

CHAPTER CONTENTS

Acupuncture points and meridians	70
Acupuncture points	70
Meridians	71
Spinal segmental mechanisms	72
Heterosegmental acupuncture	74
The serotonergic system	75
The noradrenergic system	77
Diffuse noxious inhibitory controls (DNIC)	77
Conclusion	79

6

Mechanisms of acupuncture

David Bowsher

Acupuncture has been used for more than two thousand years in China and Japan; the earliest literary reference is in The Yellow Emperor's book of internal medicine, dating from the second or third century BC. Acupuncture reached Japan in the sixth century of the Christian era, and was introduced into Europe by ten Rhijne (1683), who had learnt about it in Japan. As a therapy, it spread very slowly in Europe. The first European and American publications on acupuncture treatment appeared in the early nineteenth century (Bache 1826, Berlioz 1816, Churchill 1821, Cloquet 1826). Although acupuncture was used to a considerable extent in conventional medical practice in Europe throughout the nineteenth century, attracting such mainstream giants as Osler, its use gradually died out.

While some pioneers such as Felix Mann in the UK and a number of practitioners in France were using acupuncture extensively from the middle of the present century, it was really only in the 1970s that acupuncture captured the public interest and came to be widely practised. Films of acupuncture anaesthesia for operative surgery coming out of China following President Nixon's visit in 1972 fired the public imagination. Acupuncture received full scholarly treatment in the West in the magisterial treatise of Lu & Needham (1980).

In addition to classical acupuncture, a number of variations exist. Notable among these are Ryodoraku (Hyodo 1990, Nakatani & Yamashita 1977, Yoshio 1969) and auricular acupuncture, introduced in France by Nogier (1972). Auricular

acupuncture has been further studied by Johnson et al (1991).

Eventually, acupuncture in Western medicine came to be mainly used for pain relief (Mann et al 1973), and much later for the treatment of postoperative nausea and vomiting (Dundee et al 1986). The present chapter will be concerned entirely with an attempt to explain acupuncture in relation to pain relief.

The fact that not all subjects respond to acupuncture appears to present great difficulties to some medical scientists. Acupuncturists divide the population into responders and non-responders. Many animals may also be classed as non-responders, for instance, some rats show no prolongation of the tail-flick response latency following acupuncture (Takeshige et al, 1980a).

As will be more fully discussed below, acupuncture analgesia in people and animals is reversed or abolished by naloxone under most conditions, showing that its mechanism is opioidergic. In human subjects in whom pain was relieved by acupuncture, an increase in cerebrospinal fluid (CSF) β -endorphin level was noted (Clement-Jones et al 1980). Although CSF met-enkephalin levels did not appear to be changed in this study, it has recently been observed in the rat (Bing et al 1991) that met-enkephalin-like material is in fact released in the substance of the spinal cord itself by acupuncture-like stimulation. Recently, Takeshige et al (1990) have shown that non-responsive animals (as measured by non-prolongation of tail-flick latency) can be rendered responsive by treatment with D-phenylalanine, which inhibits the enzyme that degrades met-enkephalin. Attribution of response failure in rats to differences in enzyme mechanisms is reminiscent of the observation that humans who fail to respond to morphine for the relief of nociceptive pain appear to have differences in the enzymatic mechanisms for its glucuronidation (Bowsher 1993).

ACUPUNCTURE POINTS AND MERIDIANS

Experiments showing that, when a nerve is

blocked by local anaesthesia, acupuncture is ineffective in the territory supplied by that nerve prove that the acupuncture effect is conducted along nerves (Chiang et al 1973). From the standpoint of modern neurophysiology, this is perhaps the most important and fundamental piece of information on acupuncture.

Acupuncture points

Acupuncture is said to be effective only at certain points on the body surface, known as acupuncture points. In fact, comparison with an anatomical atlas (e.g. Williams et al 1989) shows that many of these points correspond with the points at which small nerve bundles penetrate the fascia; Chan (1984) cites two Chinese studies showing that 309 acupuncture points are situated on or very close to nerves, while 286 are on or very close to major blood vessels, which are of course surrounded by small nerve bundles (nervi vasorum).

That sympathetic nerves may also be involved was first demonstrated by Goulden (1921), who showed that acupuncture points along the sciatic nerve and its branches have a lower impedance than does the surrounding skin. Yoshio (1969) has shown that Ryodoraku points have similar properties. Many acupuncture points are of course deep within the skin. Melzack, Stillwell & Fox (1977) have shown that many of them correlate closely with Travell's 'trigger points' (Travell & Simons 1983), while Liu, Varela & Oswald (1977) have demonstrated that other points correspond to the motor points of muscles, where the nerves enter or leave them. The Hoku point (LI-4), of course, has long been known to correspond to the superficial branch of the radial nerve in the anatomical 'snuff-box'; but the foregoing demonstrates that all acupuncture points examined correspond to small nerve bundles, either cutaneous (purely sensory, or sensory plus sympathetic), vascular (mixed sympathetic and sensory), or muscular (mixed sensory and motor).

While segmental acupuncture is undoubtedly the most effective form for pain relief, acupuncture at distant points has been found empirically also

to be effective. In order to demonstrate this, ancient practitioners drew up illustrations in which 'points' were joined by lines that in Western practice are called 'meridians'; the intention was to show that stimulation at a particular point may have an effect elsewhere on the meridian, or in a viscus after which the meridian was named.

This raises two distinct issues:

1. Are the 'points' fixed entities?
2. How are 'meridians' to be interpreted in terms of modern anatomical and physiological knowledge?

If in fact the points are small nerve bundles, then of course their precise position will vary from individual to individual in accordance with normal biological variation.

Most practitioners of acupuncture find that effective points, when needled, give rise to a subjective feeling of warmth in the patient and are often revealed to the therapist as a red flare in the skin. This of course is the axon reflex, brought about by stimulation of C and A delta (A δ) fibres. Its absence merely indicates that the needle has not hit nerve fibres, and therefore has not been inserted into an effective 'point'.

