THE PHYSIOLOGY OF STIMULATION— PRODUCED ANALGESIA

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NERVE FIBRES IN THE PERIPHERY (Fig. 1)

There are essentially three types of nerve fibre bringing messages from the periphery (Fig. 1). The largest, and most rapidly-conducting fibres, known as $A\beta$, convey messages generated by low-intensity mechanical stimuli, such as touch, stroking, rubbing, or pressure. These fibres will carry many hundreds of messages per second. These large $A\beta$ fibres have a myelin sheath. There are also smaller fibres with a myelin sheath, known as $A\delta$, which carry messages generated by high-intensity mechanical stimuli, such as pinprick. These fibres carry very many fewer messages per second. The natural reaction to stimulation of $A\delta$ fibres is to withdraw. The smallest nerve fibres, which have no myelin sheath (unmyelinated or C fibres) mostly carry messages brought about by tissue damage; when these messages become conscious, human beings call them "pain". Messages in C fibres travel very slowly, and the fibres can only carry a few messages per second. The natural reaction to C fibre stimulation is for muscles to contract and remain contracted, so that the affected part, or even the whole organism, remains still – this gives the best chance of natural healing, while the withdrawal brought about by $A\delta$ fibre activation by sharp objects protects the organism from possibility of damage.

For short, we will refer to large rapidly-conducting $A\beta$ fibres as "*touch fibres*", small myelinated $A\delta$ fibres as "*pinprick fibres*", and unmyelinated C fibres as "*pain fibres*".

Two types of cutaneous stimulation have been known from time immemorial to be effective in relieving pain. The first is the instinctive action of "*rubbing* a pain better", and the second is acupuncture. Rubbing is done rapidly and lightly, so in physical terms constitutes *high-frequency low-intensity* stimulation. Acupuncture is performed with a needle, which is rotated fairly slowly (about 3 or 3 times a second), and so constitutes *low-frequency high-intensity* stimulation.

Fairly obviously, "rubbing better" must stimulate touch fibres in the skin with low thresholds. Since sustained pressure is not effective in producing pain relief, the effective touch fibres must be a special category of nerve excited only by moving (transient) stimuli and not by sustained pressure. Therapeutically, pain relief by activation of these special touch fibres is obtained by transcutaneous electrical nerve stimulation (TENS) (Wall & Sweet, 1967). It can also be obtained by the application of vibratory stimuli (Lunde-

berg, 1983), Which presumably activate movement-sensitive nerve endings in muscle.

Acupuncture presents a more difficult problem, because it was first necessary to demonstrate that nerves are involved at all. Happily experiments which showed that when a nerve is blocked with local anaesthetic, acupuncture is ineffective in the territory supplied by that nerve, demonstrate that the acupuncture effect is conducted along nerves (Chiang et al., 1973). Then it was known that acupuncture is only effective at certain points on body surface. In fact, comparison with an anatomical atlas shows that many acupuncture points correspond with the points at which small nerve bundles penetrate the fascia; Chan (1984) cites two Chinese studies which showed that 309 acupuncture points are situated on or very close to nerves, while a further 286 are on or very close to major blood vessels surrounded by small nerve bundles. That sympathetic nerves may be involved was first demonstrated by Goulden (1921) who showed that acupuncture points along the sciatic nerve and its branches had a lower resistance than the surrounding skin. Yoshio (1967) has shown that Ryodoraku points have are similar. Many acupuncture points are of course deep to the skin: Melzack et al (1977) have shown that they correlate closely with Travell's "trigger points", while Liu et al. (1977) have shown that others correspond with the motor points of muscles, where the nerves enter or leave them. The kind of nerve involved is obviously the A δ or pinprick fibre.

SPINAL CORD MECHANISMS (Fig. 2)

The next question to be asked, obviously, is where and how do these two types of nerve fibre (large and small) end in the spinal cord? Fortunately recent advances in anatomy and physiology can tell us a great deal about these questions.

