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# Nociceptive Pathways: Anatomy and Physiology of Nociceptive Ascending Pathways

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# Nociceptive pathways: anatomy and physiology of nociceptive ascending pathways

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In primates, the principal nociceptive pathways ascend in the anterolateral quadrant of the spinal cord. Among these, the spinothalamic tract (s.t.t.) is the best studied. Cells in Rexed's laminae I and V project to the ventro-posterolateral (v.p.l.) thalamic nucleus. Other cells in the same and deeper laminae terminate in the intralaminar complex. Spinothalamic tract cells may be nociceptive-specific or multireceptive. Those ending in v.p.l. have restricted, contralateral receptive fields, whereas those projecting to the intralaminar region often have large, bilateral receptive fields. Spinoreticular tract (s.r.t.) cells are concentrated in laminae VII and VIII and may be nociceptive. It is proposed that the s.t.t. contributes to sensory-discriminative processing of pain and that the s.t.t. and s.r.t. play a role in the motivational-affective components of pain. Alternative nociceptive pathways are the spinocervical and postsynaptic dorsal column tracts.

## 1. Nociceptive pathways and pain

Pain is a complex experience. It has several aspects, including sensory and motivational-affective components (Melzack & Casey 1968; Price & Dubner 1977). Furthermore, the sensory and other responses to painful stimuli are highly variable (Beecher 1959; Melzack 1973).

Under ordinary circumstances, painful stimuli are detected by specialized sensory receptors termed nociceptors (Sherrington 1906). The nociceptors signal to the central nervous system the occurrence of stimuli that threaten or actually produce damage. The characteristics of nociceptors in mammalian peripheral nerves have now been well described, at least for certain organs, such as the skin (Burgess & Perl 1973; Price & Dubner 1977).

The activity in nociceptive afferent fibres supplying the body surface is conveyed to the spinal cord largely by way of the dorsal roots, although some nociceptive fibres may gain access to the central nervous system by way of ventral roots (Coggeshall 1980). The information conveyed by the nociceptive afferent fibres is processed in the dorsal horn, in part by neurons of the substantia gelatinosa (Cervero & Iggo 1980). Both excitatory and inhibitory interactions are made possible by the intricate circuitry of the superficial layers of the dorsal horn (Melzack & Wall 1965). It is here that many different neurotransmitter substances, including a large assortment of peptide, biogenic amine and amino acid transmitters, are found in neuronal cell bodies and processes (Bowker *et al.* 1982; Chan-Palay & Palay 1977; Gibson *et al.* 1981; Glazer & Basbaum 1981; Hökfelt *et al.* 1976; Hunt *et al.* 1981; Knyihar *et al.* 1974; McLaughlin *et al.* 1975; Ruda *et al.* 1982). Some of these agents are undoubtedly used in the synaptic interactions involved in processing nociceptive information at the segmental level (Jessell & Iversen 1977; Melzack & Wall 1965). Other substances, including the biogenic amines serotonin and norepinephrine, are contained in the synaptic terminals of pathways descending

to the spinal cord from the brain stem; these substances are likely to be utilized by descending control systems that modify the activity in dorsal horn circuits. This modulation of the dorsal horn processing of nociceptive information may be responsible, at least in part, for the variable nature of pain and for the effectiveness of several therapeutic techniques in producing analgesia (Basbaum & Fields 1978; Mayer & Price 1976; Melzack 1973; Willis 1982).

After nociceptive information has been processed in the dorsal horn, it must be transmitted to the brain in order to activate the systems responsible for producing the sensation of pain and the motivational-affective responses that accompany the experience of pain. The transmission of this nociceptive information is probably the responsibility of several different ascending pathways originating from neurons located within the spinal cord grey matter. The axons of these neurons travel within the spinal cord white matter (although it has been suggested that there may be a multisynaptic ascending nociceptive pathway within the spinal cord grey matter), and they terminate in higher centres, including several parts of the thalamus and the brain stem reticular formation (Mehler *et al.* 1960).

The particular ascending nociceptive tracts that are most important for signalling pain may vary, depending upon the species. A description of the several pathways that are most likely to be important for nociception and pain follows, and instances where species differences appear to be significant are emphasized.

