study long preceded Lloyd's identification of the corresponding pathway in the cat (1943). Subsequently, much of the primary knowledge about the spinal circuitry has come from animal experiments, but human studies have retained a unique role: the ability to shed direct light on how spinal mechanisms are used in the control of voluntary movement. In the 1940–1950s, many spinal pathways were analysed in 'reduced' animal preparations with regard to their synaptic input and to their projections to other neurones.

Modern views about spinal pathways began to emerge when Anders Lundberg and colleagues showed in the 1960s and 1970s that, in the cat, each set of spinal interneurones receives extensive convergence from different primary afferents and descending tracts, and that the integrative function of spinal interneurones allows the motoneurones to receive a final command that has been updated at a premotoneuronal level. Methods have now been developed to enable indirect but nevertheless valid measurements of spinal interneuronal activity in human subjects, and these techniques have demonstrated reliability, particularly when congruent results are obtained with independent methods. Their use has allowed elucidation of how the brain modulates the activity of specific spinal

interneurones to control movement. This, together with the abnormalities of motor control resulting from lesions in the central nervous system (CNS) and the underlying pathophysiology of movement disorders, is the subject of this book.

Over recent years, reappraisal of the role of direct cortico-motoneuronal projections in higher primates including humans has led to the view that the control of movement resides in the motor cortical centres that drive spinal motoneurone pools to produce the supraspinally crafted movement. This view belies the complex interneuronal machinery that resides in the spinal cord. It is a thesis of this book that the final movement is only that part of the supraspinally derived programme that the spinal cord circuitry deems appropriate. While the capacity of the spinal cord to generate or sustain even simple movements, particularly in human subjects, is limited, the influence that it plays in shaping the final motor output should not be underestimated. The recent recording by Eberhard Fetz and colleagues from spinal interneurones during, and before, voluntary movement in the awake monkey well illustrates this role of the spinal cord. A goal of rehabilitation of patients with upper motor neurone lesions should be to harness the residual motor capacities of the spinal cord and, for this to occur, the information in this book is critical. The techniques described in this book will also allow assessment in patients of whether any regeneration is 'appropriate'.

Studying motor control in human subjects. There has been an explosion of studies on human movement and of the dysfunction that accompanies different neurological disorders, and the prime rationale for this book is to summarise the literature related to the control of spinal cord circuitry in human subjects. Of necessity, only some interneuronal circuits can be studied reliably in human subjects, and no one book can provide a complete overview of the role of spinal circuitry in normal and pathological movement: there are no data for the many circuits that cannot yet be studied in human subjects, let alone the cat. This book is intended to provide a comprehensive account of (i) how some well-recognised and defined circuits can be studied, (ii) how they are used in normal movement, and (iii) how they malfunction in disease states.

It is as well to retain some reservations about conclusions of studies in human subjects: (i) All studies on human subjects are indirect and cannot be controlled as rigorously as in the cat. (ii) Some pathways cannot be explored quantitatively, because their effects are contaminated by effects due to other afferents (e.g. effects due to group II afferents are always contaminated by group I effects whatever testing method is used). (iii) For methodological reasons (stability of the stimulating and recording conditions), isometric voluntary contractions have been the main motor tasks during which changes in transmission in spinal pathways have been investigated. However, recent technological advances now allow the investigation of spinal pathways during natural movements, including reaching and walking. (iv) With transcranial magnetic stimulation of the motor cortex, it is possible to investigate the corticospinal control of spinal interneurones, but there are little data for other descending controls from basal ganglia and the brainstem, other than vestibular projections. (v) In patients, spinal circuitry has usually been explored under resting conditions, but the functionally important deficits may appear only during attempted movements (reinforcement of spasticity during movement, dystonia).

Methodological advances. The H reflex has served motor control well but, over the last 30 years, other techniques have been developed to allow more accurate probing of spinal pathways in human subjects, providing data that can validate and extend the findings from H reflex studies. As a result, knowledge of the role of spinal pathways in normal and pathological motor control has increased greatly, and this provides a further motivation for this book. For example, the use of *post-stimulus time histograms* has allowed the investigation of single motoneurones in human subjects, the technique of *spatial facilitation* allows the exploration of the convergence of different volleys on spinal interneurones, and *transcortical stimulation* of the motor cortex allows the corticospinal control of spinal pathways to be investigated. This book details this newer knowledge for the use of

those who have an interest in the subject but who have not had time to read the rapidly accumulating original literature. Inevitably, there will be inconsistencies in conclusions from studies on intact human subjects who can respond to a stimulus. Greater validity comes from using a number of independent techniques to demonstrate the same finding, as is emphasised in the following chapters. Inconsistent or irreproducible findings can lead to controversy about the nature and the functional role of a specific pathway in normal subjects and in patients, and such inconsistencies are presented, and the validity of the method(s) used to explore that pathway is addressed. Possible future directions for the research are discussed.

Organisation of individual chapters. The different spinal pathways for which there are reliable and non-invasive methods of investigation are considered with, for each pathway:

(i) *A brief background from animal experiments*. Human investigations are indirect and it is crucial to know the essential characteristics of each pathway described in animal experiments with recordings from motoneurones and/or interneurones. Caution should always be taken in extrapolating from data obtained in 'reduced preparations' (anaesthetised, decerebrate or spinalised animals) to awake intact human subjects, but the validation of a technique for exploring a given pathway may require controls only possible in animal experiments and is more credible when there is a close analogy with animal experiments.

(ii) *A critical description of the available method(s)* that have been used to explore the relevant pathways selectively. Methodological details allowing the reader to use reliable methods are described.

(iii) *The organisation and descending control (in particular corticospinal) of these pathways in human subjects*. The basic organisation of each pathway may well be the same in humans and cats, but the strength of the projections of individual spinal pathways on different motoneurone pools and their descending control have been the subject of phylogenetic adaptations to different motor repertoires. For the human lower limb, more elaborate reflex assistance is required for bipedal stance and gait. That there has been this phylogenetic adaptation argues that spinal pathways have a functional role in human subjects and are not evolutionary relics.

(iv) *The changes in transmission in these pathways during various motor tasks*. How spinal reflex pathways are used in motor control cannot be deduced from experiments on 'reduced' animal preparations. It requires experiments performed during natural movements, as can be done in humans. This has been one major contribution of human studies to the understanding of motor control physiology. Thus, even though many of the conclusions are speculative, this book gives a large place to the probable functional implications of the described changes in transmission in spinal pathways during movement.

(v) *Changes in transmission in these pathways in patients with various lesions of the CNS*. This has provided new insights about the pathophysiology of the movement disorder in these patients.

Overall organisation of the book. The general methodologies that are used for investigating pathways are considered in a first chapter with, for each method, its advantages and its disadvantages. There is a risk that starting with a technical chapter would dissuade the non-specialist reader from delving further into the book. This *initial chapter* is useful to understand fully the particular techniques used for the investigation of the different pathways, *but it is not essential for comprehension of the following chapters*.

For those who wish to know how methods and concepts have evolved over the years and why some interpretations were erroneous even if, at the time, influential, the methods are described in detail, with their limits and caveats, and the results obtained and their interpretation(s) are critically evaluated in each chapter. Because human studies are fraught with

technical difficulties, much space has been alloted to methods and potential pitfalls.

For those who want to get to the gist of the matter reasonably quickly each chapter terminates with a résumé of its salient points. The résumés can be used on their own without reference to the detailed text. They give a practical 'recipe' on the choice of the appropriate technique and its proper use in routine clinical studies, together with data on the possible functional role of the particular pathway in motor control and in the pathophysiology of movement disorders.

The final two chapters summarise and synthesise the changes in transmission in spinal pathways during movement and how these changes contribute to motor control, and spinal mechanisms underlying spasticity and motor impairment in patients with Parkinson's disease. In these chapters, the physiological (Chapter 11) and pathophysiological (Chapter 12) roles of different spinal pathways, considered in the previous chapters, are presented with another approach: (i) how different motor tasks are controlled by spinal pathways (Chapter 11); (ii) how these pathways contribute to motor disorders (Chapter 12).

Acknowledgements

This book is dedicated to Evelyne and Katre. It would not have been possible if our wives had not appreciated the importance for us of bringing together in a single volume the accumulated knowledge on spinal mechanisms in the control of movement. They have encouraged, supported and tolerated us, understanding even when we were unreasonable, putting life on hold so that we could work.

We are greatly indebted to Paolo Cavallari, Jean-Michel Gracies, Hans Hultborn, Léna Jami, Stacey Jankelowitz, Elzbieta Jankowska, Dominique Mazevet, Leonor Mazières, Jens Nielsen, Uwe Proske and Marco Schieppati who have given generously of their time to read and comment on drafts of various chapters. Above all, particularly special thanks go to Paolo, Léna and Leonor who read the entire text.

Geneviève Bard and Mary Sweet have laboured long and hard in getting the text into presentable order, and we are grateful for their friendship, loyalty and meticulous attention to detail over our many years of association.

Finally, the studies summarised in the book represent the intellectual activity of collaborators, colleagues, students and staff. We are grateful to everyone who contributed to these studies, and to our colleagues and their publishers who have allowed us to reproduce Figures from their papers. Finally, the authors would like to thank INSERM and NH&MRC for support of their work.

Abbreviations

5-HT	5-hydroxytryptophan
ACh	acetylcholine
Aff.	affected
AHP	afterhyperpolarisation
APB	abductor pollicis brevis
Bi	biceps
CFS	critical firing stimulus
Co FRA	contralateral FRA
CPN	common peroneal nerve
CS or (Cort. sp.)	corticospinal
CUSUM	cumulative sum
Cut	cutaneous
Desc.	descending
DPN	deep peroneal nerve
ECR	extensor carpi radialis
ED	extensor digitorum
EDB	extensor digitorum brevis
EDL	extensor digitorum longus
EHB	extensor hallucis brevis
EHL	extensor hallucis longus
EMG	electromyogram
EPSP	excitatory post-synaptic potential
Erect sp	erector spinae
Exc	excitatory
FCR	flexor carpi radialis
FCU	flexor carpi ulnaris
FDB	flexor digitorum brevis
FDI	first dorsal interosseus
FDS	flexor digitorum superficialis
FHB	flexor hallucis brevis
FN	femoral nerve
FPL	flexor pollicis longus

FRA	flexion reflex afferent
Glut Max (or Glut)	gluteus maximus
GM	gastrocnemius medialis
GS	gastrocnemius-soleus
GTO	Golgi tendon organ
H	hamstrings
IN	interneurone
Inhib.	inhibitory
IPSP	inhibitory post-synaptic potential
ISI	inter-stimulus interval
L-Ac	L-acetylcarnitine
LC (or Loc. coer).	locus coeruleus
MC	musculo-cutaneous
MEP	motor evoked potential
MLR	medium-latency response
MN	motoneurone
MRI	magnetic resonance imaging
MT	motor threshold
MVC	maximal voluntary contraction
NA	noradrenaline
NRM	nucleus raphe magnus
PAD	primary afferent depolarisation
Per Brev	peroneus brevis
PL	peroneus longus
PN	propriospinal neurone
Ps	psoas
PSP	post-synaptic potential
PT	perception threshold
PTN	posterior tibial nerve
Q	quadriceps
RC	Renshaw cell
Rect Abd	rectus abdominis
RS or (Ret. Sp).	reticulo-spinal
Rubr. sp.	rubro-spinal
SLR	short-latency response
Sol	soleus
SPN	superficial peroneal nerve
SSEP	somatosensory evoked potential
Stim.	stimulus
TA	tibialis anterior
TFL	tensor fasciae latae
TMS	trans cranial magnetic stimulation
TN	tibial nerve
Tri	triceps brachii
Unaff.	unaffected
VI	vastus intermedius
VL	vastus lateralis
VS	vestibulo-spinal

1

General methodology

The following chapters discuss methods that allow the selective investigation of different spinal pathways. Whatever the pathway investigated, its activation produces changes in the excitability of spinal motoneurones, 'the final common path' in the motor system. A prerequisite for any investigation of changes in the spinal circuitry in human subjects is therefore to be able to assess changes in motoneurone excitability quantitatively, using valid reproducible methods. Several non-invasive methods have been developed, and these are considered in this chapter with their advantages and disadvantages. All are, of course, indirect, and valid conclusions can only be obtained if congruent results are obtained with different methods relying on different principles. All may be, and many have been, used in studies on patients, but here the methodology should be simple and rapid.

This initial chapter is technical and non-specialist readers could bypass it, referring back if they need to clarify how results were obtained or understand the advantages and limitations of a particular technique. However, the chapter is required reading for those who want to understand fully the particular techniques used for the different pathways and how to use those techniques.

The monosynaptic reflex: H reflex and tendon jerk

The 'monosynaptic reflex' forms the basis of the first technique available to investigate spinal pathways in animals and humans. The principle is based on the apparent simplicity of the monosynaptic projection of Ia afferents to homonymous motoneurones. Subsequent studies have shown that the so-called monosynaptic reflex is not as simple as was initially thought. We will consider successively: (i) the initial findings; (ii) the principles underlying the monosynaptic reflex testing method; (iii) the basic methodology of the H reflex; (iv) limitations related to mechanisms which can change the size of the reflex by altering its afferent volley; (v) 'pool problems' related to the input–output relationship within the motoneurone pool.

Initial studies

Animal studies

The monosynaptic reflex depends on the projection of muscle spindle Ia afferents to homonymous motoneurones and was used in the early 1940s as a tool for investigating changes in excitability of the motoneurone pool (Renshaw, 1940; Lloyd, 1941). When used as a test reflex, the monosynaptic reflex allows one to assess the effect on the motoneurone pool of conditioning volleys in peripheral afferents or descending tracts. During the 1940s and early 1950s this method was used to reveal important features of the input to spinal motoneurones. Intracellular recordings later allowed more detailed analysis of the synaptic input to motoneurones in animals (see Baldissera, Hultborn & Illert, 1981), but

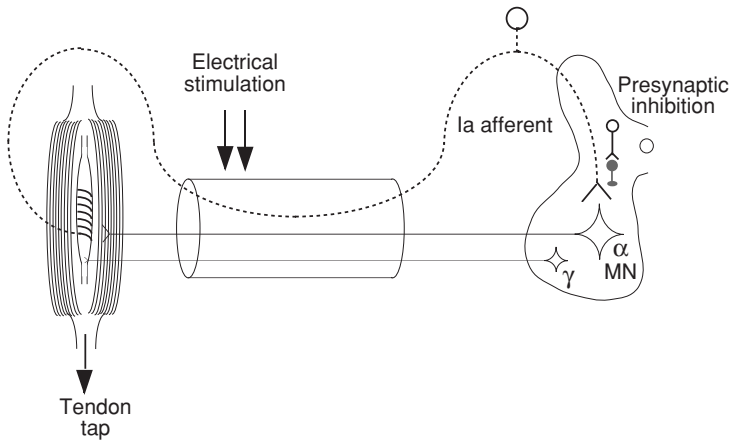

Fig. 1.1. Sketch of the pathway of the monosynaptic reflex. Ia afferents from muscle spindle primary endings (dotted line) have monosynaptic projections to α motoneurones (MNs) innervating the corresponding muscle (homonymous MNs). The H reflex is produced by electrical stimulation of Ia afferents, and bypasses muscle spindles. The tendon jerk is elicited by a tap that stretches muscle spindles and therefore also depends on the sensitivity to stretch of primary endings, a property that may be altered by the activity of γ efferents (however, see Chapter 3, pp. 117–18). The pathway of presynaptic inhibition of Ia terminals (see Chapter 8) is represented.

interestingly this greater precision did not change the main conclusions that had emerged from the experiments employing the monosynaptic reflex. This suggests that the monosynaptic reflex method produces reliable results.

Human studies

Percutaneous electrical stimulation of the posterior tibial nerve produces a synchronised response in the soleus muscle (Hoffmann, 1918, 1922). This became known as the Hoffmann reflex or H reflex (Magladery & McDougal, 1950). Magladery *et al.* (1951a) showed that the first motoneurones discharging in the H reflex do so at a latency consistent with a monosynaptic pathway (see Chapter 2). After the pioneer investigations of Paillard (1955), the H reflex, which is the equivalent of the monosynaptic reflex in animal studies, became the main tool in many motor control investigations and diagnostic studies performed on human subjects (for reviews, see Schieppati, 1987; Burke *et al.*, 1999; Pierrot-Deseilligny & Mazevet, 2000).

Underlying principles

The monosynaptic reflex arc

Pathway

Ia fibres from muscle spindle primary endings have monosynaptic excitatory projections to motoneurones innervating the muscle from which the afferents emanate (homonymous projections, Fig. 1.1). This pathway is responsible for the tendon jerk (see Chapter 2). The H reflex is produced by electrical stimulation of Ia afferents, which have a lower electrical threshold than α motor axons, particularly for stimuli of relatively long duration (see p. 6).

The H reflex, tendon jerk and short-latency spinal stretch reflex

These are all dependent on monosynaptic excitation from homonymous Ia afferents. However, the afferent volleys for these reflexes differ in many respects (cf. Chapter 3): (i) the electrically induced afferent

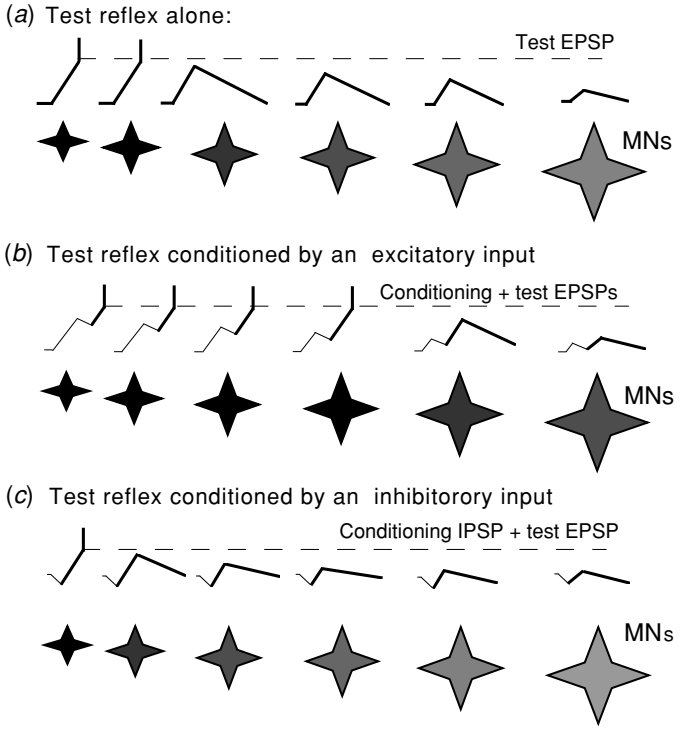

Fig. 1.2. Principles of the monosynaptic reflex. (*a*) Orderly recruitment of motoneurones (MNs) by a given Ia input: the size of the monosynaptic Ia EPSP (upper row) decreases as MN size increases (lower row). The dotted horizontal line represents the threshold for discharge of the MNs. Only the smallest MNs (black) are fired by the test Ia volley, and the excitability of subliminally excited MNs decreases from the smallest to the largest (as indicated by the decreasing tone of grey). (*b*) Facilitation by an excitatory input. There is summation of the conditioning (thin lines) and test (thick lines) EPSPs. As a result, MNs which had just failed to discharge in the control reflex are raised to firing threshold and the size of the reflex is increased. (*c*) Inhibition by an inhibitory input. There is summation of the conditioning IPSP (thin line) and of the test EPSP (the test EPSP is also reduced by changes in the membrane conductance, see p. 27). As a result, MNs which had just been recruited in the control reflex cannot be discharged, and the size of the reflex is reduced. Note that the excitability of the MNs in the subliminal fringe of excitation is also modified by the conditioning input. Modified from Pierrot-Deseilligny & Mazevet (2000), with permission.

volley for the H reflex bypasses muscle spindles and produces a single synchronous volley in group Ia and Ib afferents; (ii) the tendon tap produces a highly dynamic stretch, which activates mainly muscle spindle primary endings and elicits a prolonged discharge in Ia afferents; (iii) the short-latency Ia spinal stretch reflex is overlapped by a medium-latency response due to a group II volley from muscle spindle secondary endings (see Chapter 7).