All nerve fibres from the skin enter the spinal cord in the dorsal root and pass towards the brain without relay, to end in *the dorsal column (gracile and cuneate) nuclei* at the junction of spinal cord and brain. However, on entry to the spinal cord, these fibres give off a branch which penetrates the grey matter of the spinal cord. Some arborisations of this branch make contact in the superficial part of the dorsal horn, probably through an interneurone which releases the inhibitory substance gamma-amino-butyric acid (GABA) (Todd and McKenzie, 1989), onto the terminals of small incoming "pain" fibres (see Brown et al., 1978). Such an anatomical arrangement would explain the GABA-mediated inhibition observed by Duggan and Foong (1985) following dorsal column stimulation (see below), which drives the segmental branches responsible for TENS backwards. It is of course well-known that these systems respond to high frequencies of stimulation. We thus have a circuit capable of explaining, at *segmental level*, the pain-relieving effects of TENS and vibration. Note that this circuit does not involve any nerve terminals which release enkephalin or other naturally-occurring morphine-like substances, and therefore the analgesia produced by segmental TENS is not reversed or antagonised by naloxone (Sjölund and Eriksson, 1979), which is a drug which blocks the effects of morphine and its naturally-occurring analogues. Naloxone is in fact a very useful tool in human pain research, because it can reveal which mechanisms of pain relief are due to morphine-like substances and which not.

pain relief by acupuncture, on the other hand, is reversed or blocked by naloxone (Mayer et al., 1977; Sjölund & Eriksson, 1979; Cheng & Pomeranz, 1980), and we must thus look for an entirely different explanation of its effects. The small myelinated skin fibres which carry the

pinprick messages to the spinal cord make their principal intraspinal contact with the large cells in the most superficial part of the spinal grey matter (Kumazawa and perl, 1978) ; from here, messages about pinprick are carried direct to the brain by long fibres in the anterior and lateral part of the white matter of the spinal cord (anterolateral funiculus, ALF in figs. 2 and 4). In the region of these large cells, there are other very small cells, called “stalked cells” (cat : Bennett et al., 1982 ; man : Abdel-Maguid and Bowsher, 1984) which suppress activity in slightly deeper cells (called “SG” in fig. 2) which receive pain fibres by releasing onto them the inhibitory transmitter enkephalin, which is a naturally-occurring morphine-like substance (Ruda et al. 1984). Branches of the “pinprick” fibres also make contact with these stalked cells, called “*Enk*” in fig. 2 (Gobel et al., 1980). The SG cells, which normally receive messages from pain fibres, send their messages through other cells deeper in the spinal cord grey matter (called SR in fig. 2) which eventually project up to the brain in the anterolateral funiculus (ALF in figs. 2 and 4). It has also been shown that stalked cells do not react to frequencies of stimulation above about 3 per second (Bowsher et al., 1968 ; Harper and Lawson, 1985), which is, of course, the maximal frequency at which acupuncture is performed. These mechanisms are quite adequate to explain the segmental mechanisms of acupuncture analgesia.

At segmental level, both high-frequency low-intensity pain-relieving stimulation (TENS) and low-frequency high-intensity pain-relieving stimulation (acupuncture) are adequately explained by the gate control theory of Melzack and Wall (1965) (Fig. 3). TENS acts by closing the gate from outside—the large touch/vibration fibres are seen as pulling the gate to from the outside, and so preventing the entry of messages in pain fibres. Segmental acupuncture through blocking the messages in pain fibres as they pass through the gate, so preventing them going beyond the gate.

However, both mechanisms of stimulation-produced pain relief also act at higher levels of the central nervous system. In order to study this, we must first examine the relevant ascending and descending pathways.

ASCENDING PATHWAYS (Fig. 4)

1. Touch fibres from the skin, carrying the kind of information generated by TENS, pass up the dorsal columns of the spinal cord to end in gracile and cuneate nuclei (not shown in fig. 4). From the dorsal column (gracile and cuneate) nuclei, further nerve fibres cross over and travel up the brainstem to reach the thalamus (VP in fig. 4), whence messages are relayed to the cerebral cortex (fig. 4, PCG) and so to consciousness. However, the medial lemniscus gives off a number of branches on the way, most notably in the midbrain. The connection in which we are most interested in the present context is to the anterior pretectal nucleus (Björkeland and Boivie, 1984 ; Rees and Roberts, 1989 a) (not shown in Fig. 4). This nucleus projects to the periaqueductal grey matter (PAG in Fig. 4) (Rees and Roberts 1989 b), and thence activates the descending inhibitory system (Fig. 5) which is discussed below.

2. Information generated by pinprick passes up the anterolateral funiculus (ALF, fig. 4) on the side opposite to that on which it enters the cord (Kuru 1949). The medial brainstem reticular formation receives the majority of the ascending fibres (Bowsher 1957). It is now known that these fibres originate from the deep grey matter of the spinal cord (SR in fig. 2)