## 2. Nociceptive pathways ascending in the mammalian spinal cord

### (*a*) *Primate*

The most important nociceptive pathways in the primate spinal cord appear to ascend in the anterolateral white matter on the side contralateral to the sensory input. This statement receives support from three lines of evidence derived from clinical observations on human subjects. (1) Anterolateral cordotomies and similar lesions caused by disease processes cause analgesia on the side of the body contralateral to the lesion (Brown-Sequard 1860; Foerster & Gagel 1932; Gowers 1878; Head & Thompson 1906; Spiller 1905; Spiller & Martin 1912). (2) Pain can be perceived and be well localized to its source despite interruption of all of the ascending spinal cord pathways except those in one anterolateral quadrant (Noordenbos & Wall 1976). (3) Stimulation of axons in the anterolateral quadrant of the spinal cord in patients undergoing cordotomy may cause a sensation of pain, provided that the appropriate stimulus parameters are used (Foerster & Gagel 1932; Mayer *et al.* 1975; Sweet *et al.* 1950). These observations indicate that fibres ascending in the anterolateral quadrant of the human spinal cord are both necessary and sufficient for pain sensation.

However, participation of pathways ascending in other parts of the spinal cord white matter in nociception is not excluded, since antero-lateral cordotomies do not necessarily cause permanent analgesia. In about half of the cases reviewed by White & Sweet (1969), pain recurred at intervals of months to years after an initially successful cordotomy. A second cordotomy did not invariably restore the analgesia, and so residual intact axons of the anterolateral quadrant cannot explain the return of pain. Regeneration of nociceptive axons is likewise excluded by this observation. An alternative explanation is that other, parallel nociceptive pathways exist in the human spinal cord. These pathways may normally provide insufficient information for pain sensation, but following cordotomy there may be long-term adjustments in spinal cord function that permit these pathways to forward an adequate signal to the brain.




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The ascending nociceptive pathways in the monkey spinal cord are likely to be organized in a fashion similar to those in man. Evidence for this comes from the experiments of Yoss (1953) and of Vierck & Luck (1979), who demonstrated that anterolateral cordotomies in monkeys produce behavioural changes consistent with the development of a contralateral analgesia. Vierck & Luck re-examined their animals repeatedly over a period of months and found that the signs of analgesia produced by cordotomy, as in humans, tended to disappear with time. Thus, primates in general may have alternative nociceptive pathways, in addition to those of the anterolateral quadrant, and these alternative pathways may become more capable of transmitting information about painful stimuli after some plastic change has occurred during the months following a cordotomy.

### (*b*) *Other species*

The ascending nociceptive pathways in the spinal cords of other mammalian species may be organized differently to those of the primate. For example, cats appear to have effective nociceptive pathways in both the ventrolateral and the dorsolateral quadrants of the spinal cord (Casey *et al.* 1981; Kennard 1954), since a lesion placed in any quadrant will produce no more than a partial loss of nociceptive responsiveness. In rats and pigs, nociceptive responses are retained even after multiple, staggered hemisections of the spinal cord (Basbaum 1973; Breazile & Kitchell 1968). Thus, propriospinal systems, as well as long tracts, may participate in the neural mechanism for nociceptive responses.

## 3. Somatosensory pathways that may contribute to nociception

Electrophysiological investigations have been undertaken in several laboratories to determine which somatosensory pathways in animal subjects are likely to be nociceptive (reviewed by Willis & Coggeshall 1978). In studies on monkeys, emphasis has been placed on the spinothalamic tract, one of the somatosensory pathways ascending in the anterolateral quadrant. Some observations have also been made of the activity of spinocervical, spinomesencephalic and spinoreticular neurons in the monkey. Investigations on cats have emphasized work on dorsally-situated pathways, such as the spinocervical tract and the postsynaptic dorsal column pathway, although some studies have also been done on the spinothalamic and spinoreticular pathways, which travel in the ventrolateral quadrant. Experiments using rats have now been extended to all of these systems.