The orderly recruitment of motoneurones in the monosynaptic reflex

Figure 1.2(*a*) shows that, in the cat, the size of the test Ia excitatory post-synaptic potential (EPSP) evoked in individual motoneurones by a given afferent volley is larger in small motoneurones supplying slow motor units than in large motoneurones supplying fast units. As a result, motoneurones are recruited in an orderly sequence by the Ia input, from the smallest

to the largest, according to Henneman's size principle (see Henneman & Mendell, 1981). Motoneurones contributing to the human H reflex are recruited in a similar orderly sequence from slow to fast motor units (Buchthal & Schmalbruch, 1970). This orderly recruitment of motoneurones is preserved when they receive a variety of excitatory and inhibitory inputs (though not all, see pp. 18–20), such that facilitation will initially affect those motoneurones that just failed to discharge in the control reflex (dark grey motoneurones in Fig. 1.2(*b*)) and inhibition will affect those that had just been recruited into the control reflex (largest black motoneurones in Fig. 1.2(*a*)).

Principles of the monosynaptic reflex method

In the control situation, the test Ia volley elicited by stimulation of constant intensity causes some motoneurones to discharge producing the control test reflex (black motoneurones in Fig. 1.2(*a*)) and creates EPSPs in other motoneurones which thereby become subliminally excited (grey motoneurones in Fig. 1.2(*a*)). If motoneurones are now facilitated by a subthreshold conditioning volley, motoneurones that had just failed to fire in the control reflex will discharge when the conditioning and test EPSPs summate (Fig. 1.2(*b*)). The size of the test reflex will increase. By contrast, if motoneurones receive conditioning inhibitory post-synaptic potentials (IPSPs), the test Ia volley will not be able to discharge the motoneurones that had been recruited last into the control reflex, and the size of the test reflex will be decreased (Fig. 1.2(*c*)). The method allows one to distinguish between: (i) conditioning stimuli without effect on the excitability of motoneurones; (ii) those which evoke only subliminal excitation of the motoneurones when applied alone; and (iii) those which inhibit motoneurones. A variant of the method is to compare the amplitude of the reflex in two situations (e.g. 'natural reciprocal inhibition' of the reflex with respect to rest during voluntary contraction of the antagonistic muscle, cf. Chapter 5).

Basic methodology

H reflexes cannot be recorded with equal ease in different motor nuclei (cf. Chapter 2). In most healthy subjects *at rest*, H reflexes can usually be recorded only from soleus (Hoffmann, 1918), quadriceps (Gassel, 1963), hamstrings (Magladery *et al.*, 1951a) and flexor carpi radialis (FCR) (Deschuytere, Rosselle & DeKeyser, 1976). However, when a weak voluntary contraction is used to potentiate the reflex by raising motoneurone excitability close to firing threshold, H reflexes can be recorded from virtually all limb muscles, if the parent nerve is accessible to electrical stimulation (cf. Burke, Adams & Skuse, 1989; Chapter 2).

General experimental arrangement

Subject's posture

The subject should be comfortably seated in an armchair with the examined limb loosely fixed in a position avoiding stretch of the test muscle (see Hugon, 1973; Burke *et al.*, 1999). Thus, the lower limb is commonly explored with the hip semi-flexed (120°), the knee slightly flexed (160°) and the ankle at 110° plantar flexion. The upper limb is explored with the shoulder in slight abduction (60°), the elbow semi-flexed (110°), and the forearm pronated and supported by the arm of the chair. In patients, recordings can be performed supine, again avoiding stretch on the test muscle.

Awareness

The state of awareness of the subject may modify the amplitude of the H reflex, often in an unpredictable way. The H reflex increases during alertness, at least when the level of attention is high (Bathien & Morin, 1972). Task demands can induce variations in the

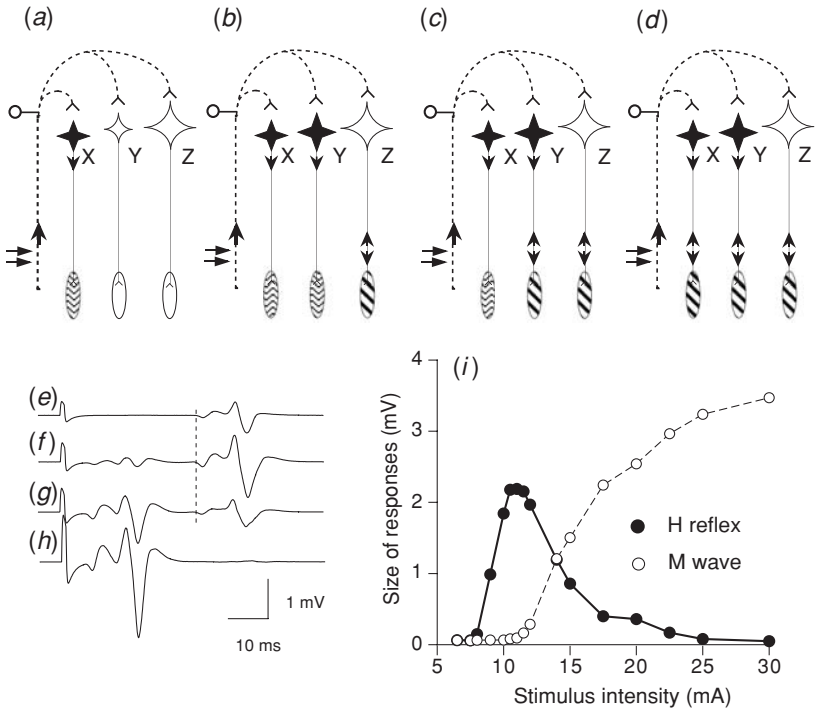

Fig. 1.3. Recruitment curve of the H and M waves in the soleus. (*a*)–(*h*) Sample EMG responses ((*e*)–(*h*)) and sketches of the corresponding volleys in Ia afferents and motor axons ((*a*)–(*d*)) when the stimulus intensity is progressively increased. MNs discharged by the Ia volley are black, muscle fibres activated by the H reflex are speckled and those activated by the M wave are hatched. (*a*) and (*e*), stimulation (9 mA) activates Ia afferents only and causes MN 'X' to fire in the H reflex. (*b*) and (*f*), stronger stimulation (12 mA) activates more Ia afferents and this causes MNs 'X' and 'Y' to fire in the H reflex, which increases in size. It also elicits a motor volley in the axon of MN 'Z' and an M wave appears in the EMG. The antidromic motor volley in MN 'Z' does not collide with the reflex response, because this MN does not contribute to the reflex. (*c*) and (*g*), even stronger stimulation (15 mA) causes MNs 'X' and 'Y' to fire in the H reflex and elicits a motor volley in the axon of MNs 'Z' and 'Y': as a result, an M wave appears in the muscle fibres innervated by MN 'Y'. The antidromic motor volley collides with and eliminates the reflex volley in the axon of MN 'Y', and the H reflex decreases. (*d*) and (*h*), yet stronger stimulation (30 mA) produces M_{max}, and the H reflex is eliminated by collision with the antidromic motor volley. The vertical dashed line in (*e*)–(*g*) indicates the latency of the H reflex. (*i*), the amplitudes of the H reflex (●) and of the M wave (○) are plotted against stimulus intensity. Modified from Pierrot-Deseilligny & Mazevet (2000), with permission.

H reflex related to the particular characteristics of the mental effort required by the task itself (Brunia, 1971). In practice, H reflexes should be recorded in a quiet room, and the influence of the mental effort involved in a difficult motor task should be taken into account. Conversely, the H reflex decreases during the early stages of sleep and is abolished during REM sleep (Hodes & Dement, 1964).

Recording the H reflex

Recording

Reflexes generally appear in the EMG as triphasic waveforms, particularly with soleus where the electrodes are not over the motor point (cf. Fig. 1.3(*e*)–(*g*)).

(i) Bipolar surface electrodes are commonly placed 1.5–2 cm apart over the corresponding muscle belly

for recording H and tendon reflexes. For the quadriceps the best place is on the anterior aspect of the thigh, 5–10 cm above the patella over the vastus intermedius. In the forearm, a selective voluntary contraction can be used as a first step to focus the reflex response on the desired motoneurone pool, because during the contraction the reflex discharge can be obtained at lower threshold in the contracting muscle.

(ii) Monopolar recordings, with an 'active' electrode over the mid-belly of the muscle and a 'remote' electrode over its tendon, have been recommended to minimise the effects of changes in geometry of the muscle during voluntary contraction (Gerilovsky, Ysvetinov & Trenkova, 1989). However, these changes are adequately taken into account if the reflex is expressed as a percentage of the maximal M wave (see p. 8) measured under the same conditions. In addition, the more distant the 'remote' electrode, the less likely is the recorded activity to come from only the muscle underlying the 'active' electrode.

Measurement

(i) Reflex latency is measured to the first deflection of the H wave from baseline, not to the first positive peak of the commonly triphasic waveform (see the vertical dashed line in Fig. 1.3(*e*)–(*g*)).

(ii) In practice it makes little difference whether the amplitude or the surface area of the reflex is assessed or whether amplitude is measured for the negative phase only or from negative peak to the following positive peak. Whichever way the H reflex is measured, the same method should be used for the maximal M wave, 'M_{max}' (see p. 8), and the amplitude of the H reflex must be expressed as a percentage of M_{max}.

Cross-talk

Pick up of the EMG potentials from an adjacent muscle can occur if there is spread of the test stimulus – electrical to another nerve (H reflex), or mechanical to another muscle (tendon jerk) (see Hutton, Roy & Edgerton, 1988). Even if this does not occur, it can still be difficult to be certain that a surface-recorded EMG potential comes exclusively from the underlying muscle rather than a synergist (e.g. responses elicited in the FCR and finger flexors after median nerve stimulation). In addition, responses evoked by a conditioning stimulus may also contaminate the test reflex, e.g. the H reflex in the antagonist FCR when studying reciprocal inhibition from wrist flexors to wrist extensors. Muscle palpation may help recognise inadvertent activation of inappropriate muscles. Another simple way of ensuring that the reflex response originates from the muscle over which it is recorded is to check that it increases during a selective voluntary contraction of that muscle.

Stimulation to elicit the H reflex

H reflexes are produced by percutaneous electrical stimulation of Ia afferents in the parent nerve. The technique is now well codified (see Hugon, 1973; Burke *et al.*, 1999).

Duration of the stimulus

The diameter of Ia afferents is slightly larger than that of α motor axons and their rheobasic threshold is lower, such that it is generally possible, particularly in soleus, to evoke an H reflex with stimuli below motor threshold (1 × MT). The strength–duration curves for motor axons and Ia afferents differ and, as a result, the optimal stimulus duration for eliciting the H reflex is long (1 ms; see Paillard, 1955; Panizza, Nilsson & Hallett, 1989). The stimulus intensity for the threshold H reflex then approaches rheobase for low-threshold Ia afferents, approximately 50% of rheobase for motor axons (Lin *et al.*, 2002).

Unipolar and bipolar stimulation

The best method for ensuring that Ia afferents are excited at lower threshold than motor axons involves placing the cathode over the nerve and the anode on the opposite side of the limb, so that current passes transversely through the nerve. The soleus and quadriceps H reflexes are commonly evoked by monopolar stimulation of the posterior tibial nerve

(cathode in the popliteal fossa, anode on the anterior aspect of the knee) and the femoral nerve (cathode in the femoral triangle, anode on the posterior aspect of the thigh), respectively. However, in areas where there are many nerves, bipolar stimulation may avoid stimulus encroachment upon other nerves: the median nerve (FCR) is so stimulated at the elbow. The same applies to the stimulation of the deep peroneal branch of the common peroneal nerve (tibialis anterior) at the fibular neck and of the sciatic nerve (hamstrings) at the posterior aspect of the thigh. It is generally stated that the cathode should then be placed over the nerve with anode distal (or lateral) to avoid the possibility of anodal block. However, there is little evidence that this is really a problem in practice.

Frequency of stimulation

Because of post-activation depression (see Chapter 2), there is reflex attenuation as stimulus rate is increased above 0.1 Hz. This attenuation requires at least 10 s to subside completely, but its effects are sufficiently small after 3–4 s to allow testing at 0.2–0.3 Hz. Use of these frequencies constitutes a compromise between reflex depression and the necessity to collect a large number of responses because of reflex variability. During a background contraction of the tested muscle, the attenuation with increasing stimulus repetition rate is reduced or even abolished (cf. Chapter 2).

Magnetic stimulation

The H reflex may also be evoked by magnetic stimulation of the parent nerve (or nerve root) and appears with the same latency as with electrical stimulation (Zhu *et al.*, 1992). One advantage of magnetic stimulation is the ease with which an H reflex can be elicited from deep nerves, such as the sciatic nerve in the thigh or the sacral nerve roots, which are difficult to access with percutaneous electrical stimulation unless needle electrodes are inserted (Abbruzzese *et al.*, 1985). However, with magnetic stimulation, the threshold for the H reflex is usually higher than that for the M wave. This difference is probably due to the extreme brevity (~0.05 ms) of the effective stimulus produced by magnetic stimulation, a stimulus duration that favours motor axons with respect to Ia afferents (Panizza *et al.*, 1992).

H and M recruitment curve

The recruitment curve

As the intensity of the electrical stimulus to the posterior tibial nerve is increased, there is initially a progressive increase in amplitude of the soleus reflex due to the stronger Ia afferent volley (Fig. 1.3(*a*), (*b*), (*e*), (*f*)). When motor threshold is reached, the short-latency direct motor response (M wave) appears in the EMG due to stimulation of motor axons ((*b*) and (*f*)). Further increases in the intensity of the test stimulus cause the M wave to increase and the H reflex to decrease ((*c*) and (*g*)). Finally, when the direct motor response is maximal, the reflex response is completely suppressed ((*d*) and (*h*)). This is because the antidromic motor volley set up in motor axons collides with and eliminates the H reflex response (Hoffmann, 1922, Fig. 1.3(*d*)). Note that, when it first appears in the EMG, the M response involves axons of the largest motoneurones (e.g. MN 'Z' in Fig. 1.3(*b*) and (*f*)), which have a high threshold for recruitment into the H reflex. Because they are not activated in the reflex, stimulation of these motor axons does not interfere with the reflex response. The variations of the H and M responses with the test stimulus intensity can be plotted as the recruitment curve of Fig. 1.3(*i*). Because of the orderly recruitment of motoneurones (see pp. 3–4), the sensitivity of the reflex to facilitation and inhibition depends on the last motoneurones recruited by the test volley (as long as the reflex is not on the descending limb of the recruitment curve, see below).

Maximal M wave (M_{max})

M_{max} is evoked by the stimulation of all motor axons and provides an estimate of the response of the entire motoneurone pool. This estimate is actually an

overestimate, because the necessarily strong stimulus will produce EMG activity in synergists in addition to the test muscle. Accordingly, the M_{max} following median nerve stimulation at the elbow comes from the FCR, finger flexors and pronator teres. Ignoring this issue, M_{max} should always be measured in the same experiment with the same recording electrode placement because: (i) comparing it with the reflex response provides an estimate of the proportion of the motoneurone pool discharging in the reflex; (ii) expressing the reflex as a percentage of M_{max} enables one to control for changes in muscle geometry due to changes in muscle length or contraction; (iii) expressing the test reflex as a percentage of M_{max} allows the investigator to be sure that the test reflex remains within the 'linear' range of the input/output relationship for the motoneurone pool (i.e. between ~10 and 60% of M_{max} for the soleus H reflex, see pp. 16–18).

The test reflex should not be on the descending limb of the recruitment curve

This is because the component of the H reflex seen in the EMG is generated by low-threshold motoneurones, which are insensitive to excitation or inhibition. Small motoneurones innervating slow motor units are first recruited in the H reflex (see pp. 3–4), whereas electrical stimulation will first activate motor axons of large diameter from high-threshold motoneurones. As a result, on the descending limb of the recruitment curve, the reflex response seen in the EMG will be produced by small motoneurones, in which the collision in motor axons has not taken place. The reflex response in the fastest motor units of the H reflex, i.e. those that were last recruited into the reflex and are thus sensitive to excitation and inhibition, will be eliminated by collision with the antidromic motor volley (Fig. 1.3(*c*) and (*g*)) (see Pierrot-Deseilligny & Mazevet, 2000).

Monitoring the stability of the stimulation conditions

If the H reflex is performed during a manoeuvre that can alter the stimulating conditions (e.g. muscle contraction, stance or gait), it is necessary to ensure that changes in the test H reflex are not due to a change in the position of the stimulating electrode. The reproducibility of a M wave can then be used to monitor the stability of the stimulation. To that end, stimulation should be adjusted to produce a small M wave in addition to the H reflex. If there is need for a test response without a M wave, the stability of stimulation can be monitored by alternating the test stimulus with a stimulus evoking a M wave through the same electrode. This procedure raises questions about the acceptable range of variability of the M wave in such studies. Some authors have used a range of $\pm 10\%$ of M_{max}, but this is a large range when compared to the changes expected in the H reflex, and changes not exceeding $\pm 10\%$ of the recorded M wave, not $\pm 10\%$ of M_{max}, are recommended. It should be realised that, during experiments involving a voluntary or postural contraction of the tested muscle, there will be changes in axonal excitability unrelated to stability of the stimulating conditions (Vagg *et al.*, 1998), and there will inevitably be some variability in the M wave from trial to trial.

Recruitment curves in other muscles

The recruitment curves for the quadriceps and FCR H reflexes are similar. However, the threshold of the M and H responses of FCR and quadriceps are generally closer than in soleus.

Tendon jerk

In proximal muscles (e.g. biceps and triceps brachii), the H reflex is difficult to record at rest without the M wave, and it then appears merged into the end of the M wave. For routine testing, it may be more convenient to test the excitability of these motoneurone pools using tendon reflexes. An electromagnetic hammer (such as a Brüel and Kjaer shaker, Copenhagen, Denmark) will produce reproducible transient tendon percussion. In healthy subjects at rest, a tendon jerk reflex can be elicited in the soleus, quadriceps, biceps femoris, semitendinosus, biceps and triceps brachii, FCR, extensor carpi radialis (ECR) and the masseter. Use of the tendon jerk introduces two complications.

Delay due to the tendon tap

The tendon tap introduces a delay, and in the soleus, the afferent volley for the tendon jerk will reach motoneurones ~5 ms later than the electrically induced volley producing the H reflex (cf. Chapter 2). An estimate of the *central* delay of the effect of a conditioning volley on a test tendon jerk may be obtained by comparing the first interstimulus interval (ISI) at which this effect occurs to the first ISI at which a heteronymous monosynaptic Ia volley delivered to the same nerve facilitates the tested motoneurones (see Mazevet & Pierrot-Deseilligny, 1994). An example would be the group Ia projection from median-innervated forearm muscles to biceps and triceps motoneurones.

Fusimotor drive

The amplitude of the reflex response produced by tendon percussion may depend on the level of γ drive directed to muscle spindle primary endings of the tested muscle (see Fig. 1.1). Accordingly, it has been argued that differences in the behaviour of H and tendon jerk reflexes reflect the involvement of γ drive in the tendon jerk (e.g. see Paillard, 1955). This belief has been called into question because H and tendon jerk reflexes differ in a number of other respects, as discussed in detail in Chapter 3. Of greater importance could well be the effects on the spindle response to percussion of the thixotropic properties of intrafusal fibres (see Chapter 3).