While a needle may mechanically stimulate nerve fibres of many types, it is most important to establish which peripheral nerve fibre type is responsible for the acupuncture effect. It was suggested some time ago (Bowsher 1976) that A δ fibres were involved, because the adequate stimulus is needleprick, while the response frequency is 2–3 Hz; these are both properties of A δ primary afferents. This theoretical hypothesis has been confirmed practically in two different ways. First, it has been demonstrated beyond doubt, by microneurographic stimulation in conscious human volunteers, that stimulation of A δ fibres gives rise to a pricking sensation, like that of being stimulated with a needle. Secondly, Wang et al (1985) showed that A δ fibres from muscle conveyed various sensations which Chiang et al (1973) had shown were essential for the acupuncture effect.

An interesting corollary arises in a disease state: Levine, Gormley & Fields (1976) found that acupuncture was ineffective when applied

to areas of skin affected by postherpetic neuralgia (PHN). In 1990, Nurmikko & Bowsher showed that, in areas of skin affected by PHN, pinprick sensation is usually absent.

Thus it may be regarded as established beyond reasonable doubt that A δ sensory units *must* be stimulated in order to produce the acupuncture effect. It should, however be mentioned that, in a number of recent papers, Kawakita and his colleagues (e.g. Kawakita 1991) have suggested that C polymodal nociceptors should also be considered as a physiological substrate of the acupuncture effect. While it cannot be excluded that stimulation of such sensory units may contribute in some measure to the acupuncture effect, both the parameters of stimulation and the perceived sensation following needle stimulation appear to us to militate strongly against the possibility that C polymodal nociceptors are the sole, or even the principal, substrate. Indeed, earlier work on suppression of the jaw-opening reflex in rats by both electroacupuncture and selective A δ stimulation (Kawakita & Funakoshi 1982) strongly support the notion that A δ fibres are principally concerned in the acupuncture effect. It may also be added that, unlike the situation with respect to A δ fibres (see below), there are no known central connections of C fibres that could explain inhibition of (other) C fibre input. Table 6.1 correlates the different sensory fibre types with their physiological functions and with their role in acupuncture analgesia and the TCM phenomenon 'De Qi'. Note that, whilst superficial acupuncture involves A δ nerve fibres, deep (muscle) acupuncture also stimulates A δ fibres. The 'soreness' component of acupuncture is the result of stimulating C fibres.

Meridians

The second issue—that of the 'correct' acupuncture points and their relation to meridians—is more complex. Some effect may be produced at any point where a nerve bundle containing A δ fibres is stimulated, owing to central effects from descending inhibitory controls (DNIC) (Bing, Villanueva & Le Bars 1991). However, powerful

Table 6.1 Neurophysiology of needling (after Thompson 1994)

Sensory Fibre ABC type	Sensory Fibre I-IV type	Diameter μm	Velocity m/s (mph)	Function	Role in analgesia*	Role in De Qi [†]
A α	1a	15–20	70–120	Annulo-spiral muscle spindles [length]		
	1b		(155–270)	Golgi tendon organ [load]		
A β	II	5–12	30–70	Touch		
			(70–155)			
A γ	II	3–6	15–30	Flower spray muscle spindles [length]	+	Numbness
			(35–70)			
A δ	III	2–5	12–30	Pinprick sensation (= first or fast pain), cold, pressure	+	Aching, distension, heaviness
			(25–70)			Soreness
C	IV	0.4–1.2	0.5–2	Aching pain (= second or slow pain), itch, heat		
			(1–4.5)			

References: Guyton 1991, Ganong 1993. * Bowsher 1988, Pomeranz & Paley 1979, Toda & Ichioka 1978, [†] Wang et al 1985, Thompson 1994.

effects are produced only following stimulation at particular non-segmental points on a meridian. As pertinently suggested by Baldry (1993), it is likely that, at least in part, we are dealing with the as yet ill-understood mechanisms of referred effects, as studied by such workers as Kellgren and Lewis before World War II (see Baldry 1993 for details). While such explanations appear to depend entirely on interactions within the somatic nervous system, attention should also be given to pathways travelling in the autonomic nervous system and interactions between the autonomic and somatic nervous systems. There is a considerable body of evidence implicating the sympathetic nervous system in acupuncture effects: the first report (Matsumoto & Hayes 1973) demonstrated a fall in blood pressure and intestinal vasodilation following electroacupuncture in rabbits. More recently, transient skin vasoconstriction followed by a longer-lasting warming effect has been demonstrated in normal human volunteers following both manual and electrical acupuncture stimulation (Ernst & Lee 1985), again revealing autonomic effects elicited by acupuncture. In fact, as early as 1977, Nakatani & Yamashita had drawn attention to the fact that Ryodoraku acupuncture points are in areas of skin containing sweat glands, and modern Ryodoraku theory attributes the heterosegmental effects of acupuncture to interactions between sympathetic and somatic nervous systems. Ogata et al (1993) have

demonstrated that sweat production in humans is reduced by acupuncture. Interestingly, it is frequently observed that patients sweat profusely during treatment with acupuncture.

It has recently been suggested (Iguchi & Sawai 1993, Yamada, Hoshino & Watari 1993) that at least some meridians may correspond to lymphatic channels. Like blood vessels, lymphatics are accompanied by fine nerve fibres, as evidenced, for example, by the pain felt following untreated hand infection that travels up the arm to the axillary lymph glands.