### (*a*) *Spinothalamic tract*

The spinothalamic tract (s.t.t.) in the monkey (figure 1) originates from neurons that are scattered throughout much of the grey matter of the spinal cord (Trevino *et al.* 1973; Willis *et al.* 1979). However, the s.t.t. appears to have a number of functional subdivisions, and neurons belonging to different components of the pathway tend to be concentrated in certain laminae of the cord (for terminology concerning the laminar organization of the spinal cord, see Rexed 1954).

Evidence supporting such a functional parcellation of the s.t.t. comes from anatomical experiments in which horseradish peroxidase (HRP) is injected into different parts of the monkey thalamus in areas known to received terminals of s.t.t. axons, such as the ventral posterior lateral (v.p.l.) nucleus or the central lateral (c.l.) nucleus of the intralaminar complex (figure 1*a*; Berkley 1980; Boivie 1979; Kerr 1975; Mehler *et al.* 1960). The HRP is then




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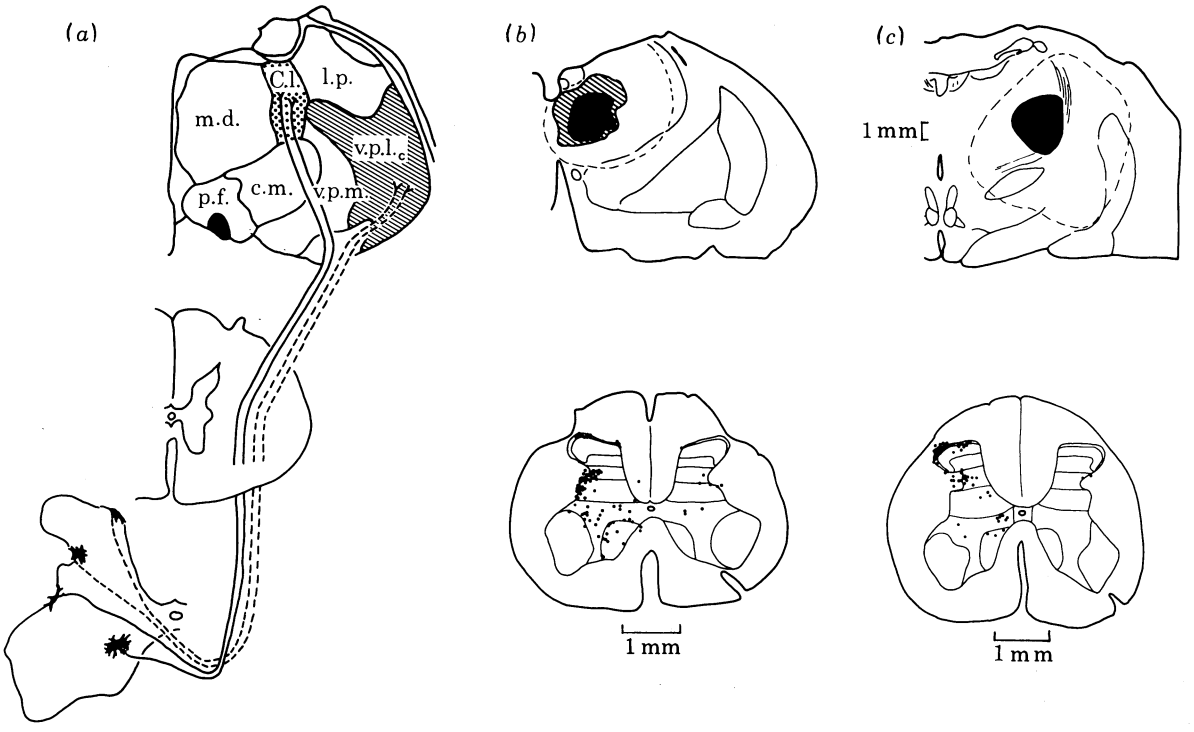