Random alternation of control and conditioned reflexes

In most investigations, the monosynaptic reflex is used as a test reflex to assess the effect of conditioning volleys on the motoneurone pool. The size of the reflex is compared in the absence (control reflex) and in the presence (conditioned reflex) of the conditioning volley. Control and conditioned reflexes should be randomly alternated, because: (i) this avoids the possibility of the subject voluntarily or involuntarily predicting the reflex sequence; and (ii) regular alternation produces erroneously large results (Fournier, Katz & Pierrot-Deseilligny, 1984), possibly due to post-activation depression (see Pierrot-Deseilligny & Mazevet, 2000).

Estimate of the central delay of a conditioning effect. Time resolution of the method

It is essential to estimate the central delay of an effect in order to characterise the neural pathway activated by a conditioning stimulus as mono-, di-, or polysynaptic. This can be done by comparing the earliest conditioning-test interval at which the test reflex is modified with the interval estimated for the simultaneous arrival of the conditioning and test volleys at spinal level. The greater the difference between these two values the longer the intraspinal circuit, and this could be because more synapses are involved. It should be noted that the H reflex method underestimates the true central delay. For example, despite the extra 0.8 ms due to the interneurone interposed in the pathway of disynaptic reciprocal Ia inhibition, the earliest conditioning-test interval with inhibition corresponds to the simultaneous arrival of the two volleys at spinal level (Chapter 5). This is due to two reasons (Fig. 1.4).

PSPs in individual motoneurones

The rise time of the EPSP is sufficiently long that the discharge of the last recruited motoneurones evoked by the monosynaptic input will not occur before the arrival of a disynaptic IPSP. This is so even though the synaptic delay at the interneurone delays the onset of the IPSP by 0.5–1.0 ms relative to the beginning of the monosynaptic EPSP (see Matthews, 1972, and Fig. 1.4(*a*)). In addition, an EPSP elicited by a conditioning volley entering the spinal cord after the test volley may summate with the decay phase of the test Ia EPSP and cause the motoneurone to discharge at a 'too early' ISI.

Motoneurones do not discharge at the same time in the test reflex

Even in the cat there is 0.5 ms between the firing of the first and last recruited motoneurones contributing to

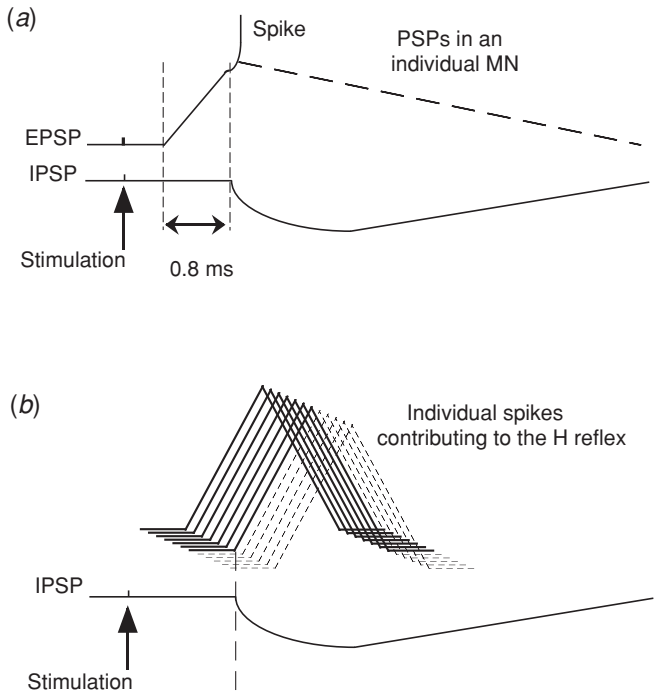

Fig. 1.4. A disynaptic IPSP can inhibit the monosynaptic reflex. (*a*) Post-synaptic (PSP) potentials in an individual motoneurone (MN): when volleys eliciting a monosynaptic Ia EPSP and a disynaptic IPSP enter the spinal cord simultaneously, the rise time of the EPSP in individual MNs allows the spike in the last recruited MNs to be inhibited by the IPSP, even though the latter does not begin until 0.5–1.0 ms after the beginning of the EPSP. (*b*) MNs contributing to the H reflex do not discharge simultaneously in the test reflex. Thus, a disynaptic IPSP elicited by a conditioning volley entering the spinal cord at the same time as the test monosynaptic Ia volley may inhibit the last spikes (thin interrupted lines) contributing to the monosynaptic reflex discharge, while the first spikes (thick continuous lines) are not modified. Adapted from Matthews (1972) (*a*), and Araki, Eccles & Ito (1960) (*b*), with permission.

the monosynaptic reflex (Araki, Eccles & Ito, 1960). In human subjects, where the afferent pathway is longer and the conduction velocity of Ia afferents slower, this interval has been estimated at 1.5 ms for the quadriceps H reflex (Fournier *et al.*, 1986) and ~2 ms for the soleus H reflex (Burke, Gandevia & McKeon, 1984). There are differences in the rise-times of mechanically and electrically evoked EPSPs (~10 ms for tendon percussion; ~2 ms for the electrically evoked volley), but this is not obvious in the reflex EMG potentials because the axons of the last recruited motoneurones have a more rapid conduction velocity than those first recruited. Figure 1.4(*b*) shows that, because of the desynchronisation at spinal level, the last individual spikes contributing to the monosynaptic test reflex discharge can be inhibited by a disynaptic IPSP elicited by a conditioning volley entering the spinal cord at the same time as the monosynaptic test volley.

The recovery cycle of the H reflex

The recovery cycle of the H reflex investigates the time course of the changes in the H reflex after a conditioning reflex for conditioning-test intervals up to 1–2 s. Such studies were in vogue in the 1950–1960s (Magladery *et al.*, 1951b, 1952; Paillard, 1955). However, the recovery cycle is no longer employed,

because it results from too many phenomena to be of practical use. Factors that could alter the test reflex include changes in excitability of Ia afferents (see below), post-activation depression (cf. pp. 13–14), presynaptic inhibition of Ia terminals activated by the conditioning volley (cf. Chapter 8), afterhyperpolarisation and recurrent inhibition of motoneurones (cf. Chapter 4), muscle spindle receptor unloading by the conditioning twitch (cf. Chapter 3), Golgi tendon organ activation by the conditioning twitch (cf. Chapter 6), and effects mediated by long loops (Táboríková & Sax, 1969).

When the conditioning and test volleys involve the same population of afferents, the conditioning discharge will change the excitability of the stimulated afferents for ~100 ms, and this is an additional complicating factor. Figure 1.5 shows the recovery cycle of the H reflex after a conditioning volley that was subthreshold for the H reflex even during contraction, comparing the results obtained with 'threshold tracking' ((*a*), see below) with those of conventional 'amplitude tracking' (*b*). There is an initial period of decreased excitability, corresponding to 'refractoriness', followed by a period peaking at 7–8 ms corresponding to 'supernormality' and a final phase corresponding to 'late subnormality'. These changes in excitability are those of the stimulated peripheral nerve axons (Chan *et al.*, 2002), and this finding indicates that two identical stimuli delivered to a nerve will not excite the same population of afferent axons when the interval between them is <100 ms.

Amplitude and threshold tracking of the compound H reflex

With threshold tracking, test stimuli are varied automatically by computer, much as in conventional threshold tracking (Bostock, Cikurel & Burke, 1998), to maintain a constant compound H reflex, the current being then referred to as the threshold for the H reflex. Reflex facilitation will produce a decrease in the required current, and reflex inhibition will produce an increase (cf. Chan *et al.*, 2002). This is illustrated in Fig. 1.5 where the curves obtained with threshold (*a*) and amplitude (*b*) tracking show reciprocal changes. A similar principle has been exploited by Shindo *et al.* (1994) in studies on the unitary H reflex (see pp. 37–9).

Advantages with threshold tracking

There are advantages with threshold tracking over amplitude tracking for H reflex studies.

(i) The results are less variable (cf. Fig. 1.5, ●).

(ii) The recorded response involves a constant population of motoneurones, and clamping the reflex response to a fixed size avoids the problem of size-related changes in test reflex sensitivity (see pp. 16–18).

(iii) The dynamic range of threshold tracking is wide, enabling threshold changes of 200% or more to be tracked. In contrast, amplitude tracking suffers from 'floor' and 'ceiling' effects: there is a limited range within which the size of test response can reflect changes in excitability and, once the response reaches maximum or is reduced to zero, further increases or decreases in excitability can no longer be reflected in the size of the test response.

Disadvantages with threshold tracking

(i) In order to maintain a constant reflex response, the intensity of the afferent volley must be altered, and this could introduce inaccuracies, because the reflex size also depends on mechanisms acting on the afferent volley (cf. pp. 12–16).

(ii) When excitability changes, there is a delay with threshold tracking before the new threshold is reached as the computer tracks to it. By contrast, with amplitude tracking, changes in reflex excitability produce instantaneous changes in the reflex response.

Limitations related to mechanisms acting on the afferent volley of the reflex

The pathway of the monosynaptic reflex is not as simple as it at first seems. Reflex size also depends on mechanisms acting on the afferent volley. As a result, many mechanisms other than changes in excitability of the motoneurone pool can alter the size of the reflex.

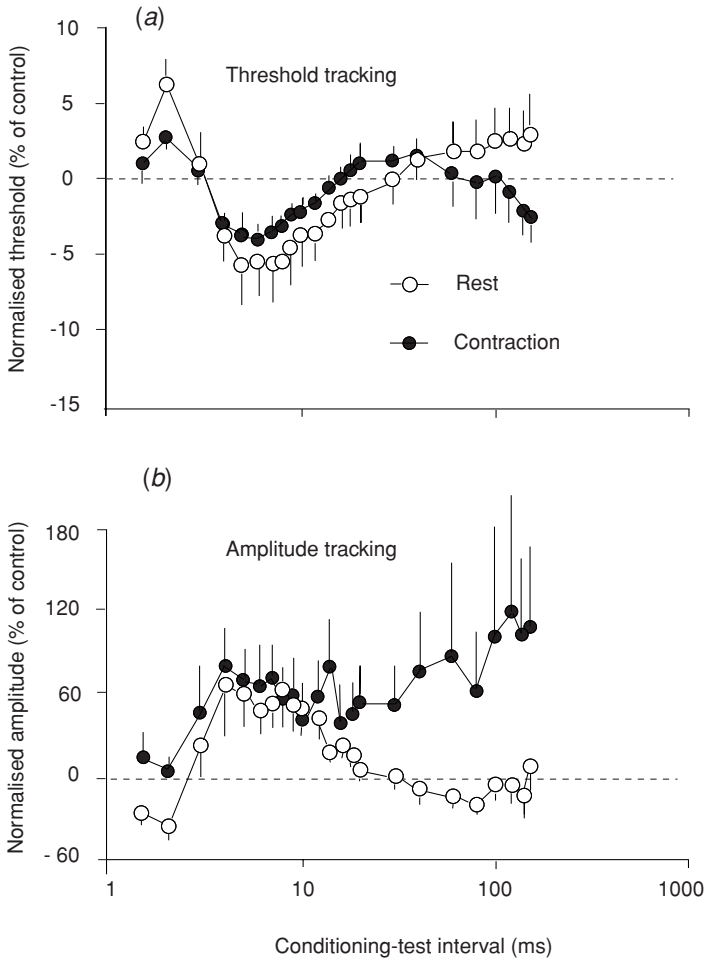

Fig. 1.5. The recovery cycle of the H reflex following a single subthreshold conditioning stimulus. The soleus H reflex was conditioned by a weak stimulus to the posterior tibial nerve (65% of the unconditioned test stimulus, subthreshold for the H reflex during contraction). Data representing the deviation from the unconditioned value (horizontal dashed line), using threshold tracking (*a*) and amplitude tracking (*b*) at rest (○) and during tonic soleus voluntary contractions (●) are plotted against the conditioning-test interval. In (*a*) the intensity of the test stimulus was altered to keep the test H reflex constant: an increase in excitability would therefore require less current. In (*b*), the test stimulus was constant: an increase in excitability would therefore increase the amplitude of the test H reflex. Note the logarithmic scale for the *x*-axis. Mean data ± SEM for six subjects. Adapted from Chan *et al.* (2002), with permission.

Alterations in the excitability of Ia afferents

Repetitive activation of cutaneous afferents (Kiernan *et al.*, 1997) and natural activity of motor axons (Vagg *et al.*, 1998) produce axonal hyperpolarization and thereby a significant reduction in the excitability of the active axons. The extent of hyperpolarization depends on the impulse load, but can be prominent. For example, with motor axons, contractions lasting only 15 s increase threshold by 10–20%, i.e. after the contraction, the stimulus had to be increased by 10–20% to activate the same number of axons

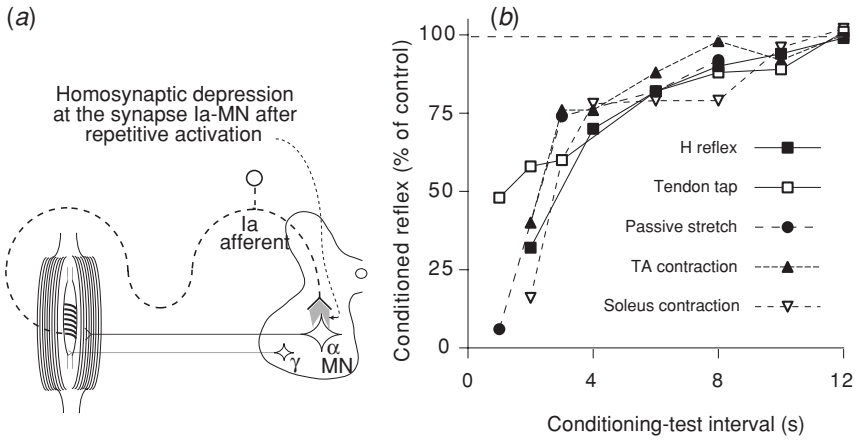

Fig. 1.6. Post-activation depression produced by different ways of activating the Ia afferent-MN synapse repetitively. (*A*) Sketch of the pathway (the grey area indicates the Ia afferent-motoneurone [MN] synapse). (*b*) The recovery of the soleus H reflex (expressed as a percentage of its control value) after various conditioning stimuli, plotted against the conditioning-test interval: preceding H reflex (■), subliminal tendon tap (□), passive dorsiflexion of the ankle (●), voluntary contraction of the tibialis anterior (▲) or of the soleus (▽). Modified from Crone & Nielsen (1989) and Hultborn *et al.* (1996), with permission.

(Vagg *et al.*, 1998). This issue is probably important for group Ia afferents and the H reflex, because the excitability of the afferents will decrease during a voluntary contraction if there is a fusimotor-driven increase in discharge from the active muscle (cf. Chapter 3). As a result, the reflex response to a fixed stimulus could change, independently of the other contraction-related changes (presynaptic inhibition of Ia afferents, post-activation depression, motoneurone excitability). Additionally, the contraction will activate Ib afferents and thereby reduce their excitability to electrical stimulation. This would reduce the number of Ib afferents in the afferent volley and the extent to which they limit the size of the H reflex (see pp. 14–16).

Presynaptic inhibition of Ia terminals

Ia terminals mediating the afferent volley of the monosynaptic reflex are subjected to presynaptic inhibition accompanied by primary afferent depolarisation (PAD). Changes in presynaptic inhibition of Ia terminals can cause major changes in the amplitude of the H reflex, and the possibility that a change in presynaptic inhibition accounts for a change in the amplitude of the H reflex must therefore always be considered. Several methods have been developed to assess presynaptic inhibition of Ia terminals in human subjects, as described in detail in Chapter 8.

Post-activation depression

A different presynaptic mechanism limiting monosynaptic reflexes is post-activation depression at the Ia fibre-motoneurone synapse, probably due to reduced transmitter release from active Ia afferents, a phenomenon which is described in detail in Chapter 2 (pp. 96–100). Post-activation depression occurs when (and only when) the conditioning stimulus or manoeuvre activates the very afferents responsible for the test response. H reflex depression has been reported to occur following a preceding H reflex (Magladery & McDougal, 1950), a subliminal tendon tap (Katz *et al.*, 1977), passive dorsiflexion of the ankle (Hultborn *et al.*, 1996), and voluntary contraction of soleus or stretch of soleus produced by contraction of tibialis anterior (Crone & Nielsen, 1989; see also Wood, Gregory & Proske, 1996). The effects of this phenomenon can be profound, as illustrated in Fig. 1.6, showing the time course

of the recovery of the soleus H reflex after these manoeuvres. In all cases, there was dramatic reflex depression at short intervals (1–2 s), with gradual recovery over 10 s. The depressive effects of the stimulus rate on reflex size are generally taken into consideration in reflex studies, but the same cannot be said for the post-activation depression occurring under other circumstances. It is likely that misinterpretations have arisen because this phenomenon was neglected in studies comparing changes in the test reflex during or after a voluntary contraction. In addition, when the effects of a conditioning volley are compared at rest and during contraction, *post-activation depression may also alter the transmission through the conditioning pathway* (e.g. see Chapter 5, p. 221), though not all afferent inputs are similarly affected (see Lamy *et al.*, 2005; Chapter 7, p. 310).

Contribution of oligosynaptic pathways to the H reflex

Limitation of the size of the H reflex

In soleus, when the intensity of the test stimulus is increased, the amplitude of the H reflex commonly reaches its peak before the antidromic volley set up in motor axons collides with and annihilates the reflex response (see p. 7). Thus, there is a limitation to the size of the H reflex independent of the collision with the antidromic volley in motor axons. Táboríková & Sax (1968) demonstrated that, in normal subjects, the percentage of soleus motoneurones activated in the H reflex by maximal stimulation of Ia afferents ranges from 24 to 100, usually ∼50%. In the homogeneous soleus, this implies the existence of factors limiting the size of the reflex.

Curtailment of the compound EPSP by an oligosynaptic IPSP

The first motoneurones discharging in the H reflex do so at a latency consistent with a monosynaptic pathway (Magladery *et al.*, 1951a). However, based on estimates from post-stimulus time histograms (PSTHs) of the discharge of single motor units, it has been argued that the duration of the compound group I EPSP underlying the H reflex is so short (some 1–2 ms) that the monosynaptic Ia component of the EPSP must be curtailed by oligosynaptic inhibition, and that this would help limit the size of the H reflex (Burke, Gandevia & McKeon, 1984). Transmission in two disynaptic inhibitory pathways could truncate the monosynaptic Ia excitation: (i) Ib inhibitory interneurones activated by the group I test volley produce autogenetic inhibition with an onset ∼0.7 ms after the onset of the facilitation due to the group Ia monosynaptic EPSP in motoneurones (Pierrot-Deseilligny *et al.*, 1981; Chapter 6, pp. 253–5); (ii) Renshaw cells are activated by the reflex discharge of low-threshold motoneurones (Chapter 4, p. 159) and could produce recurrent inhibition that would prevent the discharge of higher-threshold motoneurones.