(Kevetter et al., 1982), having been activated through the substattia gelatinosa (SG in fig. 2) by unmyelinated “pain” fibres which terminate principally in the substantia gelatinosa (Sugiura and perl, 1986), though some spinoreticular fibres also arise from the neck of the dorsal horn. A smaller component of the ascending anterolateral funiculus reaches the ventrobasal thalamus (VP in fig. 4), in company with the medial lemniscus (see above) carrying touch impulses (Bowsher 1957). This component arises principally from the tip and neck of the dorsal horn (ST in fig. 2) (Willis et al., 1979), and gives off branchess to the periaqueductal grey matter (PAG) of the midbrain in its course (Fig. 4) (Botsher 1957). Mantyh (1982) showed that this projection comes from the most superficial part of the spinal grey matter; Pechura and Liu (1986) suggested that some spino-PAG neurones also reside in the neck of the dorsal horn. It is in these areas that fine myelinated “pinprick” fibres terminate (Heimer and Wall, 1968; Rethelyi et al., 1982). Thus there exist pathways whereby pinprick information is conveyed to the PAG.

DESCENDING PATHWAYS (Fig. 5)

It was in 1964 that Tsou and Jang demonstrated that the PAG is the most effective spot in the whole central nervous system for the abolition of pain by microinjection. As the PAG was known *not* to send messages upwards to the cerebral cortex and so to consciousness, this amazing finding was conveniently ignored by Western researchers. However, in 1969 Reynolds, in the U.S.A., showed that painless surgery could be carried out on the rat during electrical stimulation of the PAG, and this led to intensive research on possible mechanisms in western laboratories. Investigations by Mayer and 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 ascending neurones carrying messages generated by painful stimuli. It is precisely the caudoventral PAG which receives the ascending spinothalamic branchess referred to in the previous section (Mantyh, 1982). Furthermore, there is evidence that there is a somatotopic (body) organisation within this part of the PAG (Soper and Melzack, 1982); this might explain why heterosegmental acupuncture cannot be obtained from *any* acupuncture point, must be applied to particular points, not necessarily within the dermatome where pain relief is to be obtained. This is perhaps best illustrated by the bodily representation in ear acupuncture points.

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 (Fig. 5). From the NRM, fibres whose transmitter substance is mainly serotonin (5-hydroxytryptamine, 5-HT in Fig. 5) descend in the dorsolateral funiculus of the spinal cord to terminate directly on the stalked enkephalin-containing interneurons in the spinal dorsal horn (Glazer and 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 (Maxwell et al. 1983; Leranath et al., 1984; Hammond et al., 1985). This could explain the “hormonal” or generalised type of acupuncture effect, as opposed to the point-to-point or neural type.

Finally, it will be recalled that the PAG receives fibres containing the naturally-occurring morphine-like substance β -endorphin (Bloom et al., 1978); these fibres descend from the

hypothalamus (Mantyh, 1982), a primitive but essential part of the forebrain concerned not only with regulation of bodily functions but also with emotion. In man, the hypothalamus is under control of the prefrontal cortex in man. It is because the pathway from hypothalamus to PAG is endorphin-containing that pain relief in man can be produced 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 et al. 1977; Richardson and Akil, 1977).

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

Thus the pathway descending from the PAG is responsible for a number of forms of stimulation-produced analgesia:

1. Via the dorsal columns and anterior pretectal nucleus (see above). This explains (i) why analgesia can be obtained when stimulation of the transected dorsal columns *above* the level of pain; and (ii) why the literature is ambivalent about the effect of naloxone on TENS and DCS: the GABA-dependent segmental mechanism is *not* naloxone-reversible because its transmitter (GABA) is *not* morphine-like but the long loop mechanism through the anterior pretectal nucleus and PAG is dependent on morphine-like transmitters and is therefore naloxone-reversible.
2. Naloxone-reversible heterosegmental acupuncture works through the spinothalamic branches projecting to PAG (Fig. 4).
3. Modulation of pain perception through the emotional or psychic state of the individual may depend on the projection from prefrontal cortex via hypothalamus to PAG.

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要 旨

1. 刺激鎮痛法 (Stimulation-produced analgesia: SPA) には、2 種類のものがある。
2. まず電気による経皮的神経刺激 (TENS)。これは高頻度、低強度の刺激で、太い低閾値有髄一次求心性神経 ($A\beta$) を賦活化する。
3. 次に鍼。これは低頻度、高強度の刺激である。小さな有髄高閾値一次求心性神経 ($A\delta$ および第 3 群の神経線維) を賦活化する。
4. 分節性作用の TENS は GABA 作働性の抑制性介在ニューロンを介して作用するため、ナロキソン可逆性はない。
5. 分節性の鍼はエンケファリン作働性の抑制性介在ニューロンを介して作用するため、ナロキソン可逆性である。
6. どちらのタイプの SPA も長い回路を通して異分節的にもはたらく。
7. TENS および脊髄後索刺激 (DCS) の場合、インパルスは脊髄後索および内側毛帯を通して上行し、中脳の水道管周囲灰白質 (PAG) に突起を出す視蓋前前核に達する。
8. また、ピン刺し刺激 (鍼) の場合、メッセージは、PAG に達する副軸索に枝を出している脊髄視床路を通して上行する。
9. PAG は、延髄の大縫線核 (NRM) を通って脊髄に (白背側索を通して) オピエート作働性の下行性突起を出しているが、そこでは侵害性刺激メッセージ伝達が、長い上行路へ伝わるのを抑制する。
10. 従って、異分節機構は、鍼および TENS の両方とも、ナロキソン可逆性である。
11. PAG、または視床下部から PAG に至る下行性抑制系のいずれかにおける植え込み電極による SPA もまた、ナロキソン可逆性である。