SPINAL SEGMENTAL MECHANISMS

Acupuncture analgesia is blocked or reversed by naloxone (Cheng & Pomeranz 1980, Mayer, Price & Ruff 1977, Sjölund & Eriksson 1979). Melzack, Stillwell & Fox (1977) have identified many of Travell's trigger points with acupuncture points. It is therefore of great interest that pain relief by trigger point injection with bupivacaine is also reversed by naloxone (Fine, Milano & Hare 1988). Han, Ding & Fan (1986) have also shown that intracerebroventricular or intrathecal injection of cholecystokinin octapeptide (CCK-8), which is an endogenous opioid antagonist, antagonizes analgesia produced both by morphine and by electroacupuncture in the rat. All these lines of evidence clearly point to an opioidergic mechanism of action for acupuncture. Table 6.2 summarizes

Table 6.3 Effect of stimulation frequency (from Thompson 1994)

Frequency	Low (2–5 Hz)	High (20–200 Hz)
Technique	Manual or electrical	Electrical: electroacupuncture
Type	High intensity/low frequency	Low intensity/high frequency
Predominant pharmacology	met-enkephalin	Dynorphins
Naloxone	β -endorphin	5-HT + NAD
	Blocks effect	Unaffected

Lee & Perl 1986). It has been shown that stalked cells do not react to frequencies of stimulation above about 3 Hz (Bowsher et al 1968, Harper & Lawson 1985), which is the optimal frequency at which acupuncture analgesia stimulation is performed. The stalked cells inhibit SG cells by releasing on to them the inhibitory opioid transmitter enkephalin (Ruda, Coffield & Dubner 1984). Stalked cells also receive a direct input from A δ pinprick fibres (Gobel et al 1980). It has recently been directly demonstrated (Bing et al 1991) that acupuncture-like stimulation in the rat induces release of enkephalin-like material in the spinal cord. Very recently, Sjölund and his colleagues (personal communication) and Hashimoto & Aikawa (1993) have shown that manual acupuncture in the rat induces inhibition in the wide dynamic range (WDR) cells, which project up to the brain, conveying impulses that will be consciously interpreted as painful. WDR cells are influenced by SG cells (Fig. 6.1), thus completing the circuit. Table 6.3 illustrates the effect of stimulation frequency on the predominant pharmacological response of the primary afferent input (A β and A δ nerve fibres).

Thus, the intraspinal terminals of primary afferent A δ (pinprick) fibres branch to supply the large Waldeyer cells in the marginal layer (lamina I) and the enkephalinergic stalked cells at the border between laminae I and II (SG) of the dorsal horn. Since A δ primary afferent fibres stimulate the stalked cells, and these in turn enkephalinergically inhibit the SG cells, we have an adequate explanation of the mechanism for segmental acupuncture interrupting the pain pathway from C fibres to the WDR cells.

HETEROSEGMENTAL ACUPUNCTURE

There is no doubt that, in clinical practice, acupuncture at certain points can relieve pain in distant regions supplied by nerves from totally different segments. It is therefore necessary to consider the physiological mechanisms that may underlie these phenomena. To do this, two distinct, but sometimes anatomically intermingled, ascending pathways must be examined, as well as the descending pathways that may inhibit the upward transmission of impulses generated by noxious stimulation.

In the spinal cord WDR, or convergent, cells (Giesler et al 1976, Willis & Coggeshall 1978) respond to most stimuli in a graded manner; noxious stimulation in the periphery causes them to fire at highest frequency. All types of peripheral afferent can therefore excite WDR cells, after relaying through variable numbers of interneurons in the dorsal horn of the spinal grey matter; WDR cells do not receive monosynaptic connections from primary afferents. Some WDR cells are to be found in lamina V, in the neck of the spinal dorsal horn, but most of them are to be found in the deeper layers (laminae VII and VIII) of the intermediate spinal grey matter. These cells send their axons to the opposite side of the spinal cord, where they ascend in the anterolateral funiculus as the spinothalamic and spinoreticular tracts (Kuru 1949, Bowsher 1957). Essentially, the spinoreticular pathway carries information generated by the stimulation of nociceptors to the reticular formation, the intralaminar thalamus and the hypothalamus (Fig. 6.2) (Burstein, Cliffer & Giesler 1987); the spinothalamic tract, on the other hand, carries

information generated by thermal and pinprick receptors to the ventroposterior thalamus (Willis & Coggeshall 1978, Willis 1985). Many of the cells projecting into the spinothalamic tract lie in the marginal zone (lamina I), and are activated by A δ pinprick receptors. It is thus of great interest that the heterosegmental acupuncture effect in the rabbit is abolished by section of the anterolateral funiculus, but not by destruction of other long ascending spinal cord pathways (Chen et al, 1975). We must therefore enquire what collateral connections of the spinothalamic pathway may be responsible for the activation, directly or indirectly, of descending inhibitory pathways. In addition, physiological research (Takeshige 1992, Tsai, Chen & Lin 1993) has shown that two transmitter systems—serotonergic and noradrenergic—are involved (Figs 6.2, 6.3), and Tsai, Chen & Lin (1993) have recently shown that central adrenergic, as well as serotonergic, neurons are excited by acupuncture stimulation.

We shall therefore consider heterosegmental acupuncture effects under these two physiopharmacological headings and finally mention a third system that may contribute to the acupuncture effect.

The serotonergic system

It has been known for some time that spinothalamic collaterals reach the midbrain periaqueductal grey matter (PAG) in the primate (Mantyh 1982a), and Zhang et al (1990) have recently shown that these axons originate from cells in lamina I.

It was in 1964 that Tsou & Jang demonstrated that the PAG is the most effective spot in the whole nervous system for the abolition of pain by microinjection of morphine. As the PAG was known *not* to send messages upwards to the cerebral cortex so that these messages did not become conscious, this amazing finding was conveniently overlooked by most researchers. However, in 1968 Reynolds showed that painless surgery could be carried out in the rat during electrical stimulation of PAG, and this led to intensive research on possible mechanisms.

Investigations by Mayer & Liebeskind (1974) showed that a descending inhibitory pathway passing down from the caudoventral part of the PAG to the spinal cord was responsible for the inhibition of neurons with ascending axons that carry messages generated by painful stimuli in the periphery (Fig. 6.2). There is evidence that there is a somatotopic organization within this part of the PAG (Soper & Melzack 1982); this might explain why heterosegmental acupuncture effects cannot be obtained from *any* acupuncture point, but only from particular points that are not necessarily within the dermatome in which it is desired to obtain pain relief.