Disynaptic limitation of the group Ia excitation

Recent experimental evidence for a disynaptic limitation of the group Ia excitation that is the basis of the H reflex has been provided for the quadriceps (Marchand-Pauvert *et al.*, 2002). The evidence is as follows. At rest and during weak contractions of quadriceps stimulation of the deep peroneal nerve produces a late facilitation of the quadriceps H reflex with a central delay of 6–12 ms (Fig. 1.12(*c*), Δ), but this is suppressed during a contraction of 10–20% maximum voluntary contraction (MVC) (Fig. 1.12(*c*), ●, and thick line in Fig. 1.7(*b*)). However, the corresponding facilitation of the on-going EMG is not suppressed (Fig. 1.12(*b*), ●). Such a discrepancy raises the possibility of an inhibitory mechanism gating the afferent volley of the test reflex, the nature of which was clarified in experiments involving PSTHs of single motor units in quadriceps (Fig. 1.7(*c*)–(*f*)). Panel (*c*) shows the peak of homonymous group I excitation evoked by femoral stimulation, panel (*d*) the weak facilitation at around 27 ms elicited by separate stimulation of the deep peroneal nerve, and (*e*) the significant reduction of the femoral excitation on combined stimulation. Suppression on combined stimulation when the stimuli by themselves produce

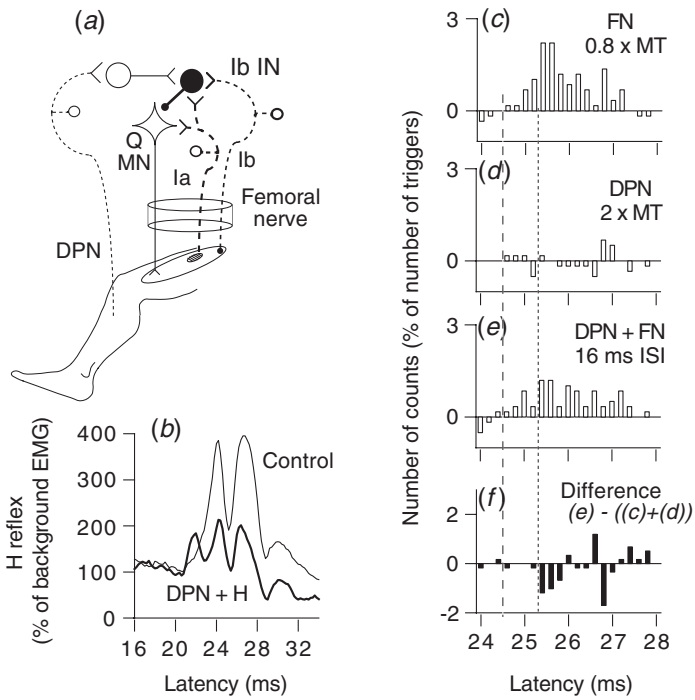

Fig. 1.7. Evidence for suppression of the H reflex by disynaptic autogenetic inhibition from afferents in the test volley. (*a*) Sketch of the presumed pathway: when facilitated by the deep peroneal nerve (DPN) volley, 'Ib' inhibitory interneurones (IN) co-activated by Ia and Ib afferents in the femoral nerve (FN) test volley truncate the monosynaptic EPSP in the last recruited quadriceps (Q) motoneurones (MN). (*b*) The rectified and averaged Q H reflex (20 sweeps, 5 kHz sampling rate) during a contraction (10% of MVC), showing control responses (thin line) and conditioned responses (thick line, stimulation of the DPN at 2 × MT, 13 ms ISI). (*c*)–(*e*) PSTHs of the discharge of a single unit in vastus lateralis (after subtraction of the background firing, 0.2 ms bin width, quadriceps contraction 20% MVC). (*c*) Stimulation of FN by itself (0.8 × MT); (*d*) the DPN by itself (2 × MT), and (*e*) both nerves, the DPN preceding the FN stimulus by 16 ms. (*f*) The suppression of the FN group I excitation, calculated as (*e*) – ((*c*) + (*d*)). The number of counts in each bin is plotted against the latency after FN stimulation (even in (*d*) where only DPN stimulation was given). Note the lack of suppression in the initial bins of the femoral group I excitation (the dashed and dotted vertical lines highlight the onset of the femoral peak at 24.6 ms and the suppression at 25.4 ms, respectively). Adapted from Marchand-Pauvert *et al.* (2002), with permission.

facilitation reflects convergence (see p. 47) of the two volleys onto common inhibitory interneurones (as in the wiring diagram in Fig. 1.7(*a*)). The suppression spared the first 0.8 ms of the femoral group I excitation. This is consistent with disynaptic inhibition elicited by the test group I volley. Because of the synaptic delay at the interneurone, the inhibitory input would reach the motoneurone after the direct monosynaptic Ia input, and there should be no change in the bins of the histogram appropriate for this interneuronal delay. Thus, post-synaptic inhibition due to afferents in the test volley should not affect the onset of the femoral excitation, and initial sparing should be demonstrable, as it was.

Can the results obtained for the quadriceps be generalised?

So far, evidence for a limitation of the H reflex by disynaptic inhibition elicited by the test group I volley

has only been demonstrated for the quadriceps. However, the limitation should be more pronounced for the soleus than for the quadriceps, because the degree of desynchronisation of the reflex discharge is more marked in the former (see p. 10). This presumably reflects the longer afferent pathway of the soleus H reflex, which would allow greater dispersion of the afferent volley and thereby a greater influence on the reflex discharge from Ib afferents activated by the test stimulus. It is therefore probable that soleus H reflexes are also truncated by disynaptic inhibitory activity. This limitation could contribute to the absence of H reflex at rest in muscles such as tibialis anterior and extensor carpi radialis (see Chapter 2, p. 81).

Recurrent inhibition

There is so far no experimental evidence for recurrent inhibition elicited by the discharge of low-threshold motoneurones preventing the discharge of higher-threshold motoneurones, and it is probable that the peak of recurrent inhibition occurs too late to curtail significantly the test H reflex (see Chapter 4).

Consequences for the use of the H reflex

The sensitivity of the H reflex to di- or oligosynaptic inhibition by afferents in the test volley limits the value of H reflex studies. Motoneurones recruited last into the reflex will be most dependent on pathways with interposed interneurones, and the changes in the reflex, e.g. during movement, are largely determined by the recruitment of these motoneurones. It is possible to test for an oligosynaptic limitation of the H reflex by the test volley by comparing systematically the effects of a given input on the H reflex and on the peak of monosynaptic group I excitation in the PSTH of single units of the same muscle. Only those changes affecting the entire excitatory peak and, in particular, the initial 0.5–1.0 ms can be considered to have affected the monosynaptic pathway. This is because the onset of the test excitation, whether in PSTHs or in the H reflex itself, should be free from contamination by non-monosynaptic inputs from afferents in the test volley (Marchand-Pauvert *et al.*, 2002).

'Pool problems' related to the input–output relationship in the motoneurone pool

Size-related sensitivity of the test reflex (non-linearity within the motoneurone pool)

The effects of a constant conditioning volley are different when the unconditioned test reflexes are of different size. This is due in part to the method of normalising the results but, in addition, there is a different sensitivity of reflexes of different size to facilitation and inhibition, reflecting a non-linear input–output relationship within the motoneurone pool. This property of the motoneurone pool has been implied by several authors (e.g. Hunt, 1955; Meinck, 1980). The question was extensively investigated in human subjects and in the cat by Crone *et al.* (1990), using conditioning stimuli that produce excitation or inhibition at pre- and post-synaptic levels.

The distorting effects of normalisation

These are illustrated in Fig. 1.8(*a*). The soleus H reflex was conditioned by a heteronymous monosynaptic Ia volley from the femoral nerve. When expressed as a percentage of the control reflex, as is the case in most studies using the H reflex, the degree of facilitation is enormous with the smallest test H reflexes, and decreases the larger the test reflex. However, this is essentially a numerical artefact produced by normalisation of a fixed degree of facilitation to an increasing control reflex.

Sensitivity of reflexes of different size to facilitation and inhibition

The 'absolute' increase, expressed as a percentage of M_{max}, is a more suitable expression of the change in reflex size. Fig. 1.8(*b*) shows the data from Fig. 1.8(*a*). The amount of facilitation initially increased as the amplitude of the control H reflex increased, reached a maximum when the control reflex was around 30% of M_{max}, and then decreased with further increases in the amplitude of the control H reflex. The finite size of the soleus motor pool must

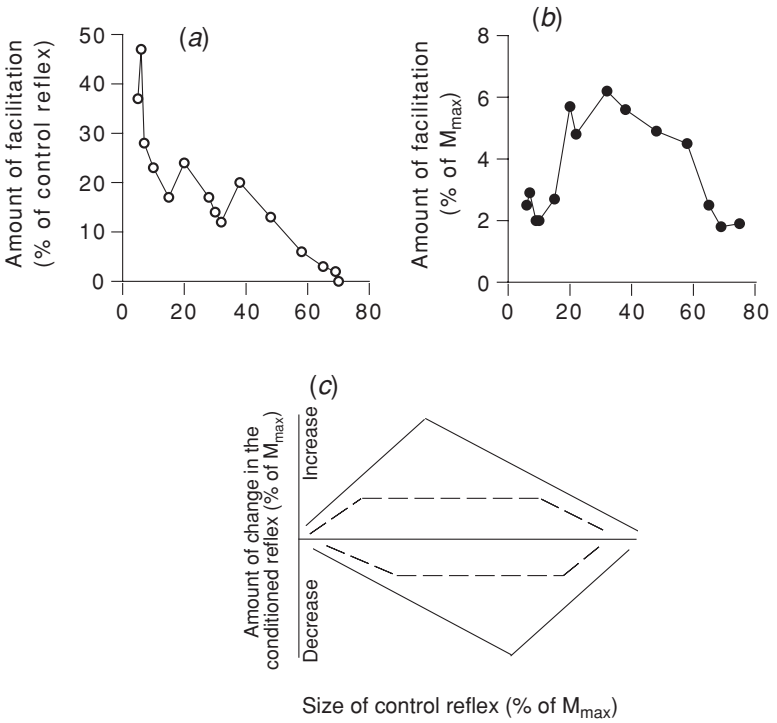

Fig. 1.8. Non-linearity within the MN pool. (*a*), (*b*) The amount of heteronymous monosynaptic Ia facilitation of the soleus H reflex (conditioned *minus* control reflex) elicited by a conditioning stimulus to the femoral nerve (1.1 × MT, 4.8 ms conditioning-test interval) expressed as a percentage of the control reflex size (*a*) or of M_{max} (*b*) and plotted against the control reflex size (in percentage of M_{max}). (*c*) Summarising diagram showing the sensitivity of monosynaptic reflexes to facilitation (upper part) or inhibition (lower part). Strong conditioning inputs, continuous lines; weak conditioning inputs, dashed lines. Modified from Crone *et al.* (1990), with permission.

put a limit to the amount of facilitation in the case of very large test H reflexes. It turned out, however, that the amount of facilitation caused by the conditioning stimulus decreased considerably before the facilitated H reflexes approached M_{max}. In human subjects and in the cat, monosynaptic reflexes of small and large size have a lower sensitivity than reflexes of intermediate size for various facilitatory and inhibitory inputs. This is summarised in the sketch in Fig. 1.8(*c*) where the amount of facilitation or of inhibition elicited by a constant conditioning input, facilitatory (upper part) or inhibitory (lower part), is plotted against the size of the control reflex. When the conditioning input is strong (continuous line), the number of additionally recruited (facilitation) or derecruited (inhibition) motoneurones first increases with increasing size of the control test reflex, and then decreases. When the effect of the conditioning input is modest (dashed lines), there is a 'plateau' region between the phases of increase and decrease.

Input–output relationship within the motoneurone pool

In the cat, the relationship between the Ia input and the reflex discharge is sigmoid (Hunt, 1955). The first part of the recruitment curve of the H reflex also conforms to a sigmoid relationship (see Fig. 1.3(*i*)). The mechanism behind this characteristic pattern

is probably a combination of the intrinsic properties of the individual motoneurones and the excitability profile of the motor pool (see Crone *et al.*, 1990), as well as the properties of the afferent volley. Whatever its mechanism, the relationship illustrating the changes in the amount of facilitation (or inhibition) with increasing control reflex size is the first derivative of the sigmoidal input–output relationship, and should be bell-shaped: 'however, if small conditioning stimuli are used the differential function will have a relatively flat peak, which could be interpreted as a plateau when dealing with inherently variable experimental data' (Capaday, 1997).

Consequences when using the monosynaptic reflex

The changes in sensitivity of the monosynaptic reflex can be large enough to lead to misinterpretations of results obtained using H reflexes. This factor must be taken into account: (i) when comparing the effects of a conditioning input under two situations (e.g. rest and contraction) which alter the size of the unconditioned H reflex; (ii) when using the spatial facilitation technique (see p. 48); (iii) when assessing the effects of conditioning stimulation on the H reflex in different subjects (a factor that has often been neglected when comparing normal and spastic subjects).

(a) When the conditioning effect is modest, the sensitivity of reflexes of medium size does not change significantly with the control reflex size as long as it remains in the 'plateau' region in Fig. 1.8(*c*). The intensity of the test stimulus should be chosen so that the control reflex remains within this range in the two situations which are compared. In practice, this implies using a control H reflex of at least 10% of M_{max} in soleus (Crone *et al.*, 1990) and quadriceps (Forget *et al.*, 1989), and 5% in FCR (Malmgren & Pierrot-Deseilligny, 1988). However, this does not guarantee a reliable comparison, because reflex responses of equal size may lie on input–output curves of different steepness (see pp. 18–20). A limitation of this strategy is that it is possible to study the behaviour of only a sample of motoneurones in the pool. This would represent no real limitation if all motoneurones in the pool behaved in a homogeneous way, but this is not the case (see pp. 18–20).

(b) When the sizes of the control reflexes evoked by the same test stimulus differ greatly in the two situations (e.g. the enormous facilitation of the H reflex at the onset of a contraction of the tested muscle), the above strategy is not feasible, and an alternative must be employed. 'Adjusting' the test stimulus intensity to keep the size of the unconditioned reflex constant may obviate the problem. However, changing the intensity of the test stimulus creates its own problem: it alters the afferent volley responsible for the reflex and, as seen above, this could introduce inaccuracies, because the reflex size also depends on mechanisms acting on the afferent volley (see pp. 12–16).

Conclusions

Because of the non-linearity of the input–output relationship of the motoneurone pool, and of the possible changes in the recruitment gain of the reflex (see below), there is no absolutely reliable way of comparing results obtained with the H reflex under all circumstances. The results of reflex studies should therefore be confirmed in single unit recordings (pp. 28–39).

Changes in the recruitment gain of the reflex

Definition

Changes in the size of the test reflex evoked by a conditioning input are commonly used to estimate the mean input to different motoneurones in the pool. However, problems can occur if the distribution of the conditioning input within the motoneurone pool differs from that of the monosynaptic Ia excitatory input, i.e. the input does not affect small motoneurones preferentially. Such a skewed distribution of conditioning inputs may produce a change in the

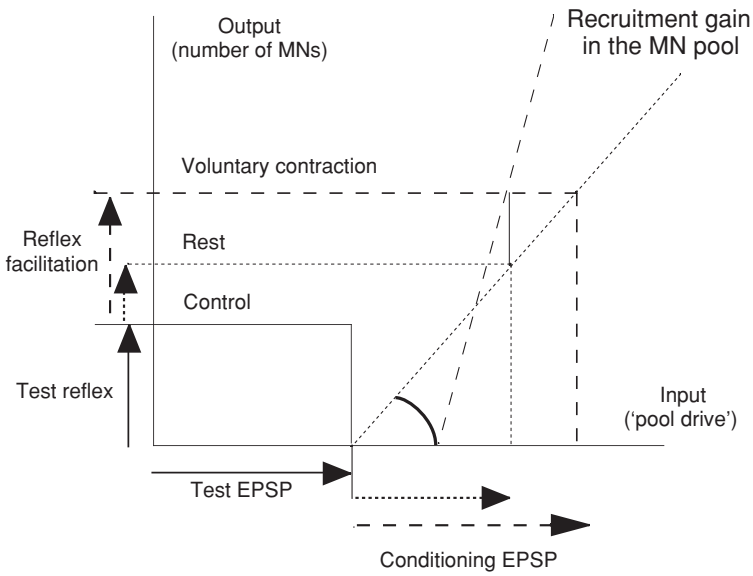

Fig. 1.9. Recruitment gain in the motoneurone pool. The input–output relationship for the soleus motoneurone pool is represented at rest (dotted oblique line) and during a possible change in the 'recruitment gain' occurring during contraction (dashed oblique line). Inputs: (i) the unconditioned test EPSP (continuous horizontal arrow), (ii) the conditioning femoral EPSP at rest (dotted horizontal arrow) and at the onset of soleus voluntary contraction (dashed horizontal arrow), and the 'recruitment gain' of the reflex (= the slope of the relationship). Output (i.e. the number of motoneurones recruited in the reflex) is represented by vertical arrows: unconditioned test reflex (continuous line; the intensity of stimulation having been 'adjusted' to produce control reflexes of the same size at rest and during contraction), and the amount of femoral-induced facilitation of the reflex at rest (dotted line) and at the onset of soleus voluntary contraction (dashed line). Modified from Pierrot-Deseilligny & Mazevet (2000), with permission.

'recruitment gain' of the reflex (Kernell & Hultborn, 1990).

Change in the slope of the input–output relationship

Figure 1.9 presents the input–output relationships for the soleus motoneurone pool under two situations, rest (dotted lines) and voluntary contraction (dashed lines), for a single example: the enhanced femoral-induced facilitation of the soleus H reflex observed at the onset of a soleus contraction. The femoral facilitation represents a heteronymous monosynaptic Ia projection, and its enhancement is due to decreased presynaptic inhibition of Ia terminals (see Chapter 8, p. 355). The input to the motoneurone pool (the 'pool drive') includes three factors: (a) the Ia EPSP evoked by the test volley; (b) the conditioning effect due to the femoral monosynaptic Ia projection; (c) the 'recruitment gain' of the reflex, i.e. the slope of the input–output relationship (which is assumed to be linear for this example). The vertical arrows on the left show the size of (i) the unconditioned test reflex, adjusted so that its size remains constant, (ii) the reflex facilitation produced by the conditioning femoral EPSP at rest, and (iii) the increased femoral facilitation of the reflex at the onset of contraction. If the slope of the input–output relationship were not modified during contraction, the increased femoral facilitation of the reflex at the onset of contraction would reflect a bigger conditioning EPSP (dashed horizontal arrow), presumably due to a decrease in presynaptic inhibition of Ia afferents. However, increased

reflex facilitation could occur if the various inputs associated with contraction had different effects on low- and high-threshold motoneurones, thus compressing the range of thresholds in the motoneurone pool (much as occurs when playing an accordion). This would increase the slope of the input–output relationship of the test reflex, as illustrated by the dashed oblique line in Fig. 1.9. As a result, a constant conditioning Ia EPSP would fire more motoneurones during contraction than at rest and produce greater facilitation of the reflex, without this being due to change in the specific pathway explored. Conversely, a decrease in the recruitment gain of the reflex could produce a decrease in the reflex facilitation evoked by a constant EPSP.

How to control for a change in 'recruitment gain'

A change in the 'recruitment gain' of the reflex has been observed in the tibialis anterior after stimulation of the sural nerve, where it resulted from a skewed distribution of cutaneous inputs within the motoneurone pool, with inhibition of early-recruited and facilitation of late-recruited motoneurones (Nielsen & Kagamihara, 1993; cf. Chapter 9, p. 425). The only way to discount this possibility with certitude is to record PSTHs of single units in order to detect whether the conditioning heteronymous Ia EPSP is changed in individual units (e.g. see Katz, Meunier & Pierrot-Deseilligny, 1988). However, it is somewhat reassuring that changes in the recruitment gain have so far been observed only in heterogeneous muscles with fast and slow units, like the tibialis anterior, and not in more homogeneous muscles, such as soleus.