Fig. 1

Fig. 2

The Dorsal Horn—This graphic demonstrates the components of the dorsal horn. $A\beta$ peripheral afferents from pinprick receptors end on the marginal zone (M) cells in lamina I and send axon branches to inhibitory enkephalinergic interneurons (Enk) on the lamina I-II boundary. $A\delta$ influences also reach lamina V, where cells of origin of spinothalamic (ST) axons are situated. These cross to the other side of the spinal cord and ascend into the anterolateral funiculus (ALF) toward the ventrobasal thalamus. Polymodal nociceptors reach the spinal cord in primary afferent C fibers (C). Their SP-transmitting axons end in synaptic contact with substantia gelatinosa (SG) cells in lamina II. The C fiber terminals are contacted presynaptically by collateral branches of large low-threshold cutaneous afferents ($A\beta$), whose main branches ascend into the ipsilateral dorsal columns (DC). The SG cells also are inhibited by the Enk interneurons on the lamina I-II border, in a naloxone-reversible fashion. Enk cells can be driven by peripheral $A\delta$ afferents and by serotonergic (5-HT) fibers descending into the dorsolateral white funiculus of the spinal cord. SG neurons indirectly activate cells of origin of spinothalamic (SR) axons in laminae VII and VIII. SR axons, in company with ST fibers, ascend into the crossed ALF to end in the reticular formation and the intralaminar thalamus.

Fig. 3

Gate control.

At its simplest, the gate control theory postulates that impulses from small (pain) peripheral nerve fibres push open a gate, or door, and enter the central nervous system. The stronger the pain, the greater the force opening the gate. Opposing this are two forces tending to close the gate. The first comes from outside (i.e. the periphery) and consists of large cutaneous sensory fibres, activated, for example, by the process of "rubbing it better". The second consists of inhibitory control systems descending from the brain and activated by motivation, such that, for example, at the time of rescuing a baby from a burning house, one is unaware of the pain.

Fig. 4

Central Pain Pathways—The anterolateral funiculus (ALF) of the spinal white matter contains two kinds of long ascending fibers: spinothalamic (ST) axons, principally activated by Aδ (pinprick) peripheral afferents, and spinothalamic (SR) axons, activated mainly, but indirectly, by C (tissue damage) peripheral afferents. Above the spinal cord, ST fibers remain on the lateral border of the brain stem and, after giving off collaterals to the periaqueductal gray (PAG) in the midbrain, terminate in the ventrobasal thalamus. The ventrobasal thalamus has two parts: the ventroposterior nucleus (VP), which projects point-to-point to the first somatic sensory area in the postcentral gyrus (PCG), and the posterior group (PO) of cells, which project to the second somatic sensory area in the region of the insula and parietal operculum. In the brain stem, SR fibers swing medially and end at various levels of the reticular formation; the longest SR axons reach the intralaminar nuclei (ILN) of the thalamus. The reticular formation also projects to the ILN, which gives rise to the so-called "diffuse" thalamocortical projection. This projection reaches all areas of the neocortex, although with prefrontal predominance.

Fig. 5

Descending Control Systems—Cells in the infundibular region (INF) of the hypothalamus give rise to β-endorphin-containing axons (β-END), which pass through the periventricular gray (PVG) region in the wall of the third ventricle and end in the periaqueductal gray (PAG) region of the midbrain. This region also is innervated by ascending spinothalamic collaterals. Fibers arising from PAG cells, whose transmitter substance (?) is at present unknown, pass down the brain stem to terminate in the nucleus raphe magnus (NRM) in the midline of the reticular formation of the medulla oblongata. NRM axons, whose transmitter substance is serotonin (5-HT), descend through the dorsolateral funiculus (DLF) of the spinal white matter to activate the inhibitory enkephalinergic interneurons in the substantia gelatinosa of the spinal gray.