FIGURE 1. The cells of origin and course of the primate spinothalamic tract are shown schematically in (*a*). The projection to the lateral thalamus is largely from neurons of the marginal zone and neck of the dorsal horn (axons shown by dashed lines), whereas that to the medial thalamus is in part from cells of the ventral horn (axons shown by solid lines). Abbreviations of thalamic nuclei: c.l., central lateral; c.m., central medial; l.p., lateral posterior; m.d., medial dorsal; p.f., parafascicular; $v.p.l._c$, caudal part of the ventral posterior lateral; v.p.m., ventral posterior medial. Parts (*b*) and (*c*) show the results of an experimental study in which horseradish peroxidase (HRP) was injected either medially or laterally into the monkey thalamus and the distribution of the spinothalamic tract (s.t.t.) cells that were labelled by the HRP following its retrograde transport were mapped. The sites of (*b*) the medial and (*c*) the lateral injections are shown above and the locations of the s.t.t. cells below. (Parts (*b*) and (*c*) are from Willis *et al.* (1979.)

transported retrogradely to the cell bodies of the neurons giving rise to that particular spinothalamic projection, and the neurons thus labelled are then demonstrated histochemically in sections of the spinal cord. Figure 1*c* shows the distribution of s.t.t. cells projecting to the lateral part of the monkey thalamus into or near (for example the posterior medial nucleus) the v.p.l. nucleus, and figure 2*b* shows the locations of s.t.t. cells that project to medial regions of the thalamus, into the vicinity of the central lateral nucleus of the intralaminar complex. Evidently, s.t.t. neurons projecting to the region of the v.p.l. nucleus are concentrated in the uppermost layer of the dorsal horn (Rexed's lamina I) and in the neck of the dorsal horn (Rexed's lamina V), whereas a larger proportion of the s.t.t. cells that project to the medial thalamus are in more ventral parts of the spinal cord grey matter (Rexed's laminae VI–VIII). Both populations of s.t.t. cells project largely contralaterally, since more than 90% of the labelled neurons are found on the side opposite the thalamic injection (Willis *et al.* 1979).

Comparable HRP studies have been done in the cat and the rat. These investigations have revealed an interesting species difference. S.t.t. cells projecting to the lateral part of the thalamus do occur in lamina I of the cat lumbosacral enlargement, but there are few such cells in lamina V; instead, most s.t.t. cells in the cat lumbosacral enlargement are in laminae VII and VIII (Carstens & Trevino 1978). By contrast, the distribution of s.t.t. cells in the rat more closely resembles that in the monkey than that in the cat (Giesler *et al.* 1979*a*, *b*). A special projection




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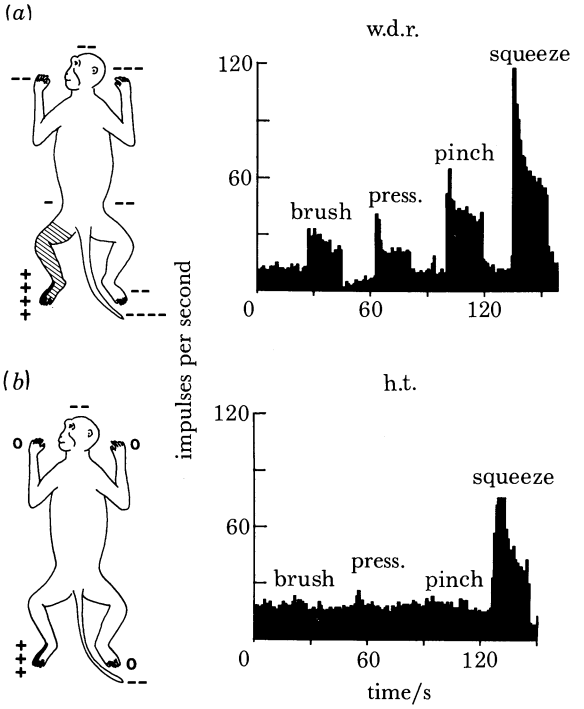