The pathway descending from the PAG, whose transmitter substance is probably neurotensin (Beitz 1982), relays in the nucleus raphe magnus (NRM) of the medulla oblongata. From the NRM, fibres whose transmitter substance is mainly serotonin (5-hydroxytryptamine, 5-HT) descend in the dorsolateral funiculus (DLF) of the spinal cord to terminate directly on the stalked enkephalin-containing interneurons in the spinal dorsal horn (Glazer & Basbaum 1984), which were discussed above. There are also serotonin-containing nerve terminals ending freely in the superficial part of the spinal cord grey matter (Hammond, Tyle & Yaksh 1985, Leranthe, Maxwell & Verhofstad 1984, Maxwell, Leranthe & Verhofstad 1983). This could explain the 'hormonal' or generalized type of acupuncture effect, as opposed to the point-to-point or neural type. Increased serotonin levels in mast cells and platelets have been reported following acupuncture (Souvannakitti et al 1993, Wu & Deng 1993). Both these latter phenomena might (but very cautiously) be considered an explanation of those acupuncture effects that outlast direct synaptic inhibition.

Finally, as mentioned earlier, the PAG receives fibres containing the naturally occurring morphine-like substance β -endorphin (Bloom et al 1978); these fibres descend from the arcuate region of the hypothalamus (Mantyh 1982b), a primitive but essential part of the forebrain concerned not only with regulation of bodily functions but also with emotion. In humans, the

hypothalamus is under the control of the prefrontal cortex, a region whose blood flow is increased by painful stimuli (Lassen, Ingvar & Skinhøj 1978, Tsubokawa et al 1981). It is because the pathway from hypothalamus to PAG is endorphin-containing that pain relief in humans can be obtained by stimulating electrodes implanted in the PAG or in the periventricular region anterior to it (Richardson 1982) in which the hypothalamo-PAG fibres run. This morphine-like pain relief is reversed by naloxone (Hosobuchi, Adams & Linchitz 1977, Richardson & Akil 1977).

Within the PAG itself, there are inhibitory interneurons that are themselves inhibited by the long-descending β -endorphin-containing hypothalamo-PAG fibres, which accounts for the release of activity in the PAG-NRM pathway and thus inhibition in the spinal cord via the inhibitory NRM-spinal pathway.

Modulation of pain perception through the emotional or psychic state of the individual may depend on the projection from the prefrontal cortex through the hypothalamus to the PAG.

Because the type of acupuncture effect descending through PAG is eventually serotonergic, it is antagonized by methysergide (Takeshige, Sato & Komugi 1980).

The noradrenergic system

In the cat and monkey, lamina I of the spinal grey matter, in addition to projecting to PAG, also sends collaterals to the locus coeruleus in the pons (Craig 1992), which is the principal brainstem source of noradrenergic axons. Unlike the serotonergic axons descending from the NRM, noradrenergic fibres do not operate through enkephalinergic interneurons (stalked cells) in the spinal cord, but bring about direct inhibition on the many types of spinal cell with which they make synaptic contact (Fig. 6.3).

A massive spinal projection, ascending in the anterolateral funiculus, to the gigantocellular reticular region has long been known in humans (Bowsher 1957). Takeshige and his colleagues (1992) have also implicated the paragigantocellular reticular nucleus in the descending adrenergic system whose activity is elicited by acupuncture

stimulation, because the inhibitory effects of direct stimulation of this structure are antagonized by phentolamine. However, they point out that the paragigantocellular reticular nucleus does not itself contain any noradrenergic cells; nor does it project directly to the spinal cord. It must therefore relay to a noradrenergic structure before directly influencing spinal activity. This may be the locus coeruleus, or some other noradrenergic lower brainstem cell group whose axons project into the spinal cord. For example, in the primate, Carlton et al (1991) have identified noradrenergic cells in the C1 area of the medulla and pontomedullary junction whose axons descend on the edge of the lateral white funiculus of the spinal cord to the superficial dorsal horn, the intermediate and the circumcanalicular grey matter. Takeshige (1992) believes that the descending noradrenergic system, like that descending from PAG, is ultimately controlled from the prefrontal cortex and the arcuate nucleus of the hypothalamus.

Diffuse noxious inhibitory controls

Diffuse noxious inhibitory controls (DNIC) (Fig. 6.3) is the name given to a powerful pain-suppressing system described by Le Bars (Le Bars, Dickenson & Besson 1979) and his collaborators. Much research by this group has shown that DNIC is an opioidergic mechanism acting on spinal cord WDR neurons (see above), which transmit pain-generated information toward the brain. Direct input of A δ -generated information elicited by acupuncture to the subnucleus reticularis dorsalis in the caudal medulla has been demonstrated in the rat and monkey (Villanueva et al 1988, 1990); this is probably the same region as was shown to receive convergent nociceptive information in the cat by Bowsher (1970). The subnucleus reticularis dorsalis projects downward through the dorsolateral funiculus to the dorsal horn of the spinal cord at all levels (Bernard et al 1990). Bing, Villanueva & Le Bars (1991) have shown that this mechanism is brought into play by needle stimulation at both acupoints and non-acupoints on the body surface. The fact that stimulation at non-acupoints elicits