Plateau potentials

In animal experiments it has been demonstrated that motoneurones and interneurones in the spinal cord can develop plateau potentials due to persistent inward currents that outlast the input and can thereby distort the relationship between input current and firing rate. In the extreme, plateau potentials can produce self-sustained firing (for review, see Hultborn, 1999). Plateau potentials would change the slope of the input–output relationship of the motoneurone pool (Hultborn *et al.*, 2003), and evidence for plateau-like behaviour has been demonstrated for human motoneurones (Gorassini, Bennett & Yang, 1998; Gorassini *et al.*, 2002). They may play a role in normal motor behaviour: plateau-like behaviour can be triggered by voluntary effort (Collins, Burke & Gandevia, 2001, 2002), particularly if it produces cramps (Baldissera, Cavallari & Dworzak, 1994). This newly discovered possibility would greatly distort the input–output relationship of the H reflex, and should be considered in situations where plateau-like behaviours can appear. It is uncertain whether phasic inputs such as those associated with the H reflex or tendon jerk are sufficient to trigger plateau potentials, even during voluntary effort. If so, there is a problem. If not, there is a concern that H reflex studies might provide insight into circuitry but not how that circuitry is normally used.

Normative data and clinical value

Normative data

Amplitude

The amplitude of the H reflex varies widely in normal subjects, and amplitude measurements in patients are therefore of little value except when pathology is asymmetrical. In human subjects there is no handedness-related side asymmetry in the H_{max}/M_{max} ratio for soleus and FCR (Aymard *et al.*, 2000).

Latency

Reflex latencies depend on the duration of the stimulus current, being longer the longer the stimulus (Mogyoros *et al.*, 1997). This means that the minimal latency for the reflex arc is not measured using a stimulus of 1 ms duration, an issue that is relevant if test and conditioning stimuli of different duration are used in an experiment. Reflex latencies have a strong correlation with the length of the reflex

pathway (measured as limb length or more simply as height) and a weak but significant correlation with age (Schimsheimer *et al.*, 1987). With older patients, it may be more accurate to use the height reported by the patient rather than that measured at the time of the test because the length of neural pathways does not change with age. Latency must be measured to the onset of the first deviation of the EMG potential from baseline. The following values are from the study of Schimsheimer *et al.* (1987) in which the stimulus duration was 1.0 ms:

Soleus H reflex: (94 control subjects)
mean latency: 30.0 ± 2.1 ms (mean ± SD)
right/left difference (i.e., symmetry): 0.09 ± 0.70 ms (mean ± SD)
H reflex = 3.00 + 0.1419 × height (in cm) + 0.0643 × age (in years) ± 1.47 (± SD)
FCR H reflex: (80 control subjects)
mean latency: 16.84 ± 1.33 ms (mean ± SD)
right/left difference: 0.002 ± 0.42 ms (mean ± SD)
H reflex = 0.44 + 0.0925 × height (in cm) + 0.0316 × age (in years) ± 0.83 (± SD)

Clinical value

H reflexes have a defined role in diagnostic testing, particularly when assessing polyneuropathies or when assessing proximal conduction. If testing is performed during a voluntary contraction, H reflexes can be recorded for all spinal segments innervating the upper and lower limbs, including those likely to be compromised by, e.g. disc prolapse (see Chapter 2, p. 95). Reflexes are attenuated in peripheral neuropathies (see p. 95) and the soleus H reflex is exaggerated in spastic patients (see Chapter 12, p. 562).

Critique: limitations, advantages and conclusions

The technique of the H reflex is simple, but strict methodology is required for valid interpretations of the results. The physiological mechanisms affecting the reflex discharge are not quite as simple as they first seem, and the complexity of the so-called monosynaptic reflex pathway imposes limitations on H reflex studies. Reflex size depends on the excitability of the motoneurones, but also: (i) on mechanisms acting on the afferent volley, and (ii) on 'pool problems' related to the input–output relationship in the motoneurone pool. However, they can usually be controlled by parallel investigations recording from single motor units (see pp. 28–39), and these should be performed systematically when studying motor control physiology in human subjects. Because it enables a comparison of the results obtained at rest and during movement, the H reflex remains the only available method with which it is possible to investigate how transmission in spinal pathways is changed when human subjects undertake motor tasks.

The F wave

Underlying principles and basic methodology

Antidromic re-excitation of motoneurones

A supramaximal electrical shock delivered to a nerve often elicits a late response, termed the F wave because it was initially recorded in muscles of the foot (Magladery & McDougal, 1950). The F wave occurs only when the stimulus excites motor axons directly, producing a M wave, and is produced by an antidromic motor volley (cf. Eisen & Fisher, 1999). Because the F response in single motor units is seen only when the axon of the unit has been activated (Trontelj, 1973), it is believed that the F response is evoked by antidromic reactivation ('backfiring') of motoneurones (for review see Eisen & Fisher, 1999; Espiritu, Lin & Burke, 2003). An antidromic volley in a single motor axon may produce an F wave, provided that the axon hillock and proximal axon are not refractory when the antidromic action potential discharges the soma. Biologically, the F wave is an artefact: F waves would occur under

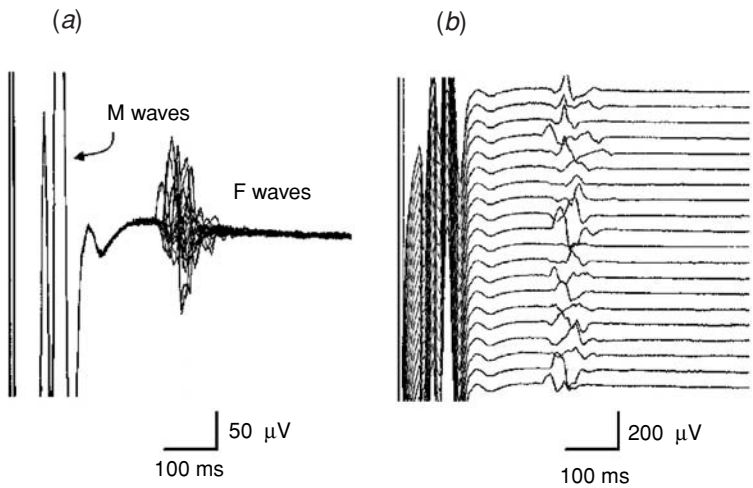

Fig. 1.10. F waves of the thenar muscles in response to supramaximal stimulation of the median nerve at the wrist at 1 Hz. (*a*) 20 consecutive responses superimposed at relatively high gain. (*b*) The same 20 responses shown in raster format, at lower gain. Note the variability of latency and morphology of consecutive responses. This occurs because different motoneurones produce F waves in each trial and the number of responding motoneurones per trial is very low, often only one.

natural conditions only if a motor axon had an ectopic focus that gave rise to an antidromic impulse. Studying F waves can provide little insight into how motoneurones behave normally because this manner of exciting the motoneurone differs from its excitation through a synaptic event.

Motoneurones involved in the F wave

It has been postulated that recurrent discharges only occur in a limited number of motoneurones, in part because the initial segment may not be excitable again after the antidromic impulse enters the somata of the motoneurones. If so, blockage at the initial segment may occur more commonly in the smaller, slower conducting motoneurones which are more rapidly depolarised, leading to preferential activation of the larger, faster conducting motoneurones. (Kimura *et al.*, 1984). Moreover, if some motoneurones in a muscle can produce H reflex discharges in response to the maximal afferent volley set up by the supramaximal stimulus for the F wave, F waves will not be recordable for these presumably low-threshold slowly conducting motor units (Esperitu, Lin & Burke, 2003). This is the case in panels *D* and *H* of Fig. 1.3: motoneurone 'Z' could produce an F wave because it was not activated in the H reflex but motoneurones 'X' and 'Y' could not.

Characteristics of the F wave

Occurrence in different muscles

F waves can occur when the nerve innervating any muscle is stimulated, but they may not be identifiable when their latency is so short that they merge with the end of the M wave. In contrast to the H reflex, the F response is most readily recorded in intrinsic hand and foot muscles, and it has attained special interest for the investigation of these muscles.

Variability and persistence

The F waves typically vary from trial to trial in amplitude, latency and shape (Fig. 1.10(*a*), (*b*)) because different motoneurones contribute to successive responses. The persistence is the percentage of

stimuli that produce F waves: it is usually >80% for the median, ulnar and tibial nerves, but can be as low as 5% for the peroneal nerve (Eisen & Fisher, 1999).

Latency

The F wave appears with a latency similar to the H reflex, slightly longer for soleus but slightly shorter for the thenar muscles (Burke, Adams & Skuse, 1989).

Amplitude

With stimuli delivered at a frequency of 1 Hz or less, the morphology of successive F waves varies considerably from trial to trial, reflecting the activity of different motor units in the muscle (Fig. 1.10(*b*)). The amplitude of individual F waves is normally that of a single motor unit, below 5% of M_{max} (Eisen & Odusote, 1979). This is because the axon hillock is reactivated in only a small number of motoneurones (usually 1–2) in response to the stimulus. The variability of latency and morphology results from different motoneurones 'backfiring' in different trials.

Chronodispersion

Clinical studies ordinarily assume that the minimal and maximal F wave latencies represent the fastest and slowest motor conduction times to and from the spinal cord, respectively. Thus, the degree of spread of latency of consecutive F waves (F chronodispersion) is often taken as a measure of the spread of conduction velocities of motor axons innervating the muscle (Yates & Brown, 1979). However, such measures apply only to those motoneurones that generate F waves. Reasons for the under-representation of slowly conducting motor units in F wave measurements are mentioned above. Comparison of F waves in tibialis anterior, abductor pollicis brevis and soleus has shown that there is an inverse relationship between F wave chronodispersion and F wave persistence at rest, and the shorter the chronodispersion the easier to elicit the H reflex in the motoneurone pool. During a steady contraction that allows the H reflex to appear in the tibialis anterior and the abductor pollicis brevis, overall F wave activity in these muscles increases in amplitude but decreases in duration. These findings are consistent with the view that reflex discharges prevent F waves in low-threshold motor units, and that chronodispersion is affected by the extent of reflex activity. In other words, chronodispersion and related F wave measures (such as mean F wave latency) do not assess motor properties exclusively (Espiritu, Lin & Burke, 2003).

F wave as a measure of excitability of motoneurones

Low sensitivity of the F response to changes in motoneuronal excitability

It has been suggested that the size of the F response depends on motoneurone excitability (Fisher, 1992). However, the sensitivity of the F response to changes in motoneurone excitability is much less than that of the H reflex. For example, the sensitivity of soleus motoneurones to the heteronymous monosynaptic Ia excitation from quadriceps is ten times less when assessed with the F wave than with the H reflex (Hultborn & Nielsen, 1995).

Comparison of the H and F responses

In contrast to the H reflex, the F response is not elicited by a group Ia volley, and it has therefore been argued that a comparison of the two responses could provide an indirect estimate of changes in presynaptic inhibition of Ia terminals. However, Hultborn & Nielsen (1995) have shown that the comparison of H and F responses may not be valid, for several reasons.

(i) Because re-excitation depends on a somatic spike elicited at a time when the axon is not refractory, a decreased F response may be seen when strong facilitation of motoneurones produces a very short initial segment-soma delay as well as with inhibition (which prevents the somatic spike). In addition, as seen above, because an H reflex discharge protects motoneurones from antidromic invasion, the increased H reflex occurring with

higher motoneuronal excitability would decrease the number of motoneurones that could produce an F response.

(ii) The two responses do not recruit preferentially the same motor units: small units with slow axons for the H reflex (p. 4), but large units with fast axons for the F response (p. 22).

(iii) The methods of activation of the motoneurones in the H reflex and the F response are so different that their sensitivity may be drastically different, even when the changes in motoneurone excitability are evenly distributed across the neuronal membrane. For all these reasons, the F wave provides a flawed measure of the excitability of the motoneurone pool.

Clinical applications

Peripheral neuropathies

F wave studies are sensitive in detecting acquired demyelinating polyneuropathies, where the latency of the F wave may be quite prolonged (see Eisen & Fisher, 1999). In acute demyelinating polyneuropathies, this may be the only conduction abnormality, apart from absence of H reflexes. In chronic demyelinating polyneuropathies, F waves may be absent.

Proximal lesions

F waves provide one of the few well-standardised tests of proximal conduction available for the assessment of motor conduction in nerve root and plexus lesions. A major limitation in the upper limb is that nerve root compression more commonly involves segments other than C8-T1 (innervating intrinsic hand muscles in which F waves can be easily recorded).

Spasticity

An increased mean F wave amplitude is a good reflection of spasticity: the mean F wave amplitude is then above 5% of M_{max} and often above 10% (see Eisen & Fisher, 1999; Chapter 12, pp. 562–3).

Conclusions

F waves are useful in routine clinical studies to assess motor conduction to and from the spinal cord but have a limited role in motor control investigations.

Modulation of the on-going EMG activity

Initial studies

Gassel & Ott (1969, 1970) showed that the time courses of the changes in the monosynaptic reflex and in the on-going averaged rectified EMG of triceps surae produced by a conditioning stimulus were similar.

Underlying principles and basic methodology

Basic methodology

The on-going EMG is full-wave rectified to sum both positive and negative deflections in the raw EMG and then averaged. The background EMG activity is measured, by assessing the EMG in the period preceding the conditioning stimulus (e.g. see Fig. 1.11(*c*)) or immediately following it or by randomly alternating conditioned and unconditioned trials, measuring the background EMG activity in the latter. Short sequences of 50–100 s are recommended to avoid muscle fatigue when using 'strong' contractions of >20% of MVC. The data recorded during 2–4 sequences may then be averaged to produce a single run containing 100–200 conditioned responses. The grand average is expressed as a percentage of the unconditioned baseline EMG. The baseline contraction level can be calibrated by comparing it to the averaged rectified EMG produced by a MVC for ~10 s. The rectified EMG is then plotted against the conditioning stimulus. An excitatory input to motoneurones will produce an increase in the on-going EMG activity (Fig. 1.12(*b*)), and an inhibitory input a suppression (Fig 1.11(*c*)). Note, however, that

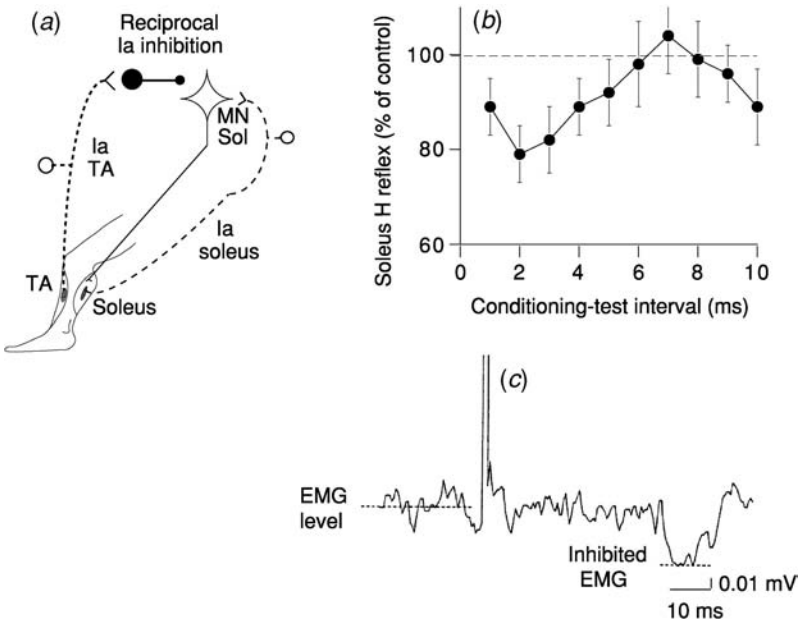

Fig. 1.11. Reciprocal Ia inhibition from ankle flexors to soleus measured by the H reflex technique and stimulus-triggered averaging of the on-going voluntary EMG activity. (*a*) Sketch representing the pathway of disynaptic reciprocal Ia inhibition from tibialis anterior (TA) to soleus (Sol) motoneurones (MN). The conditioning stimulus was applied to the deep peroneal nerve (1.2 × MT) and the subject performed a soleus voluntary contraction 5% of maximum voluntary contraction (MVC). (*b*) Time course of the inhibition of the soleus H reflex (conditioned reflex expressed as a percentage of its control value); the inhibition starts at the 1 ms ISI, is maximal (∼22%) at the 2 ms ISI and lasts only 4 ms. (*c*) Modulation of the rectified on-going soleus EMG. The EMG inhibition (difference between the two dashed horizontal lines) amounts to ∼60% of the background EMG level and lasts ∼15 ms. Adapted from Petersen, Morita & Nielsen (1998), with permission.

suppression may also result from a disfacilitation of motoneurones due to suppression of the excitatory input at a premotoneuronal level. Disfacilitation produces a smaller suppression of the EMG than inhibition of the motoneurones because it is not accompanied by changes in the membrane conductance of the motoneurones, which are the major factor suppressing motoneurone discharge with postsynaptic inhibition (see below).

Other methods

Other methods of treating the raw EMG, such as integrating the averaged unrectified EMG (advantageous when studying a relatively synchronous discharge of the motoneurones, e.g. see Fig. 2.3(*b*)) have been recommended (Poliakov & Miles, 1992).

Recruitment order of motoneurones

In isometric voluntary contractions motoneurones are recruited with increasing contraction force from slow to fast in a similar orderly sequence as in the H reflex (Milner-Brown, Stein & Yemm, 1973; Aimonetti *et al.*, 2000), in accordance with Henneman's 'size principle' (see p. 4).

Estimate of the central delay

The central delay can be deduced from the expected time of arrival of the conditioning volley at the segmental level of the motoneurone pool being tested. The calculations involve measuring the latency of the H reflex in the tested pool and correcting this value for the difference between the afferent conduction times of the conditioning and homonymous Ia

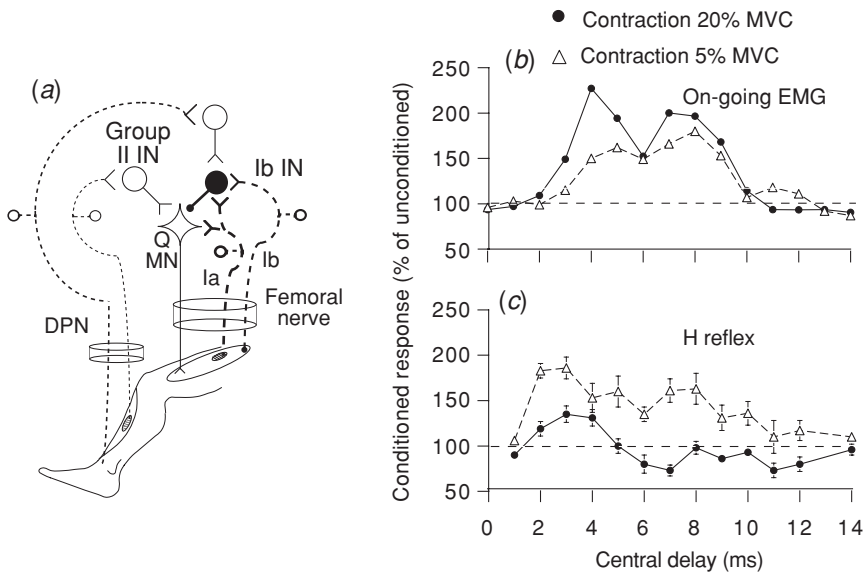

Fig. 1.12. Comparison of the changes in the on-going EMG and the H reflex of the quadriceps, and estimate of the central delay of the changes in the on-going EMG. (*a*) Sketch of the presumed pathways activated by a deep peroneal nerve (DPN) volley: the group II volley from pretibial flexors activates excitatory group II interneurones (IN) facilitating quadriceps (Q) motoneurones (MN), whereas other afferents (possibly joint afferents from the ankle) activate excitatory INs projecting onto Ib inhibitory INs co-activated by Ia and Ib afferents in the test volley. (*b*), (*c*) Results obtained in the same subject during the same experimental session. Effects of DPN stimulation on the on-going EMG activity (*b*) and the H reflex (*c*) of the Q during a weak tonic contraction involving only a few motor units (△) and a relatively strong tonic contraction of Q (20% MVC, ●). The difference in afferent conduction times between the fastest Ia afferents in the DPN and femoral volleys from stimulation sites to the segmental level for Q MNs was 6 ms (see Meunier *et al.*, 1990). (*b*) Changes in the rectified averaged EMG of Q (100 sweeps, 1 kHz sampling rate), normalised to the background level, plotted against the central delay: the latency of the H reflex being 21 ms, the 0 central delay (arrival of the DPN volley at the segmental level of Q MNs) was 27 (21 + 6) ms. Despite the normalisation to the enhanced level of the ongoing control EMG, early and late facilitations of the EMG are greater with the 20% contraction than with the 5% contraction. (*c*) The size of conditioned H reflex is expressed as a percentage of unconditioned reflex and is plotted against the central delay. Each symbol represents the mean of 20 measurements, vertical bars 1 ± SEM. The central delay of zero corresponds to a 6-ms ISI, i.e. when the femoral and DPN volleys would have arrived simultaneously at the Q MN pool. Modified from Marchand-Pauvert *et al.* (2002), with permission.

volleys from the stimulation sites to the spinal cord (see the legend of Fig. 1.12).