FIGURE 2. Response properties of examples of two classes of s.t.t. cells that could be activated antidromically from the v.p.l.$_c$ nucleus of the monkey thalamus. The receptive fields of the s.t.t. cells are shown at the left. Excitatory fields are indicated by plus signs and inhibitory fields by minus signs. The blackened area in each excitatory field is the most sensitive zone, and the hatched area in the upper figurine indicates a less sensitive surrounding zone. The single pass peri-stimulus time histograms at the right show the background activity of the cells and the responses to graded intensities of noxious stimulation of the excitatory receptive fields. The s.t.t. cell in (*a*) could be activated by brushing the skin with a camel's hair brush, but it was most effectively excited by squeezing the skin with forceps. Intermediate responses resulted from the application of arterial clips having different closing forces (pressure = press.; pinch). This s.t.t. neuron was classified as a 'wide-dynamic range' (w.d.r.) cell, because of its broad sensitivity to a range of stimulus intensities. Another term for such a cell would be 'multireceptive', since there must be a convergent input to the cell from both sensitive mechanoreceptors and from nociceptors onto such cells. The s.t.t. cell in (*b*) was activated only by the most intense stimulus used, squeezing with forceps. s.t.t. Neurons of this type can be called 'high threshold' (h.t.) or 'nociceptive-specific' cells. (From Willis (1981).)

has been demonstrated in the cat from cells of lamina I to the nucleus submedius, and there is a comparable projection of s.t.t. cells in the rat and monkey, although it is not yet certain if the s.t.t. cells are in lamina I in these species (Craig & Burton 1981).

There is now ample evidence to show that many s.t.t. neurons are nociceptive. Figures 2–5 demonstrate the responses of primate s.t.t. cells to noxious mechanical and thermal stimulation of the skin, noxious chemical stimulation of muscle, and noxious mechanical, thermal and chemical stimulation of a visceral structure, the testicle (Chung *et al.* 1979; Foreman *et al.* 1979; Kenshalo *et al.* 1979; Milne *et al.* 1981; Willis 1981). With respect to the effects of mechanical stimulation of the skin, s.t.t. cells may respond either exclusively to noxious intensities of stimulation (figure 2*b*) or to both innocuous and noxious intensities, with a greater excitation following noxious strengths of stimulation (figure 2*a*). It is not clear what the functional implication is of a convergent input from mechanoreceptors and nociceptors onto the same s.t.t. cell. The s.t.t. cells whose responses are illustrated in figures 2–5 all projected to the v.p.l. nucleus, as shown by antidromic activation from that nucleus (Trevino *et al.* 1973). The neurons generally have receptive fields on the side of the body contralateral to the side of the thalamus




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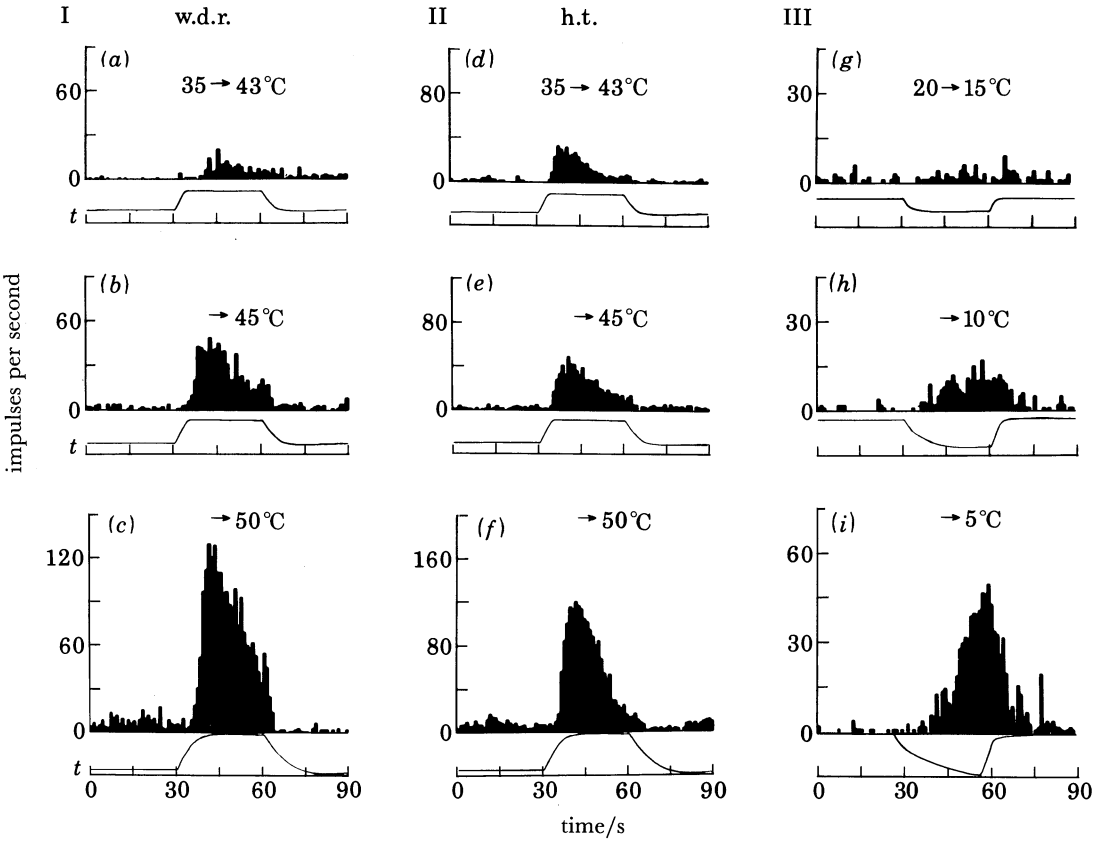