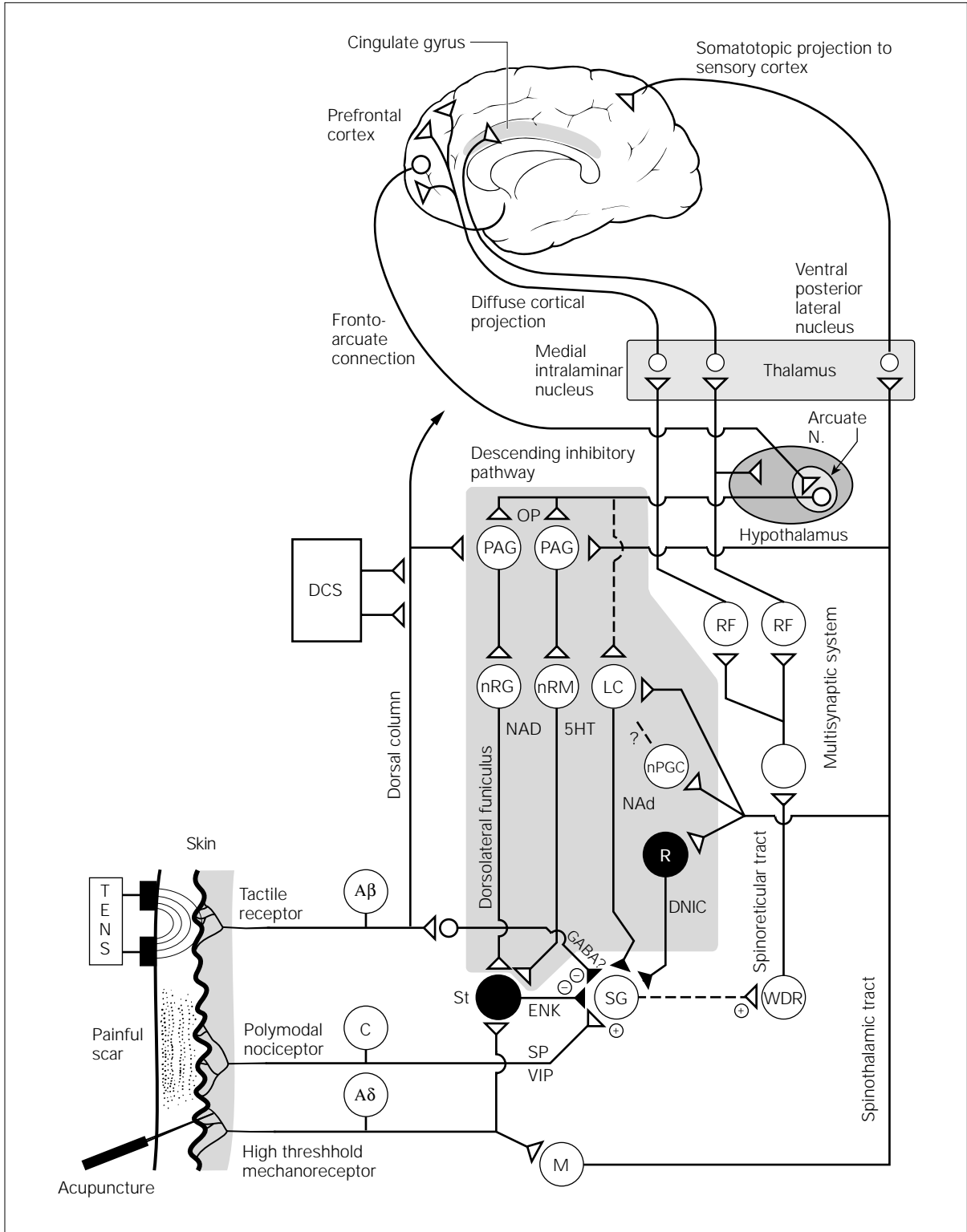


Figure 6.3 (*facing*) Adrenergic mechanism of acupuncture. Marginal cells (M), activated by A δ pinprick receptors, in addition to their projections to the ventral posterior lateral nucleus and the PAG (through the nucleus raphe magnus (NRM) and nucleus raphe gigantocellularis (NRG) cells) also send axon branches to the following: (a) Subnucleus reticularis dorsalis (R) in the caudal medulla oblongata. Descending projections from this structure bring about inhibition of noxiously generated information arriving at the spinal cord (SG) in C nociceptors. This is the DNIC mechanism (see text).

(b) Nucleus paragigantocellularis lateralis (PGC), which indirectly (? via the locus coeruleus LC, see (c) below) brings about noradrenergically mediated inhibition at spinal cord level. (c) The locus coeruleus at the junction of medulla oblongata and pons. Its noradrenergic axons (NAD) are directly inhibitory to those spinal neurons with which they enter into synaptic contact. OP = opioid peptides, DCS = dorsal column stimulation.

Note: The figure also includes the A β primary afferent tactile receptor, which projects to the dorsal column and in addition, via an interneuron to the SG cells. Thus activation of the tactile receptor sends impulses to the dorsal column and also, via the interneurone, leads to an inhibition of the SG cells, probably through the release of γ -aminobutyric acid (GABA). The latter action will prevent information generated by noxious stimulation being transmitted further; this is believed to be the principal mechanism of transcutaneous electrical nerve stimulation (TENS) (see Ch. 11). (After Thompson & Filshie 1993, derived from Bowers 1992)

DNIC does not mean that when stimulation is performed at acupoints DNIC does not contribute to the acupuncture effect, particularly the short-term effect, as has recently been emphasized by Hashimoto & Aikawa (1993). The involvement of DNIC in the human acupuncture effect receives support from the recent research of Marchand & Li (1993), who reported pain reduction in *all* skin locations by electroacupuncture.

CONCLUSION

1. Acupuncture stimulates A δ or Group III small myelinated primary afferents in skin and muscle.
2. Segmental acupuncture operates through a circuit involving inhibitory enkephalinergic stalked cells in the outer part of lamina II (SG) of the spinal grey matter, which are directly contacted by A δ /Group III primary afferents.
3. Heterosegmental acupuncture is brought about by both a generalized neurohormonal mechanism, involving the release of free β -endorphin and apparently also of met-enkephalin, and by two descending neuronal mechanisms, the first of which is serotonergic and the second adrenergic. A third descending system (DNIC)

may also contribute in a minor way to the acupuncture effect:

(a) The system is influenced by the pre-frontal cortex and descending through the hypothalamus (arcuate nucleus) and the PAG to the NRM of the medulla oblongata and thence to the spinal cord, where enkephalinergic stalked cells are activated. This system has discrete but ill-understood somatotopy, which may depend on classical referral of stimuli, on viscerosomatic interactions, and/or on a somatotopic organization existing within the PAG.

(b) Noradrenergic cells in the lower brainstem are excited both by influences ascending directly from the spinal cord, and also relaying through the nucleus paragigantocellularis, and by influences descending from the prefrontal cortex through the hypothalamic arcuate nucleus.