Changes in the on-going EMG and in the H reflex need not be identical

Inhibition of the motoneurone pool

The on-going EMG is more sensitive to inhibition than the monosynaptic reflex. For example, during a voluntary contraction of soleus, the peroneal-induced reciprocal Ia inhibition elicits only weak inhibition of the soleus H reflex, but more profound suppression of the on-going EMG of soleus (see Chapter 5, pp. 203–4). The duration of inhibition is also much longer when assessed as the modulation of on-going EMG (15 ms, Fig. 1.11(*c*)) than when using the H reflex (2–3 ms, Fig. 1.11(*b*)). These findings probably reflect a number of factors.

Artefact of normalisation

This is analogous to the apparently greater sensitivity of small H reflexes to inhibition or facilitation when expressed as a percentage of their control value (see p. 16). If only a *small* fraction of the pool is active (e.g. 5% MVC), inhibition (expressed as a percentage of control EMG value) will have a profound effect on the on-going EMG, whereas with the H reflex the same inhibition, which affects only the last-recruited motor units, will suppress a limited part of a test reflex of reasonable size (~15% of M_{max}).

Hyperpolarisation and changes in conductance

Secondly, the hyperpolarisation of motoneurones during the decay phase of the Ia IPSP could be sufficient to prevent the asynchronous firing of motoneurones in the EMG but not their synchronous response to the large monosynaptic Ia EPSP evoking the H reflex. This second explanation is consistent with animal experiments. The monosynaptic reflex is significantly depressed only during the initial phase of the underlying IPSP when the hyperpolarisation is accompanied by changes in the membrane conductance of the motoneurones, and is depressed little during the following decay phase (Araki, Eccles & Ito, 1960).

Further cause of discrepancy

A further factor that could cause a discrepancy between the changes in the H reflex and the on-going EMG is discussed below.

Mechanisms gating the afferent volley of the H reflex

A conditioning volley can affect the mechanisms acting on the afferent volley of the test H reflex (cf. pp. 12–16), and this is a further reason for a discrepancy between changes in the H reflex and the on-going EMG. An example of such a discrepancy is illustrated in Fig. 1.12, which compares the modulation by a peroneal volley of the on-going EMG activity (*b*) and of the H reflex (*c*) of the quadriceps. During weak tonic contraction of quadriceps, the H reflex and the on-going voluntary EMG underwent qualitatively similar biphasic facilitations, with early non-monosynaptic group I and subsequent group II excitations (see Chapter 7, pp. 293–7). In this instance, the effects obtained with the two methods were similar. In contrast, the changes in the H reflex and in the on-going voluntary EMG were different during stronger voluntary contractions of ~20% MVC. The reflex facilitation was replaced by inhibition at central delays of 6–12 ms, while the on-going EMG was facilitated more than with the weak contraction. The discrepancy between the EMG and H reflex modulations during the strong voluntary contractions suggests the existence of an inhibitory mechanism gating the afferent volley of the test reflex. As discussed on pp. 14–15, this is due to potentiation by the peroneal volley of oligosynaptic inhibition produced by group I afferents in the test volley for the H reflex. More generally, this illustrates that, while the results obtained with the two methods depend on motoneurone excitability, the H reflex also depends on factors that can alter the efficacy of the group I afferent volley in firing motoneurones. In this respect, changes in presynaptic inhibition of Ia terminals have been inferred from discrepancies between changes in the H reflex amplitude and in the on-going EMG recorded in the same muscle during various motor tasks (see Chapter 8, p. 340).

Critique: limitations, advantages and conclusions

Advantages

Ease and rapidity of the experiment

Gassel and Ott (1969, 1970) pointed out that the method allows one to obtain the full time course of the changes in motoneuronal excitability much more easily and rapidly than when using the monosynaptic reflex. This is a distinct advantage when investigating patients.

Absence of test stimulation

It is often difficult to ensure that the stimulus for the H reflex remains constant when overt movement occurs (such as in phasic contractions, cycling or gait). In addition, the gain of the input-output relationship on which the H reflex is operating (see pp. 18–20) may change as a function of the recruitment level during a motor task and at the same recruitment level in different tasks (see Capaday, 1997). Modulation of the on-going EMG has the merit of avoiding such limitations.

Comparison of the modulation of the on-going EMG obtained in different situations

It is possible with this method to compare easily the effects of conditioning stimuli on the on-going EMG recorded during various motor tasks, at an equivalent level of EMG activity. Thus, for example, it has been possible to compare: (i) cutaneomuscular responses in hand muscles during precision and grip tasks (Chapter 9, pp. 427–8), (ii) reciprocal Ia inhibition of ankle muscles during voluntary contraction and gait (Chapter 5, pp. 227–9), (iii) heteronymous recurrent inhibition of ankle muscles during voluntary contraction and postural adjustments (Chapter 4, pp. 183–4), and (iv) peroneal-induced group II excitation to quadriceps during voluntary contraction and gait (Chapter 7, pp. 318–19).

Limitations

Active motoneurone pool

The most obvious limitation of the method is that it can only be used in an active motoneurone pool. The method does not allow changes in transmission in neural pathways to be studied when moving from rest to activity.

Temporal resolution

The temporal resolution of the method is limited because of the different conduction velocities for individual motor units and the duration of their EMG potentials. It is therefore not possible with this method to estimate with precision the central delay of an effect evoked by conditioning stimulation. In addition, it is likely that the latency of onset of inhibition is overestimated when measured to the onset of the decrease in rectified EMG because the averaged rectified EMG trace cannot decrease until the end of the motor unit EMG potential.

Initial facilitation and subsequent suppression

Initial facilitation is obligatorily followed by a suppression, that results from the post-spike afterhyperpolarisation (AHP) and recurrent inhibition of the motoneurones. Accordingly, when there is an initial facilitation (due, e.g. to monosynaptic Ia excitation), differences in later events observed between two motor tasks may be difficult to interpret unless the initial facilitation is not modified.

Type of motoneurones involved

Surface EMG studies cannot reveal whether the different motoneurones in the pool respond uniformly to the stimulus, i.e. whether high-threshold motoneurones respond differently to low-threshold motoneurones.

Conclusions

Modulation of rectified on-going EMG activity recorded with surface electrodes has the great advantage of simplicity. This method gives a general overview of the response to a stimulus, but it is usually not a quantitative measure of motoneurone activity and its temporal resolution is weak.

Post-stimulus time histograms (PSTHs) of the discharge of single motor units

Changes evoked by a conditioning stimulus in a motoneurone pool depend on the distribution of

conditioning effects within the pool (see pp. 18–20). Such 'pool problems' are not an issue when studying the responses of single motor units. The ability to record post-stimulus histograms (PSTHs) of the discharge of single motor units represented a major breakthrough in motor control investigations in human subjects (for review, see Awiszus, 1997). Indeed, when a motoneurone is activated voluntarily, the effect of a particular input can be determined by constructing a histogram of the occurrence of motoneurone discharges following repeated presentation of a suitable stimulus. Pioneering studies were performed by Stephens, Usherwood & Garnett (1976), who pointed out that 'this procedure extracts from the naturally occurring spike train only those changes in firing time-locked to the stimulus'.

Underlying principles

Extraction of the changes in firing probability time-locked to the stimulus

The method does not assess the amplitude of a post-synaptic potential (PSP) in a motoneurone, but the resulting changes in its probability of discharge. The principles are presented in the sketch of Fig. 1.13, which shows the construction of the PSTH (bottom row) based on the time of occurrence of motor units potentials in a voluntarily activated motoneurone with the repeated presentation of a stimulus. When a motoneurone is activated voluntarily (first row), motor unit EMG potentials are recorded (second row) and converted into standard trigger pulses by a variable window discriminator (third row). Stimuli are delivered to produce an EPSP in the motoneurone, insufficient to cause the motoneurone to discharge in response to every stimulus, and a computer measures the latency of the trigger pulses following each stimulus. When the stimulus-induced EPSP does not reach discharge threshold for the motoneurone, the first spike to occur after the stimulus will be due to the motoneurone's background discharge, i.e. the 'spontaneous' spike in Fig. 1.13 (thin dashed lines in the first two rows of the figure). Its latency is unaffected by the stimulus. 'Spontaneous' spikes occur randomly with respect to the stimulus and, after many stimuli are delivered, the PSTH will be flat. However, if the EPSP produces a motoneurone discharge, a spike will occur after the stimulus at a latency determined by the latency of the EPSP (thick continuous lines of the first two rows of Fig. 1.13). With repetition, there will be an increased number of motoneurone discharges at that particular latency, creating a peak in the PSTH due to the increased probability of motoneurone discharge in response to the EPSP (bottom row). If the conditioning stimulus elicits an IPSP in the motoneurone, there will be a trough in the PSTH at the corresponding latency (Ashby & Labelle, 1977).

Different models

A number of different models have been proposed for estimating the size of PSPs underlying the changes in firing probability of a repetitively activated motor unit (for review, see Miles, 1997). Most of these models are theoretical and lack the synaptic noise which is particularly important in determining the discharge of spikes (Matthews, 1996). Kirkwood & Sears (1978, 1982) observed that the relationship between the shape of the primary peak in the PSTH and 'the common excitation potential' could be described as the sum of two linear terms, one being proportional to the EPSP and the second to its first derivative. Their conclusion was tested directly by Gustafsson & McCrea (1984). They confirmed that the shape of the PSTH for EPSPs and IPSPs is a combination of the PSP itself and of its first derivative, the influence of the derivative being less when the PSP is small with respect to the synaptic noise.

Basic methodology

Different authorities have adopted different methodologies for generating PSTHs, and the discussion below focuses on one of these (Fournier *et al.*, 1986), but with some reference to other techniques.

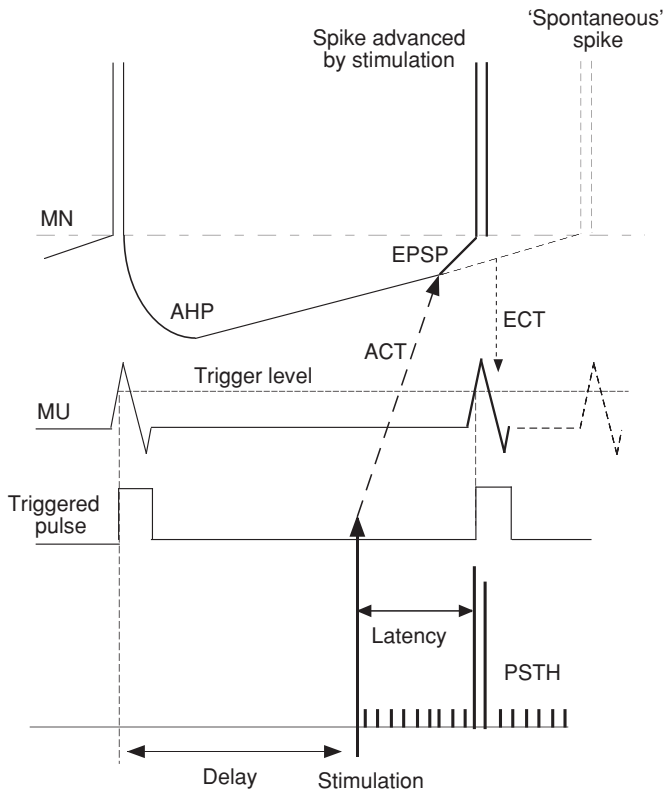

Fig. 1.13. The experimental design used in constructing PSTHs for single motor units. First row: consecutive spikes in the MN, with the post-spike afterhyperpolarisation (AHP) following the first spike and the firing level (dashed horizontal line). Second row: corresponding motor unit (MU) potentials. Third row: conversion of the MU potentials into trigger pulses by a discriminator with variable trigger level. The vertical thick arrow indicates the timing of stimulation, delivered with a fixed delay after the previous MU discharge. The latencies of MU potentials following stimulation are measured, and a histogram of these latencies is constructed (fourth row). The dashed spike and MU potential represent when the discharge due to the 'spontaneous firing' of the MN would have occurred. After an afferent conduction time (ACT, dashed oblique upward arrow) and a central delay, the stimulus produces an EPSP that advances the MN spike and the corresponding MU potential (thick continuous lines). The efferent conduction time (ECT) is represented by the dotted vertical downward arrow. Adapted from Fournier *et al.* (1986), with permission.

Recording

How to isolate one motor unit?

It is necessary to record reliably from a single motor unit that is voluntarily activated. To record from single motor units does not necessarily require needle electrodes. With the help of visual and auditory feedback, carefully placed surface electrodes and some training, most subjects can isolate a single unit by controlling a liminal contraction so that the motor unit action potential is the only one visible on the screen or is of greatest size. When there are several active units, it may be possible to isolate one of them with a window discriminator with variable upper and lower levels. Of necessity, the units so isolated are of low threshold, recruited at levels of force below 5% MVC, and presumably represent small motoneurones with slowly conducting axons.

A significant technical advance has been the use of differential surface electrodes (DE-2.3, Delsys Inc., Boston, USA), with which it is possible to isolate units during contractions as strong as 20% of MVC (Marchand-Pauvert *et al.*, 2002). However, recordings from high-threshold units still require the use of needle electrodes or intramuscular wires. Sophisticated template-matching paradigms now allow the automatic identification of a number of different motor units in the same recording sequence (e.g. see LeFever & De Luca, 1982; Miles, Le & Türker, 1989).

How to be sure that the results originate from the same unit?

The EMG potentials of different motor units may differ only slightly in shape and size. A simple procedure allows one to ensure that potentials recorded during the same session originate from the same unit (Fournier *et al.*, 1986). A conditioning stimulus is delivered, triggered by the motor unit potential but with a zero delay. The afferent volley will arrive at the motoneurone when it is still refractory due to the AHP, and this will prevent the conditioning EPSP from firing the motoneurone. If these stimuli cause a peak in the histogram, the data in the PSTH are from more than one motor unit or are contaminated by another unit.

Stability of the frequency of firing of the unit

Because the size of the peak (or trough) recorded in the PSTH to a constant conditioning stimulus varies with the motoneurone's discharge rate (see below), it is essential that the discharge remains as stable as possible, between 5 and 10 Hz in different muscles. It is important that there is stable background firing in the absence of stimulation, because irregularities in the background firing can produce the appearance of false peaks (or troughs) in the final PSTH (see p. 35).

Characterisation of the recorded units

The threshold and size of motor units may be inferred from the force at their recruitment, the macro-potential area of the EMG potential and the twitch contraction time (see Milner-Brown, Stein & Yemm, 1973; Aimonetti *et al.*, 2000).

Recordings from pairs of motor units

When comparing results obtained for low-threshold (slow) units and high-threshold (fast) units, it may be difficult to be certain whether different results are due to a difference in the inputs to these units or to the fact that high-threshold fast units require a stronger descending excitatory (and peripheral) drive. This can be tested by recording simultaneously with needle electrodes from pairs of units (one low-threshold, the other high-threshold), in which case there will be, of necessity, the same descending excitatory and peripheral drives (Aimonetti *et al.*, 2000).

Stimulation

Stimuli delivered randomly

Stimuli may be delivered randomly with respect to the motoneurone discharge (Stephens, Usherwood & Garnett, 1976; Ashby & Zilm, 1982b). The size of the peak elicited by a given EPSP then decreases when the frequency of firing increases (Ashby & Zilm, 1982a), because the higher the frequency, the higher the probability of the EPSP occurring during the AHP following a previous discharge. This simple method requires a longer recording because the EPSP will often reach the motoneurone during the AHP following a discharge and be unable to make the motoneurone discharge again. The more efficient alternative is to avoid the AHP by triggering the stimulator from the motor unit potential (see below). However, there is an advantage in delivering the stimuli randomly: if more than one motor unit can be discriminated reliably in the recording, it is possible to construct PSTHs off-line for each unit for the same recording sequence. This allows a more valid comparison of the responses of different units.

Stimulation may be triggered by the discharge of the single motor unit (Fournier et al., 1986; Fig. 1.13)

Each stimulus is then triggered at a fixed delay after the preceding motor unit action potential, but with the overall stimulus repetition rate limited to 2–3 Hz. This technique has advantages under two different conditions. (i) Stimuli can be delivered so that the peak of excitation occurs towards the end of the AHP following the previous motoneurone discharge, when the probability that the EPSP can make the motoneurone discharge is highest. (ii) Conversely the AHP can be used to attenuate the monosynaptic discharge of the motor unit. The monosynaptic discharge of a motoneurone is followed by a depression due to the AHP, and this will obscure later EPSPs or IPSPs. Preventing the monosynaptic discharge of the motoneurone could allow these late synaptic effects to become apparent. This can be done by delivering the stimulus at an appropriately short delay following the previous discharge. The delay is chosen so that the AHP reduces the probability of firing due to the monosynaptic EPSP, but not the effects of the late synaptic events which occur later on the recovery from the AHP. With this method of discharge-triggered stimulation, the size of the peak elicited by a given EPSP increases with the frequency of firing: the higher the frequency the lower the possibility of the EPSP occurring during the critical period of the AHP (see Katz, Meunier & Pierrot-Deseilligny, 1988). Note, however, that, while the technique may prevent discharge due to the monosynaptic input, the late events will be distorted in amplitude by the subliminal excitation produced by that input. When the stimulus is triggered by the preceding motor unit discharge, it is essential that there be counts in bins preceding the increased probability of discharge. Otherwise the AHP could be obscuring the onset of the peak. This is important because the initial 0.5–1.0 ms of the peak represents the only unequivocally monosynaptic component of the group I peak (cf. p. 34). A disadvantage of triggering the stimulus from the motor unit discharge is that, of necessity, only that one motoneurone can be studied in the recording sequence, even when more than one motor unit is active.

Intensity of the stimulation

The intensity of stimulation should be below threshold for a compound response (be it the H reflex, polysynaptic response or motor evoked potential) because, if not, small motor unit potentials might exceed the trigger level when superimposed on the compound response. This would cause a peak in the PSTH at the appropriate latency even when there was no effect on the discharge probability of the unit being studied.

Assessment of the timing of the changes in firing probability

Recording window

A computer cannot distinguish between counts due to the unit (i.e. those that must be analysed) and those due to stimulus artefact and/or the compound M wave. It is convenient to delay the beginning of the recording until such activity has subsided.