FIGURE 3. Responses of s.t.t. cells to noxious thermal stimuli. The neuron whose responses are shown in column I was a 'wide dynamic range' or 'multireceptive' s.t.t. cell. The single pass peristimulus time histograms show the responses of this cell to graded intensities of noxious heat stimuli (skin temperature in the excitatory receptive field was elevated from an adapting temperature of 35 °C to 43, 45 and 50 °C in (*a*), (*b*) and (*c*), respectively). The lower trace in each record shows the time course of the temperature change. The responses in column II were for a 'high-threshold' s.t.t. cell, with the use of the same series of noxious heat stimuli. The responses in column III were recorded from still another s.t.t. cell. In this case, noxious cold stimuli were applied to the receptive field (adapting temperature was 20 °C, and the stimuli lowered the temperature to 15, 10 and 5 °C in G–I, respectively). (I and II are from Kenshalo *et al.* (1979); III is from Willis (1983).)

to which the cell projects, and the receptive fields tend to be relatively restricted in size. Some of the same s.t.t. cells send a collateral projection to the medial thalamus, with terminals in the region of the central lateral nucleus (Giesler *et al.* 1981). Other s.t.t. cells project just to the vicinity of the central lateral nucleus. These often have very large receptive fields, and the cells are often nociceptive specific; that is, they respond to noxious but not to innocuous mechanical stimuli (Giesler *et al.* 1981). Figure 6 shows the responses of one of these medially projecting cells to the application of noxious heat stimuli to various parts of the body surface.

S.t.t. cells not only have excitatory receptive fields, but they may also have inhibitory receptive fields (Gerhart *et al.* 1981). The inhibitory receptive fields may encompass much of the surface of the body and face, and the adequate stimulus is generally a noxious one. The excitatory and inhibitory receptive fields of an s.t.t. cell are illustrated in figure 7. Inhibitory receptive fields of nociceptive neurons are of particular interest, since they may help explain certain therapeutic manoeuvres that help relieve pain, such as transcutaneous nerve stimulation and acupuncture (Chung *et al.* 1984*a*, *b*).