(c) Cells of the subnucleus reticularis dorsalis are influenced by high-intensity inputs from both acupuncture and non-acupuncture points; axons descending from the subnucleus reticularis dorsalis bring about widespread inhibition (DNIC effect).

REFERENCES

- | | |
|---|--|
| <p>Abdel-Maguid T E, Bowsher D 1984 Interneurons and proprioneurons in the adult human spinal grey matter and general somatic afferent cranial nerve nuclei. <i>Journal of Anatomy</i> 139:9–20</p> <p>Bache F 1826 Cases illustrative of the remedial effects of acupuncture. <i>North American Medical and Surgical</i></p> | <p><i>Journal</i> 1:311–321</p> <p>Baldry P E 1993 <i>Acupuncture, trigger points and musculoskeletal pain</i>, 2nd edn. Churchill Livingstone, Edinburgh</p> <p>Beitz A J 1982 The sites of origin of brainstem neurotensin and serotonin projections to the rodent nucleus raphe</p> |
|---|--|

- magnus. *Journal of Neuroscience* 2:829–834
- Bennett G J, Ruda M A, Gobel S, Dubner R 1982 Enkephalin-immunoreactive stalked cells and lamina IIb islet cells in cat substantia gelatinosa. *Brain Research* 240:162–166
- Berlioz L V J 1816 Mémoires sur les maladies chroniques, les évacuations sanguines et l'acupuncture. Croullebos, Paris
- Bernard J F, Villanueva L, Carroue J, Le Bars D 1990 Efferent projections from the subnucleus reticularis dorsalis (SRD): A *Phaseolus vulgaris* leucoagglutinin study in the rat. *Neuroscience Letters* 116:257–262
- Bing Z, Cesselin F, Bourgoin S, Clot A M, Hamon M, Le Bars D 1991 Acupuncture-like stimulation induces a heterosegmental release of Met-enkephalin-like material in the rat spinal cord. *Pain* 47:71–77
- Bing Z, Villanueva L, Le Bars D 1991 Acupuncture-evoked responses of subnucleus reticularis dorsalis neurons in the rat medulla. *Neuroscience* 44:693–703
- Bloom F E, Battenberg E, Rossier J, Ling N, Guillemin R 1978 Neurons containing β -endorphin in rat brain exist separately from those containing enkephalin: Immunocytochemical studies. *Proceedings of the National Academy of Sciences USA* 75:1591–1595
- Bowsher D 1957 Termination of the central pain pathway in man: The conscious appreciation of pain. *Pain* 80:606–622
- Bowsher D 1970 Place and modality analysis in caudal reticular formation. *Journal of Physiology* 209:473–486
- Bowsher D 1976 Role of the reticular formation in response to noxious stimulation. *Pain* 2:361–378
- Bowsher D 1988 Introduction to the anatomy and physiology of the nervous system, 5th edn. Blackwell, Oxford
- Bowsher D 1992 The physiology of stimulation-produced analgesia. *Pain Clinic (Tokyo)* 12:485–492
- Bowsher D 1993 Paradoxical pain. *British Medical Journal* 306:473–474
- Bowsher D, Mallart A, Petit D, Albe-Fessard D 1968 A bulbar relay to centre médian. *Journal of Neurophysiology* 31:288–300
- Burstein R, Cliffer K D, Giesler G J 1987 Direct somatosensory projection from the spinal cord to the hypothalamus and telencephalon. *Journal of Neuroscience* 7:4159–4164
- Carlton S M, Honda C N, Willcockson W S, Lacrampe M, Zhang D, Denoroy L, Chung J M, Willis W D 1991 Descending adrenergic input to the primate spinal cord and its possible role in modulation of spinothalamic cells. *Brain Research* 543:77–90
- Chan S H H 1984 What is being stimulated in acupuncture: evaluation of the existence of a specific substrate. *Neuroscience and Biobehavioral Reviews* 8:25–33
- Chen Y C, Jen Y L, Teh H C, Yao H P, Shu C C 1975 Studies on spinal ascending pathway for effect of acupuncture analgesia in rabbits. *Scientia Sinica* 18:651–658
- Cheng R S S, Pomeranz B H 1980 Electroacupuncture analgesia is mediated by stereospecific opiate receptors and is reversed by antagonists of Type I receptors. *Life Sciences* 26:631–638
- Chiang C Y, Chang C T, Chu H L, Yang L F 1973 Peripheral afferent pathway for acupuncture analgesia. *Scientia Sinica* 16:210–217
- Churchill J M 1821 A treatise on acupuncture, being a description of a surgical operation originally peculiar to the Japanese and Chinese, and by them denominated zinking, now introduced into European practice, with directions for its performance, and cases illustrating its success. Simpkins and Marshall, London
- Clement-Jones V, McLoughlin L, Tomlin S, Besser G M, Rees L H, Wen H 1980 Increased beta-endorphin but not met-enkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain. *Lancet* 2:946–949
- Cloquet J G 1826 Traité de l'acupuncture. Becket-Jeune, Paris
- Craig A D 1992 Spinal and trigeminal lamina I input to the locus coeruleus anterogradely labeled with *Phaseolus vulgaris* leucoagglutinin (PHA-L) in the cat and the monkey. *Brain Research* 584:325–328
- Dundee J W, Chestnutt W N, Ghaly R G, Lynas A G A 1986 Traditional Chinese acupuncture: a potentially useful anti-emetic? *British Medical Journal* 293:583–584
- Ernst M, Lee M H M 1985 Sympathetic vasomotor changes induced by manual and electrical acupuncture of the Hoku point visualized by thermography. *Pain* 21:25–33
- Fine P G, Milano R, Hare B D 1988 The effects of trigger point injections are naloxone reversible. *Pain* 32:15–20
- Ganong W F 1993 Review of medical physiology, 16th edn. Appleton & Lange, Connecticut, p 53
- Giesler G, Menétrey D, Guilbaud G, Besson J-M 1976 Lumbar cord neurons at the origin of the spinothalamic tract in the rat. *Brain Research* 18:320–324
- Glazer E J, Basbaum A I 1984 Axons which take up [3 H] serotonin are presynaptic to enkephalin immunoreactive neurons in cat dorsal horn. *Brain Research* 289:389–391
- Gobel S, Falls W M, Bennett G J, Abdelmoumène M, Hayashi H, Humphrey E 1980 An E. M. analysis of the synaptic connections of horseradish peroxidase filled stalked cells and islet cells in the substantia gelatinosa of the adult cat spinal cord. *Journal of Comparative Neurology* 194:781–807
- Goulden E A 1921 The treatment of sciatica by galvanic acupuncture. *British Medical Journal* 1:523–524
- Guyton A C 1991 Textbook of medical physiology, 8th edn. WB Saunders, Philadelphia, pp 499–500
- Hammond D L, Tyle G M, Yaksh T L 1985 Effects of 5-hydroxytryptamine and noradrenaline into spinal cord superfusates during stimulation of the rat medulla. *Journal of Physiology (London)* 359:151–162
- Han J S 1984 Progress in the pharmacological studies of acupuncture analgesia. In: Paton S W, Mitchell J, Turner P (eds) *Proceedings IUPHAR Ninth International Congress of Pharmacology*, vol 1. Macmillan, London, pp 387–394
- Han J S, Ding X Z, Fan S G 1986 Cholecystokinin octapeptide (CCK-8): Antagonism to electroacupuncture analgesia and a possible role in electroacupuncture tolerance. *Pain* 27:101–115
- Harper A A, Lawson S N 1985 Electrical properties of rat dorsal root ganglion neurones with different peripheral nerve conduction velocities. *Journal of Physiology (London)* 359:47–63
- Hashimoto T, Aikawa S 1993 Needling effects on nociceptive neurons in rat spinal cord. *Proceedings of the 7th World Congress on Pain IASP, Seattle*, p 428
- Hosobuchi Y, Adams J E, Linchitz R 1977 Pain relief by electrical stimulation of central gray matter in humans and its reversal by naloxone. *Science* 197:183–186
- Hyodo M 1990 Ryodoraku treatment. *Japanese Society of Ryodoraku Medicine*, Osaka
- Iguchi K, Sawai Y 1993 Correlation between the meridians and acute lymphangitis. *Proceedings of the 3rd*