Estimation of the latency of a change in discharge probability

Within the recording, analysis is focused on the region of expected and/or visually identifiable peaks and troughs in the histogram. Consecutive bins with an increase (or a decrease) in firing probability are grouped together and tested with a χ^2 test to determine whether the firing probability after stimulation within the group differs from that in the control situation. A peak of excitation (or a trough of suppression) is accepted if there is a significant increase (or decrease) in firing probability in a group of adjacent bins. The latency of the first bin of the change in firing probability is taken to be the latency of the effect, but must be corrected for the trigger delay on the motor unit action potential. The trigger pulse that is fed into the computer is generated on the rapidly

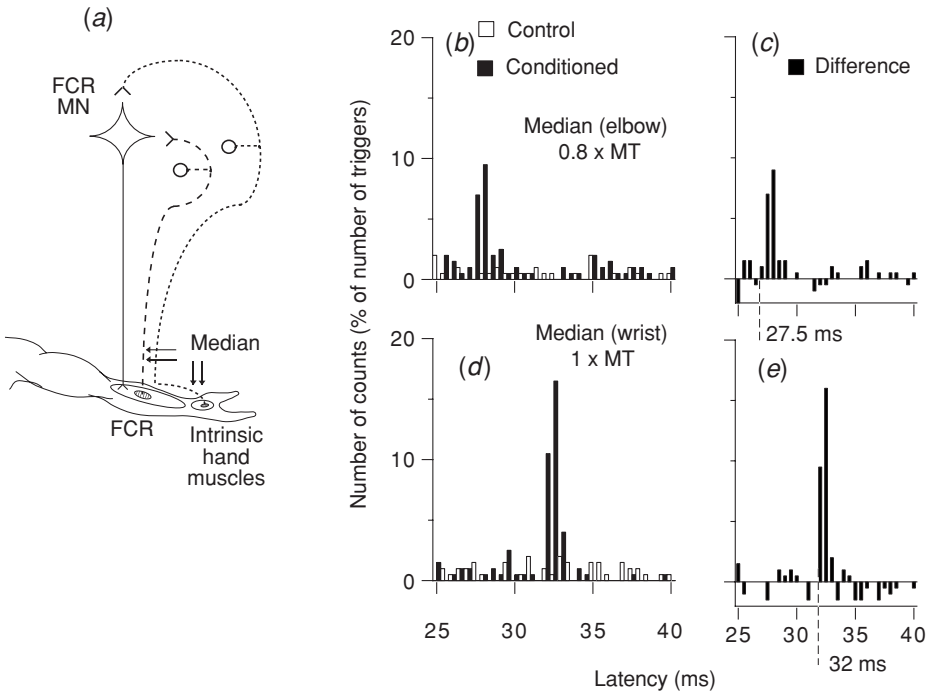

Fig. 1.14. Changes in firing probability of a FCR motor unit after stimulation of the homonymous and heteronymous group I afferents. (*a*) Sketch of the presumed pathways: a flexor carpi radialis (FCR) motoneurone (MN) receives monosynaptic excitation from homonymous (dashed line) and heteronymous (dotted line) Ia afferents, the latter from intrinsic hand muscles innervated by the median nerve. (*b*)–(*e*) PSTHs (0.5 ms bin width) after stimulation of homonymous Ia afferents in the median nerve at elbow level (0.8 × MT (*b*), (*c*)), and of the median nerve at wrist level just below 1 × MT ((*d*), (*e*)). The number of counts (expressed as a percentage of triggers) is plotted against the latency after stimulation. □ and ■ in (*b*) and (*d*) show the control and conditioned histograms, respectively, and columns in (*c*) and (*e*) the difference between them. Vertical dashed lines in (*c*) and (*e*) indicate the latency of the early homonymous (27.5 ms (*c*)) and heteronymous (32 ms (*e*)) peaks, respectively. Distance between wrist and elbow electrodes: 0.30 m. Conduction velocity in the fastest Ia afferents in the median nerve: 69 m s^{-1}. The difference in latencies of heteronymous and homonymous peaks (32–27.5 = 4.5 ms) is explicable by the difference in afferent conduction times (0.30/69 = 4.35 ms). Adapted from Marchand-Pauvert, Nicolas & Pierrot-Deseilligny (2000), with permission.

rising phase of the EMG potential, a few milliseconds after its onset, and this delay must be subtracted from the latency of the peak (or trough) in the PSTH (see Fig. 2.2(*c*), (*d*)). However, when comparing the effects of different conditioning stimuli, the trigger delay will be the same for all changes in firing probability of any one motor unit, provided that the recordings come from the same sequence. The trigger delay does not affect the difference in latencies in two PSTHs, and this is the critical measurement in such experiments (e.g. Fig. 1.14). The time resolution of the method depends only on the bin width. However, the narrower the bin width, the greater the number of stimuli necessary to produce a significant increase in each bin of the peak.

CUSUM

Ellaway (1978) devised a procedure (cumulative sum or CUSUM) to enhance the detection of small

changes in firing probability. The first step in constructing a CUSUM involves estimating the mean count in the bins of a control histogram (or the mean count in the pre-stimulus bins). The mean value is then subtracted from the counts in each bin of the entire PSTH. The residual counts in each bin are then summed sequentially (bin 1, then bins 1 + 2, then bins 1 + 2 + 3, etc. . . .) and plotted against time after the stimulus. The resulting function is an integral with respect to time. Normalisation of the counts in the PSTH as counts/stimulus/bin results in a measure with units of impulses/stimulus/s. Given that the CUSUM is the time integral of the PSTH, its units are then impulses/stimulus. The onset of a period of increased (or decreased) firing probability is indicated in the CUSUM by the onset of a positive (or negative) slope, and this allows a more confident estimate of latency than could reasonably be achieved using the raw histogram which inevitably contains irregular bin-to-bin fluctuations. In the CUSUM, the duration of an excitatory event is given by the duration of the increasing phase of the CUSUM. If the discharge then falls below control levels, the CUSUM begins to fall, but if it does not, the CUSUM remains at the higher level (as one would expect with a true integral).

Estimating the central delay of an effect

The latency of a peak (or trough) in the PSTH is the sum of the afferent and efferent conduction times plus the central delay of the pathway. To estimate the latter, it is convenient to record another PSTH for the same unit for homonymous monosynaptic Ia excitation, and to compare the latencies. Since it is the same unit, the trigger delay and the efferent conduction time are the same. The afferent conduction times for the homonymous Ia and the relevant afferent volleys may be estimated from the conduction velocities of the fibres (e.g. Fig 1.16) and the distance from stimulation sites to the spinal cord (cf. Chapter 2, pp. 70–3). From these calculations it is possible to compare the central delay of the tested effect to that of homonymous monosynaptic Ia excitation.

Changes in the mono- and non-monosynaptic components of the Ia peak

As discussed above (pp. 14–16), oligosynaptic pathways activated by the test volley can limit the extent of group I excitation. Only those changes affecting the entire excitatory peak and, in particular, the initial 0.5–1.0 ms have affected the monosynaptic pathway (cf. p. 16). This can only be ensured in experiments using PSTHs from single motor units because the temporal resolution of compound EMG responses is limited (see p. 28). To be certain that the first bins are capturing the true onset of monosynaptic excitation it is necessary that there are counts in earlier bins (see p. 32).

Assessment of the size and significance of the peaks and troughs in the PSTH

When stimulation is delivered randomly with respect to the firing of the unit

The background firing is then calculated during the period immediately preceding the stimulus. Using 1 ms bins, Mao *et al.* (1984) accepted a period of increased (or decreased) firing probability if the firing probability in 3 or more adjacent bins was above (or below) the mean background firing plus 2 SD.

When stimulation is triggered by the previous discharge

The probability of firing then depends on the AHP following the previous discharge. In the control situation, there is a progressive increase in the probability of discharge with increasing time intervals as the AHP subsides. To take such changes in firing probability into account, a control histogram of firing probability is constructed without stimulation. The control and conditioned situations (□ and ■, respectively, in Figs. 1.14(*b*), (*d*) and 1.15(*b*)) are randomly alternated in the same sequence and the control count is subtracted from the conditioned count for each bin in the PSTH (Figs. 1.14(*c*), (*e*) and 1.15(*c*)). A χ^2 test is used within different time-interval windows

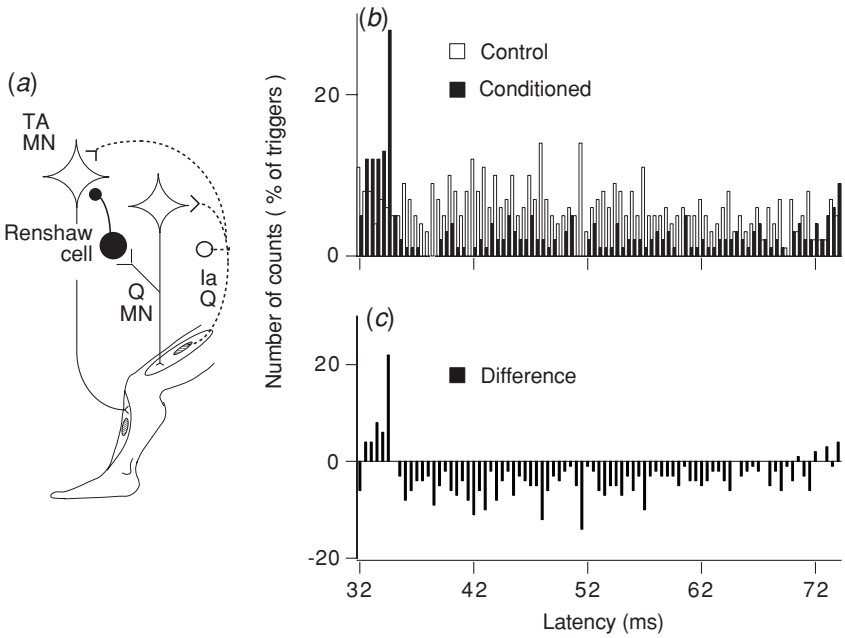

Fig. 1.15. Heteronymous Ia facilitation and recurrent inhibition from quadriceps to tibialis anterior. (*a*) Sketch of the presumed pathway: heteronymous Ia afferents from quadriceps (Q) produce monosynaptic excitation of a tibialis anterior (TA) motoneurone (MN), and recurrent collaterals from Q motor axons inhibit the TA MN through Renshaw cells. (*b*), (*c*) PSTHs (1 ms bin width, number of counts as a percentage of number of triggers) for a TA unit. (*b*) Control (□) and conditioned (■) histograms. (*c*) Difference between conditioned and control histograms. Femoral nerve stimulation that produced an H reflex in the quadriceps (20% of M_{max}) also produced an early peak of excitation in the TA motor unit, at a latency consistent with monosynaptic Ia excitation, followed by short-latency long-lasting recurrent inhibition. Adapted from Meunier *et al.* (1990), with permission.

to determine the extent to which the distribution of firing probability after stimulation differs from that in the control situation. A peak of excitation (or a trough of suppression) is accepted as genuine if there is a significant increase (or decrease) in firing probability in a group of adjacent bins. Sequences in which irregularities in the *control* sequence contribute significantly to the difference between the two situations are not retained for further analysis. As discussed earlier, bin-to-bin variability in the control PSTH is commonly due to failure to maintain a steady background discharge rate. Figure 1.14(*b*), (*c*) shows the large homonymous monosynaptic Ia peak evoked in a FCR unit by stimulation of the median nerve at the elbow. Stimulation of afferents in the median nerve at the wrist from intrinsic muscles of the hand elicited a peak at a longer latency ((*d*), (*e*)), and this difference in latency was explicable by the difference in the afferent conduction times for the homonymous and heteronymous Ia volleys (see the legend of Fig. 1.14). Figure 1.15 shows that the PSTH can also effectively demonstrate inhibition: in this case, recurrent inhibition from quadriceps to tibialis anterior.

Normalisation of the results

It is convenient to express the number of counts in each bin as a percentage of the number of triggers. Although the relationship between the amplitude of a peak (or a trough) in the PSTH and that of the underlying PSP is complex (see p. 29), the larger the

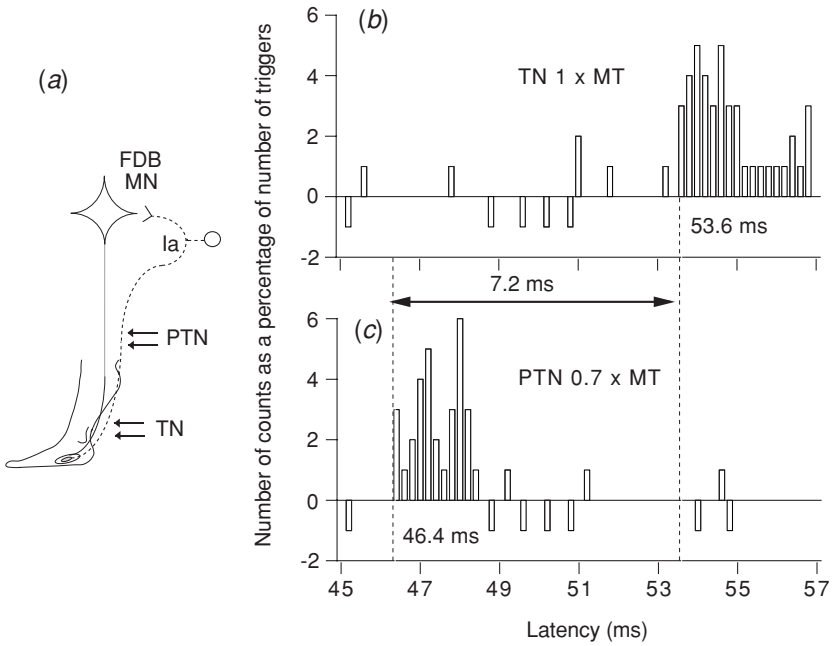

Fig. 1.16. Conduction velocity of tibial Ia afferents between the ankle and knee. (*a*) Sketch of the experimental paradigm: Ia afferents, with monosynaptic excitatory projections on homonymous motoneurones (MN), from intrinsic plantar muscles (flexor digitorum brevis, FDB) are stimulated at the ankle and knee. (*b*), (*c*) PSTHs (after subtraction of the background firing, 0.2 ms bin width) for a FDB unit are shown after stimulation of the tibial nerve (TN) at ankle level (1 × MT (*b*)) and of the posterior tibial nerve (PTN) at knee level (0.7 × MT (*c*)). The difference between the latencies was 7.2 (53.6–46.4) ms, and the distance between the electrodes 42 cm. This gives a conduction velocity (CV) of 58 m s^{-1} (0.42/0.0072). Modified from Marque *et al.* (2001), with permission.

PSP the higher the peak or the deeper the trough. Thus, the absolute size of the peak (or trough) can be estimated as the sum of the differences (conditioned *minus* control counts) in the different consecutive bins with increased (or decreased) firing probability contributing to a given peak or trough.

Assessment of the conduction velocity of Ia afferents

The PSTH method may also be used to calculate the conduction velocity of Ia afferents. The calculations involve measuring the latency of the monosynaptic Ia peaks measured in PSTHs for the same unit after stimulation of homonymous Ia fibres at two different sites (Chapter 2, p. 72), and dividing the distance between the two stimulation sites by the difference in the latencies (see Fig. 1.16).

Critique: limitations, advantages and conclusions

Limitations

Voluntary activation

The most obvious limitation of the method is that, like the modulation of the on-going EMG, PSTHs can be constructed only for an active motoneurone pool. Some subjects find it difficult to maintain the discharge of a specific motor unit in isolation, and when more activity develops there is a risk of spurious

counts not due to the original unit. Needle electrodes can allow better unit isolation but are inherently unstable, and less suited for the multiple recordings needed to characterise a response fully. Hook-wire electrodes allow selectivity and stability, but cannot be moved easily to record from different motor units in a different site in the muscle.

Afterhyperpolarisation

When Ia or corticospinal volleys produce a clear peak in the PSTH, the following AHP can suppress firing and obscure weaker effects of longer latency. Weak late effects may then be demonstrated (i) by decreasing the stimulus intensity (though this could reduce the size of the late effects), and (ii) by using the AHP to suppress the early peak. This would involve triggering the stimulus earlier after the previous spike so that the early peak falls within the AHP, but not so early that the late activity was also obscured (see p. 32).

Multiple peaks (or troughs)

The rising phase of the EPSP synchronises spikes at a fixed interval after the stimulus and generates secondary and tertiary peaks and troughs in the PSTH reflecting the auto-correlation function of the motoneurone discharge. These 'synchronisation-related errors' occur with time lags of the same order as the spontaneous mean inter-spike interval (Türker & Powers, 1999, 2003). Thus, the double peaks which occur in the PSTH at shorter intervals may be safely attributed to double EPSPs, e.g. the two peaks in Fig. 1.18(*f*) are probably due to corticospinal D and I waves evoked by transcranial electrical stimulation of the motor cortex (see p. 42).

Conclusions

The PSTH is a powerful technique that allows single motoneurones to be investigated in human subjects with good time resolution. It can be applied in virtually all muscles and, if needle or wire electrodes are used, high-threshold and low-threshold units can be studied. It is an indispensable complement to H reflex experiments to overcome various 'pool problems', to detect oligosynaptic limitation of the reflex by the test volley or to ensure a change in presynaptic inhibition of Ia terminals. The only important limitations are that it requires selective voluntary contraction involving only one detectable unit, and this unit may not be representative of the motoneurone pool. It is also impossible to document the changes in transmission produced by voluntary effort. For this reason the unitary H reflex described by Shindo *et al.* (1994) is important (see below).

Unitary H reflex

Underlying principles and basic methodology

Underlying principles

By carefully controlling the stimulus it is possible to study the H reflex of single motor units. An ingenious (but demanding) method has been described by Shindo *et al.* (1994), utilising essentially the same principles as those used for threshold tracking of the compound H reflex (cf. p. 11), but doing so for a single motor unit and estimating the size of the test Ia EPSP necessary to reach firing threshold for that unit.

Recording

The EMG potential of a single motor unit discharging in the H reflex is recorded with a needle electrode. This constitutes a 'unitary' H reflex, a single soleus motor unit potential contributing to the compound soleus H reflex.