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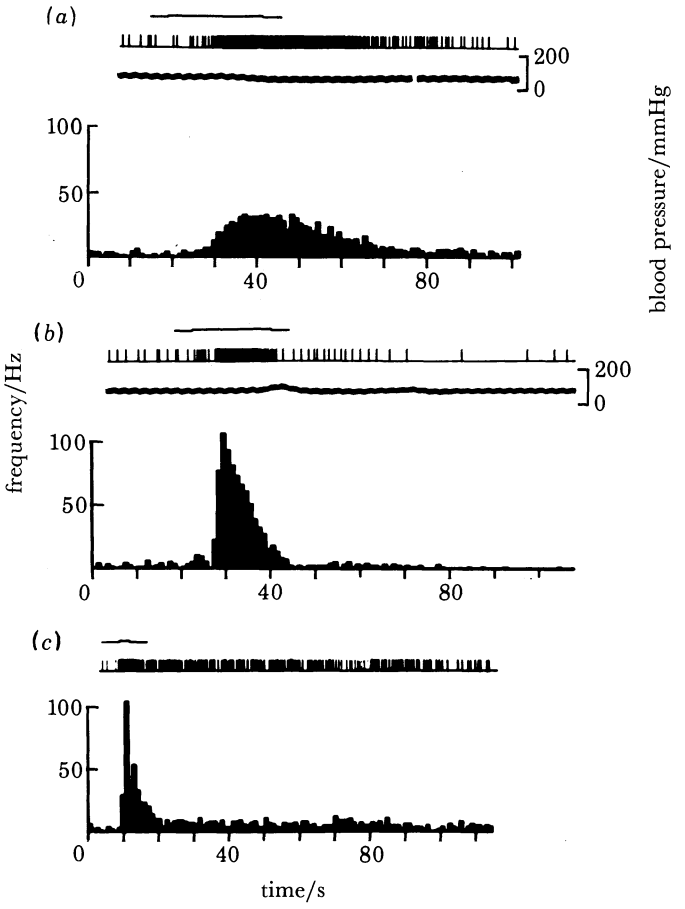


FIGURE 4. The excitation of an s.t.t. cell after activation of muscle afferent fibres by algesic chemical substances. In (*a*), bradykinin was injected intra-arterially into the circulation of the triceps surae muscles in a monkey. The pen-recorder trace and the single pass peristimulus time histogram show the enhanced discharge of an s.t.t. cell in response to this stimulus. The systemic blood pressure is also shown (1 mmHg ≈ 133.3 Pa). In (*b*), serotonin (5-HT) was injected in a similar fashion. In (*c*), hypertonic saline was injected directly into the muscle. (From Foreman *et al.* (1977).)

Nociceptive responses comparable to those just described for s.t.t. cells in the monkey have also been reported for s.t.t. cells in the cat and the rat (Craig & Kniffki 1982; Dilly *et al.* 1968; Fox *et al.* 1980; Giesler *et al.* 1976; McCreery & Bloedel 1975; Meyers & Snow 1982), and similar findings have been obtained in the monkey by other investigators (Albe-Fessard *et al.* 1974; Price *et al.* 1978).

### (*b*) *Spinoreticular tract*

A second major pathway that ascends in the anterolateral quadrant of the spinal cord and that is likely to contribute to nociception is the spinoreticular tract (figure 8*a*) (Bowsher 1957, 1961; Mehler *et al.* 1960). Although there is also a spinoreticular projection to precerebellar nuclei in the brainstem, what is meant by the term here is the projection to medial parts of the brainstem reticular formation, which in turn projects to the thalamus, especially to the intralaminar region (Bowsher 1975; Nauta & Kuypers 1958).

The cells of origin of the spinoreticular tract (s.r.t.) have been mapped by the HRP technique