- world conference on acupuncture, Kyoto, p 270
- Johnson M I, Hajela V K, Ashton C H, Thompson J W 1991. The effects of auricular transcutaneous electrical nerve stimulation (TENS) on experimental pain threshold and autonomic function in healthy subjects. *Pain* 46:337–342
- Kawakita K 1991 Role of polymodal receptors in the peripheral mechanisms of acupuncture and moxibustion stimulation. In: Manchanda S K, Selvamurthy W, Mohan Kumar V (eds) *Advances in physiological sciences*. New Delhi, pp 731–739
- Kawakita K, Funakoshi M 1982 Suppression of the jaw-opening reflex by conditioning A-delta fiber stimulation and electroacupuncture in the rat. *Experimental Neurology* 78:461–465
- Kumazawa T, Perl E R 1978 Excitation of marginal and substantia gelatinosa neurons in the primate spinal cord: indications of their place in dorsal horn functional organization. *Journal of Comparative Neurology* 177:417–434
- Kuru M 1949 *Sensory paths in the spinal cord and brain stem of man*. Sogensaya, Tokyo
- Lassen N A, Ingvar D H, Skinhøj E 1978 Brain function and blood flow. *Scientific American* 239:50–59
- Le Bars D, Dickenson A H, Besson J-M 1979 Diffuse noxious inhibitory controls (DNIC). I—Effects on dorsal horn convergent neurones in the rat; II—Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. *Pain* 6:283–327
- Leranth C S, Maxwell D J, Verhofstad A A J 1984 Ultrastructure of serotonin-immunoreactive boutons in the substantia gelatinosa of the rat's spinal cord. *Journal of Physiology (London)*, 355, 20P
- Levine J D, Gormley J, Fields H L 1976 Observations on the analgesic effects of needle puncture (acupuncture). *Pain* 2:149–159
- Liu Y K, Varela M, Oswald R 1977 The correspondence between some motor points and acupuncture loci. *American Journal of Chinese Medicine* 3:347–358
- Lu G D, Needham J 1980 *Celestial lancets: a history and rationale of acupuncture and moxa*. Cambridge University Press, Cambridge
- Mann F, Bowsher D, Mumford J, Lipton S, Miles J 1973 Treatment of intractable pain by acupuncture. *Lancet* 2:57–60
- Mantyh P W 1982a The ascending input to the midbrain periaqueductal gray of the primate. *Journal of Comparative Neurology* 211:50–64
- Mantyh P W 1982b Forebrain projections to the periaqueductal gray in the monkey, with observations in the cat and rat. *Journal of Comparative Neurology* 206:146–158
- Marchand S, Li J 1993 The effect of electro-acupuncture on perceived heat pain at different body locations. *Proceedings of the 7th World Congress on Pain*, p 427
- Matsumoto T, Hayes M F 1973 Acupuncture, electric phenomenon of the skin, and post-vagotomy gastrointestinal atony. *American Journal of Surgery* 125:176–180
- Maxwell D J, Leranth C S, Verhofstad A A J 1983 Fine structure of serotonin-containing axons in the marginal zone of the rat spinal cord. *Brain Research* 266:233–260
- Mayer D J, Liebeskind J C 1974 Pain reduction by focal electrical stimulation of the brain: An anatomical and behavioral analysis. *Brain Research* 68:73–93
- Mayer D J, Price D D, Rafii A 1977 Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. *Brain Research* 121:368–372
- Melzack R, Stillwell D M, Fox E J 1977 Trigger points and acupuncture points for pain: correlations and implications. *Pain* 3:3–23
- Nakatani Y, Yamashita K 1977 *Ryodoraku acupuncture*. Ryodoraku Research Institute, Osaka
- Nogier P F M 1972 *Traité d'Auriculothérapie*. Maisonneuve, Moulins-les-Metz
- Nurmikko T, Bowsher D 1990 Somatosensory findings in postherpetic neuralgia. *Journal of Neurology, Neurosurgery and Psychiatry* 53:135–141
- Ogata A, Umeyama T, Ogawa T, Kobayashi S, Sugeno Y, Kugimiya T, Hanaoka K 1993 Effects of low-frequency electro-acupuncture on psychological sweating. *Proceedings of the 3rd World Conference on Acupuncture, Kyoto*, p 157
- Pomeranz B, Paley D 1979 Electroacupuncture hypalgesia is mediated by afferent nerve impulses: an electrophysiological study in mice. *Experimental Neurology* 66:398–402
- Reynolds D V 1968 Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science* 164:444–445
- Rhijne W ten 1683 *Dissertatio—de Acupunctura*. Leers, Den Haag
- Richardson D E 1982 Analgesia produced by stimulation of various sites in the human β -endorphin system. *Applied Neurophysiology* 45:116–122
- Richardson D E, Akil H 1977 Pain reduction by electrical brain stimulation in man. *Journal of Neurosurgery* 47:178–194
- Ruda M A, Coffield J, Dubner R 1984 Demonstration of postsynaptic opioid modulation of thalamic projection neurons by the combined techniques of retrograde horseradish peroxidase and enkephalin immunocytochemistry. *Journal of Neuroscience* 4:2117–2132
- Sjölund B H, Eriksson M B E 1979 The influence of naloxone on analgesia produced by peripheral conditioning stimulation. *Brain Research* 173:295–302
- Soper W Y, Melzack R 1982 Stimulation-produced analgesia: evidence for somatotopic organization in the midbrain. *Brain Research* 251:301–312
- Souvannakitti L, Akasreenont P, Ketsa-ard K, Chotewuttakorn S, Thaworn A 1993 Platelet serotonin in headache patients treated by new trend acupuncture. *Proceedings of the 7th World Congress on Pain*, p 429
- Sugiura Y, Lee C L, Perl E R 1986 Central projection of identified, unmyelinated (C) afferent fibers innervating mammalian skin. *Science* 234:358–361
- Takeshige C 1992 Synaptic transmission in acupuncture analgesia. *Showa University, Japan*
- Takeshige C, Murai M, Hachisu M 1980a Parallel individual variation in effectiveness of electro-acupuncture, morphine analgesia and dorsal PAG-SPA and its abolishment by d-phenylalanine. *Acupuncture and Electro-Therapeutics Research* 5:251–268
- Takeshige C, Sato T, Komugi H 1980b Role of periaqueductal central gray in acupuncture anaesthesia. *Acupuncture and Electro-Therapeutics Research* 5:323–337
- Takeshige C, Sato T, Mera T, Hisamitsu T, Fang J 1992 Descending pain inhibitory system involved in