Stimulation

The posterior tibial nerve is stimulated to produce an H reflex. The excitability of a single motoneurone is assessed as the stimulus intensity that activates the unit at rest with a 50% probability, referred to as the 'critical firing stimulus' (CFS). This stimulus intensity

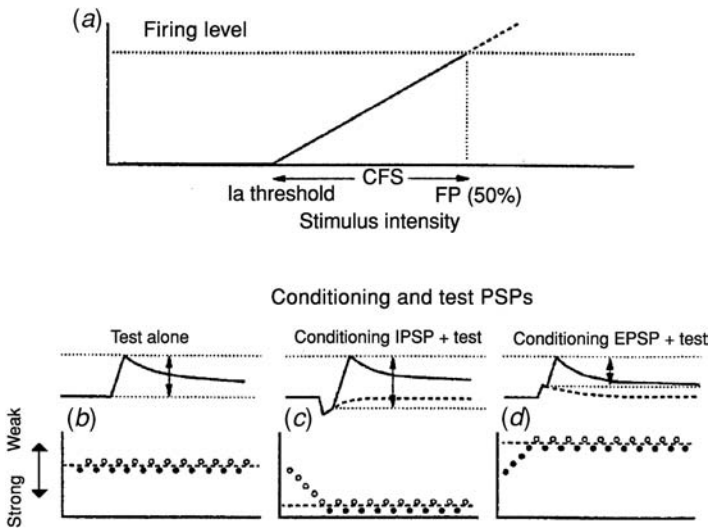

Fig. 1.17. The principle of the CFS method (unitary H reflex). (*a*) The size of the test EPSP increases almost linearly with the increase in stimulus intensity. The 'CFS' is the difference between the Ia threshold (measured as the weakest stimulus to produce a Ia peak in the PSTH of the voluntarily activated unit) and the stimulus necessary at rest to discharge the motoneurone in the H reflex with a firing probability of 50% ($FP_{50\%}$). (*b*)–(*d*) The size of the test Ia EPSP (top) and the resulting changes in the sequence of stimulation to reach $FP_{50\%}$ (bottom) in the control condition (*b*) in the presence of a conditioning IPSP (*c*) and a conditioning EPSP (*d*). The sizes of the test EPSPs (double-headed arrows in the top row of sketches in (*b*)–(*d*)) correspond to the CFS. Conditioning inhibition and facilitation are shown as increases and decreases in the CFS, respectively. Presence (●) and absence (❍) of discharge of the motor unit are shown in the bottom row. (*b*) In the control situation, the firing probability is 50%. (*c*) When there is a conditioning IPSP, the motor unit does not discharge (❍) until stimulus intensity is increased (downward) to reach $FP_{50\%}$. (*d*) When there is a conditioning EPSP, the motor unit discharges (●) and stimulus intensity has to be decreased (upward) to reach $FP_{50\%}$. Adapted from Shindo *et al.* (1994), with permission.

is expressed relative to the threshold intensity for the group Ia EPSP, which is estimated by measuring the threshold for the homonymous peak in PSTHs of the same unit when voluntarily activated. It is assumed that the latter threshold represents the threshold for the test EPSP in the motoneurone under study. At rest, the test stimulus intensity is determined automatically by computer. Repeated automatic adjustments of the test stimuli make the firing probability of the unit converge to 50% ($FP_{50\%}$) (❍ and ● showing the absence and the presence of firing of the unit, respectively, in the bottom rows of Fig. 1.17(*b*)–(*d*)). The stimulus intensity is increased if the unit fails to discharge in response to the preceding stimulus (❍ in *C*), and decreased if the unit does discharge (● in *D*).

Significance of changes in CFS produced by conditioning stimuli

Figure 1.17(*a*) shows diagrammatically the relationship between the intensity of the test stimulus and EPSP size within a single motoneurone. The Ia threshold indicates the weakest stimulus intensity that affects the discharge probability of the voluntarily activated motoneurone. The intensity that produces $FP_{50\%}$ corresponds to the weakest stimulus intensity that causes the motor unit to discharge with a 50% probability when at rest, and the difference between these intensities is the CFS, an indirect measure of the size of the test Ia EPSP necessary to make the motoneurone discharge when at rest. When conditioning stimuli hyperpolarise or

depolarise the motoneurone, there are appropriate changes in the CFS (double-headed arrows in the sketches in the top rows of Fig. 1.17(*b*)–(*d*)). The CFS for a motor unit should therefore be a function of the test Ia EPSP in the corresponding motoneurone, measured as the voltage excursion between the resting membrane potential and the firing threshold of the motoneurone. The relationship between the CFS and the size of the test EPSP is approximately linear, and the size of the CFS can be used as a measure of the size of the average test Ia EPSP. When conditioning stimuli produce an IPSP, the resulting hyperpolarisation prevents the unit from firing (○ in Fig. 1.17(*c*)). A stronger stimulus intensity is then required to produce an EPSP sufficiently large for the motoneurone to fire with a probability of 50%. Conversely, when conditioning stimuli produce depolarisation, the sum of the conditioning and test EPSPs causes the unit to fire with a probability greater than 50% (● in (*d*)), and the stimulus intensity must be reduced to produce the smaller test EPSP required to reach the $FP_{50\%}$ (Fig. 1.17(*d*)). The technique was validated by the demonstration that the sensitivity to femoral-induced heteronymous Ia facilitation was the same for the unitary and the compound soleus H reflexes.

Critique: limitations, advantages and conclusions

Advantages

(i) Conditioning effects may be explored avoiding any 'pool problems' (see pp. 16–20), and may be compared at rest and during contraction. (ii) As with the H reflex, and unlike the PSTH, varying the conditioning-test interval allows the full time course of an effect to be investigated without the risk that weak effects at long latency are obscured by the AHP or by recurrent inhibition elicited by a large conditioning monosynaptic discharge (Ia or corticospinal in origin) (see p. 37).

Limitations

(i) A single motor unit must be held for a long time using a needle electrode – first for a number of PSTHs (to document the threshold for the Ia EPSP) and then during the experimental studies.
(ii) The method can be applied only in muscles in which an H reflex is recordable at rest.
(iii) Only motor units of relatively low threshold can be studied.

Stimulation of the motor cortex

The development of techniques to stimulate the motor cortex through the intact scalp and skull allows studies of corticospinal function in intact co-operative human subjects, and has led to new diagnostic procedures and considerable advances in motor control physiology. Most of the pioneer work was undertaken by Marsden, Rothwell and colleagues, and this section is largely based on a comprehensive review by Rothwell (1997).

EMG responses evoked by cortical stimulation

Motor evoked potentials (MEPs) evoked by transcranial stimulation

These are recorded by surface electrodes over the corresponding muscle belly as is done for reflex studies. MEPs may be recorded at rest. However, as for the H reflex, a weak voluntary contraction raises the active motoneurone pool to firing threshold, thereby potentiating the response and helping to focus the MEP on the target muscle. In addition, the appropriate cortical circuits are facilitated by the voluntary activity, and this is particularly relevant when using magnetic stimulation, which activates the corticospinal system trans-synaptically (see below).

Surface electrodes are not selective

Surface electrodes can record EMG potentials generated at a distance. The detection of cross-talk is particularly important in the context of motor cortex stimulation, because: (i) the stimulus is not focal; (ii) even if it were, the response rarely involves a single

muscle; (iii) the effect observed following stimulation at a given site over the motor cortex depends on the existing level of background activity and can be reversed by switching voluntary activity from agonists to antagonists; (iv) reorganisation of the motor cortex may occur after neurological lesions. Crosstalk may be recognised by muscle palpation (except with near-threshold stimuli), and by the fact that the frequency content of EMG activity generated at a distance is narrower, the power spectrum being shifted to lower frequencies (see Capaday, 1997).

PSTHs

PSTHs of single motor units may be constructed after cortical stimulation. The intensity of the stimulation should then be set so that during voluntary activation of a unit cortical stimulation only changes its firing probability (i.e. the unit does not contribute to a compound MEP, or can be reliably recorded in isolation, usually with a needle electrode).

Mono- and non-monosynaptic transmission of corticospinal excitation

The sharp increase and short duration of the early peak in the PSTH of single units and its short latency (see Fig. 1.18(*f*)) strongly suggest that the onset of the excitation involves monosynaptic transmission, as might be expected from studies in higher primates. However there is considerable evidence (see Chapter 10) that, in human subjects, a significant component of the corticospinal excitation of upper limb motoneurones is relayed through propriospinal interneurones rostral to the motoneurone pool.

Electrical stimulation

The impetus for transcranial stimulation came from the studies of Merton and Morton (1980). They used a single high-voltage transcranial capacitive discharge and showed that stimulation over the motor cortex could produce a twitch of contralateral limb muscles.

Methodology

Anodal transcranial stimulation has a lower threshold than cathodal stimulation (Rothwell *et al.*, 1987; Burke, Hicks & Stephen, 1990). Merton and Morton used a bipolar electrode arrangement. For activation of hand muscles, the anode was placed 7 cm lateral to the vertex and the cathode at the vertex; for activation of the leg muscles, the anode was placed at the vertex and the cathode 6 cm anterior. Close bipolar stimulation with an inter-electrode distance 2 cm or less is more focal, but less effective, since higher stimulus intensities are needed to produce EMG responses (Cohen & Hallett, 1988), and this is more painful.

Multiple descending volleys elicited by cortical stimulation

In monkeys, a single stimulus applied at threshold intensity to the surface of the motor cortex activates pyramidal tract axons *directly*, eliciting a descending pyramidal volley termed the D wave ('D' for 'direct', due to direct stimulation of the corticospinal neurone or its axon). With higher stimulus intensities, the size of the D wave increases and the stimulus begins to recruit a series of subsequent volleys, 'I waves', which descend the pyramidal tract with the same velocity as the D wave, at intervals of ~1.5 ms (Patton & Amassian, 1954). I waves are due to transsynaptic activation of pyramidal tract neurones, and are so termed because the corticospinal neurones are activated 'indirectly'. Precisely how I waves are generated is unknown, i.e. whether they result from successive discrete excitatory inputs to the corticospinal neurone, whether they involve alternating excitatory and inhibitory inputs, or whether an essentially single input sets up a reverberating response from the neurone. The I waves are recruited in a particular order as stimulus intensity is increased. The reason for this is that the stimulus intensities necessary to recruit I waves are higher than those needed for D waves. Thus, at intensities above threshold for I waves, the stimulus will have already activated a number of corticospinal neurones in the preceding

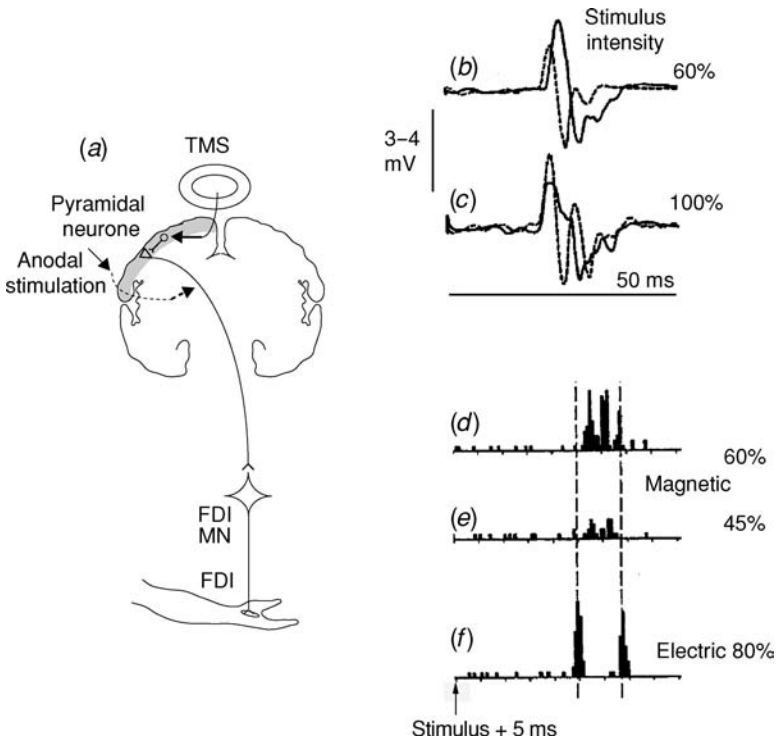

Fig. 1.18. Comparison of EMG responses evoked in human muscle by electrical and magnetic transcranial stimulation. (*a*) Sketch of the presumed pathways: a pyramidal neurone projecting to a first dorsal interosseus (FDI) motoneurone (MN) is activated at the level of its axon (dashed arrow) by anodal electrical stimulation, and trans-synaptically (continuous arrow) by transcranial magnetic stimulation (TMS). (The grey matter is only sketched in the motor area of the stimulated hemisphere.) (*b*), (*c*) Surface EMG responses in pre-activated FDI muscle after different intensities of stimulation (60% (*b*), and 100% (*c*)) following electrical stimulation (anodal, dashed lines) and TMS (induced current flowing in posterior-anterior direction over the lateral part of the motor strip, continuous lines) (from Day *et al.*, 1989). (*d*)–(*f*) Comparison of the effects of anodal electrical stimulation (*f*) and TMS (at intensities of 60% and 45% (*d*), (*e*)) on the PSTH of the same FDI motor unit (calibration 2.5 ms). The two peaks in (*f*) are thought to be due to corticospinal D and I waves. Adapted from Rothwell (1997), with permission.

D wave. These may be refractory during the first I-wave input and only able to respond in the second or the third I wave. In human subjects, the recruitment of D and I waves after transcranial electric stimulation seems very similar to that seen after direct stimulation of the exposed motor cortex in monkeys. Intra-operative recordings during scoliosis surgery from the spinal epidural space of descending volleys produced by transcranial stimulation show initial recruitment of an early rapidly conducted D wave followed by a series of I waves that have a similar conduction velocity as the D wave (Boyd *et al.*, 1986; Burke, Hicks & Stephen, 1990). From a practical point of view, only with relatively weak transcranial electrical stimuli does the D wave arise at cortical level: with relatively strong stimuli, the shortest latency component of the D wave produced by scalp stimulation probably arises from the decussation of the pyramids (Rothwell *et al.*, 1994). At threshold, D wave responses to transcranial electrical stimulation probably arise from the axon, several nodes distant to the cell body (see Rothwell, 1997).

Motor evoked potentials (MEPs) elicited by electric stimulation

Figure 1.18(*b*), (*c*) (dashed line) shows the EMG potential produced in the first dorsal interosseus (FDI) muscle by anodal electrical stimulation of the brain. The latency of EMG responses elicited by electrical stimulation is short, and the calculated central motor conduction time from the cortex to spinal motoneurones (using F wave estimates of peripheral conduction times) is about 4 ms for biceps motoneurones at C5 and 5 ms for C8 hand muscles (see Rothwell *et al.*, 1991). Such short latencies suggest that at least the onset of the MEP is produced by activity in the fast-conducting corticospinal axons, probably the monosynaptic component of the corticospinal tract.

Changes induced in the PSTH of single units

The PSTH of a FDI unit in Fig. 1.18(*f*) shows that anodal electrical stimulation produces an early peak with a sharp increase and short duration, probably due to the D wave activating the motoneurone monosynaptically (Day *et al.*, 1989). Increasing the stimulus intensity recruits further peaks which follow the initial peak at intervals of ∼1.5 ms, and are thought to be due to the arrival at the motoneurone pool of I-wave volleys. This is illustrated in Fig. 1.18(*f*), where the initial peak is followed ∼4 ms later by a second peak due to the I_2 wave (pyramidal neurones being refractory at the latency of the I_1-wave, cf. above).

Disadvantages

The major problem with transcranial electrical stimulation is that only a small fraction of the current flows into the brain. Much of the current flows between the electrodes on the scalp and produces strong discomfort, local pain and contraction of the scalp muscles.

Magnetic stimulation

Like electrical stimulation, transcranial magnetic stimulation of the motor cortex (TMS) readily evokes EMG responses in contralateral muscles. However, the magnetic field can penetrate scalp and skull with minimal discomfort, perhaps only that due to the contraction of scalp muscles. TMS is therefore now used exclusively for clinical studies and almost exclusively in research studies. In general, electrical stimulation is only used (with TMS) when testing the excitability of corticospinal neurones (cf. p. 44). Because the responses in arm muscles appear to behave differently to those in the leg, they will be considered separately.

General methodology

The magnetic stimulation coil

This consists of coils of wire connected to a large electrical capacitance. When the capacitance is discharged, a large but transient current flows through the coil, some several thousand ampères within 200 μs. The current produces a magnetic field of up to 3 tesla oriented perpendicular to the coil (see Barker, Jalinous & Freeston, 1985). The skull presents a low impedance to magnetic fields of this frequency, and the magnetic field induces eddy currents in superficial layers of the brain at right angles to the field. It is these which stimulate the neural tissue, specifically the axons of cortical neurones. It is worth noting that the neural tissue is stimulated electrically with both forms of transcranial stimulation. What differs is the method of delivery.

Electrical currents induced by the magnetic field

These flow parallel to the surface of the brain. The magnetic field falls off rapidly with distance from the coil: with a typical 12 cm-diameter round coil, the strength falls by half at a distance of 4–5 cm from the coil surface (Hess, Mills & Murray, 1987). Experiments in monkeys suggest that, even at the highest stimulus intensities, there is no significant activation of corticospinal fibres outside the grey matter (Edgley *et al.*, 1990).

Stimulation using different coils

With standard round coils, the induced current in the brain flows from an annulus underneath the

coil, which is usually some 8–12 cm in diameter. The direction of current flow in the coil is optimal for stimulation of the left hemisphere when counter-clockwise and the right when clockwise. Coils wound in a figure-of-8 shape provide a more focal stimulus, and the lowest threshold occurs when the induced current in the brain flows from posterior to anterior at an angle approximately perpendicular to the line of the central sulcus (Mills, Boniface & Schubert, 1992). Cone-shaped coils are now often used to evoke responses in foot, leg or thigh muscles.

Responses in upper limb muscles

Longer latency of EMG responses evoked by magnetic stimulation

When current in the coil flows in an antero-medial to a latero-posterior direction (i.e. in the direction opposite to that of the induced current in the brain), the latency of EMG responses evoked in active muscles is 1–2 ms longer than those evoked by threshold transcranial electrical stimulation (Day *et al.*, 1989). This holds for both the MEP (Fig. 1.18(*b*)) and the earliest peak in the PSTHs from single units (Fig. 1.18(*d*)–(*f*)).

Trans-synaptic activation of pyramidal tract neurones by cortical stimulation

The most likely explanation for the difference in latency of the EMG responses in human hand muscles is that originally put forward by Day *et al.* (1989): magnetic stimulation at threshold activates pyramidal tract neurones trans-synaptically (continuous horizontal arrow in the sketch in Fig. 1.18(*a*)) to produce I waves in the pyramidal tract, whereas electrical stimulation activates axons directly to produce D waves (dashed horizontal arrow in Fig. 1.18(*a*)). This view has been confirmed by epidural recordings in conscious co-operative patients of the corticospinal volleys produced by transcranial electrical and magnetic stimulation (di Lazzaro *et al.*, 1998). Thus, the latency difference between EMG responses produced by the two techniques is the time taken for trans-synaptic activation of pyramidal neurones following excitation of cortical elements oriented parallel to the surface, such as stellate cells or cortico-cortical connection fibres (see Rothwell, 1997).

TMS can also activate pyramidal axons directly

A D wave is produced in corticospinal axons to upper limb motoneurones when the coil is rotated or the intensity of stimulation is increased significantly (e.g. see Fig. 1.18(*c*); Werhahn *et al.*, 1994). Direct recordings of descending activity obtained in anaesthetised human subjects during surgery have shown that TMS can produce D waves with a lower threshold than I waves (Burke *et al.*, 1993), but: (i) the combination of relaxation and deep anaesthesia is then likely to depress the synaptic activity responsible for generating I waves (Hicks *et al.*, 1992); (ii) the threshold for recruiting such D waves in the pyramidal tract in unconscious individuals is usually two or more times higher than the usual threshold for producing EMG responses in normal active muscles (Berardelli *et al.*, 1990; Burke *et al.*, 1993; Fujiki *et al.*, 1996). The situation has, however, been complicated by further recordings of corticospinal volleys in two unanaesthetised subjects using epidural leads: stimulation using clockwise current through a large circular coil appeared to be more diffuse than with a figure-of-8 coil and induced D waves preferentially in one of the two subjects (Di Lazzaro *et al.*, 2002), much as occurs regularly in the anaesthetised patients.

Responses in leg muscles

The responses evoked by either anticlockwise transcranial magnetic or anodal electrical stimulation of the leg area are of equal latency in the tibialis anterior (Priori *et al.*, 1993). This was thought to indicate that both activate pyramidal axons at the same site, at a point near the cortical surface, where they bend to leave the cortex and curve towards the internal capsule (Priori *et al.*, 1993). The implication is that magnetic stimulation of the leg area readily produces D-wave activity. An alternative possibility was raised by Nielsen, Petersen and Ballegaard (1995). They found that the EMG responses evoked