- acupuncture analgesia. *Brain Research Bulletin* 29:617–634
- Takeshige C, Tanaka M, Sato T, Hishida F 1990 Mechanism of individual variation in effectiveness of acupuncture analgesia based on animal experiment. *European Journal of Pain* 11:109–113
- Thompson J W 1994 Acupuncture: current ideas on mechanisms of action. Summary from lecture to meeting of Pain Society. April 14th–16th, UMIST, Manchester
- Thompson J W, Filshie J 1993 Tens and acupuncture. In: Doyle D, Hanks G, MacDonald N (eds) *Oxford textbook of palliative medicine*. Oxford University Press, Oxford, ch. 4.2.8
- Toda K, Ichioka M 1978 Electroacupuncture: relations between forelimb afferent impulses and suppression of jaw opening reflex in the rat. *Experimental Neurology* 61:465–470
- Travell J G, Simons D G 1983 Myofascial pain and dysfunction. *The trigger point manual*. Williams and Wilkins, Baltimore
- Tsai H-Y, Chen Y-F, Lin J-G 1993 Studies of mechanism of electroacupuncture analgesia in the central monoaminergic neurons. *Proceedings of the 3rd World Conference on Acupuncture, Kyoto*, p 194
- Tsou K, Jang C S 1964 Studies on the site of analgesic action of morphine by intracerebral microinjection. *Scientia Sinica* 13:1099–1109
- Tsubokawa T, Katayama Y, Ueno Y, Moriyasu N 1981 Evidence for involvement of the frontal cortex in pain-related cerebral events in cats: increase in local cerebral blood flow by noxious stimuli. *Brain Research* 217:179–185
- Villanueva L, Bouhassira D, Bing Z, Le Bars D 1988 Convergence of heterotopic nociceptive information onto subnucleus reticularis dorsalis neurons in the rat medulla. *Journal of Neurophysiology* 60:980–1009
- Villanueva L, Cliffer K D, Sorkin L S, Le Bars D, Willis W D 1990 Convergence of heterotopic nociceptive information onto neurons of caudal medullary reticular formation in monkey (*Macaca fascicularis*). *Journal of Neurophysiology* 63:1118–1127
- Wang K M, Yao S M, Xian Y L, Hou Z 1985 A study on the receptive field of acupoints and the relationship between characteristics of needle sensation and groups of afferent fibres. *Scientia Sinica* 28:963–971
- Williams P L, Warwick R, Dyson M, Bannister L H (eds) 1989 *Gray's anatomy*, 37th edn. Churchill Livingstone, Edinburgh
- Willis W D 1985 *The pain system*. Karger, New York
- Willis W D, Coggeshall R E 1978 *Sensory mechanisms of the spinal cord*. Plenum Press, New York
- Wu J, Deng X 1993 The mast cell biologically-active substances and electroacupuncture analgesic effect. *Proceedings of the 7th World Congress on Pain*, p 429
- Yamada K, Hoshino T, Watari N. 1993 Histological study of acupoint. *Proceedings of the 3rd World Conference on Acupuncture, Kyoto*, p 274
- Yoshio N 1969 Introduction to Ryodoraku. *Acupuncture Digest* 3:70–78
- Zhang D X, Carlton S M, Sorkin L S, Willis W D 1990 Collaterals of primate spinothalamic tract neurons to the periaqueductal gray. *Journal of Comparative Neurology* 296:277–290