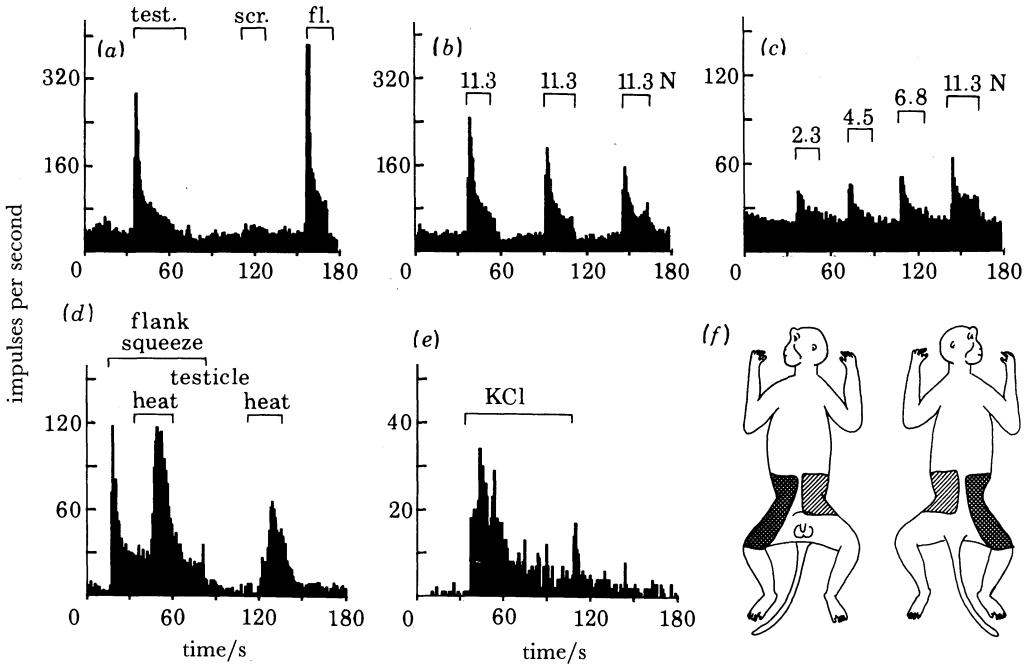


FIGURE 5. Activation of s.t.t. cells by noxious visceral stimulation. The single pass peristimulus time histogram in (*a*) shows the responses of an s.t.t. cell to compression of the testicle (test.) and to squeezing the skin over the flank (fl.) but not of the scrotum (scr.). The histogram in (*b*) shows the adaptation of the same neuron to repeated testicular compressions (11.3 N). The record in (*c*) shows the graded responses of another s.t.t. cell to progressively greater testicular compressions. (*d*) and (*e*) show the effects of squeezing the skin over the flank, noxious heating and noxious chemical stimulation (with KCl) of the testicle on another s.t.t. cell. All of the s.t.t. cells were of the 'wide dynamic range' or 'multireceptive' variety, and they were located at the T12 or L1 segmental levels. The cutaneous receptive fields of two of the cells are shown in (*f*). (From Milne *et al.* (1981).)

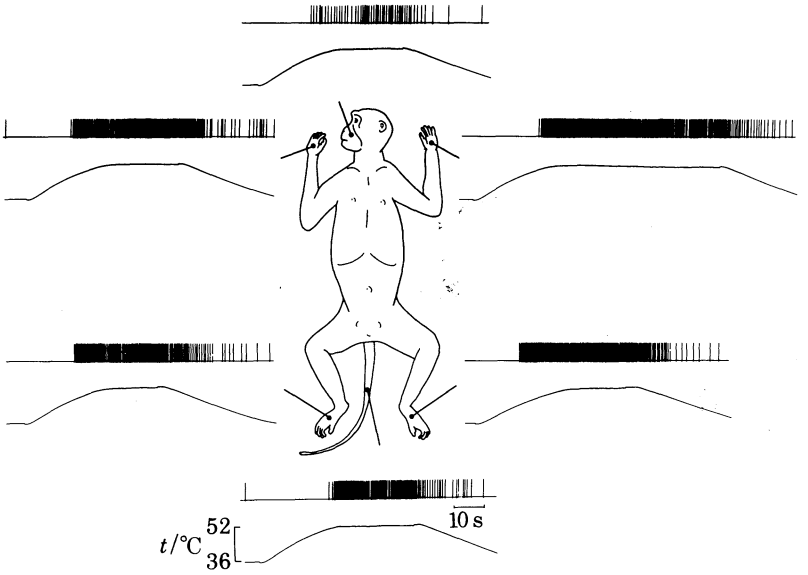


FIGURE 6. Excitation of an s.t.t. neuron that projected to the medial thalamus. The s.t.t. cell was located in the lumbosacral enlargement, and it could be activated antidromically from the region of the medial but not the lateral thalamus. The neuron could be activated when noxious heat was applied to any part of the surface of the body or face tested. The pen-recorder traces show the activity of the cell before and during noxious heating of the skin. The lower traces are the temperature recordings. (From Giesler *et al.* (1981).)




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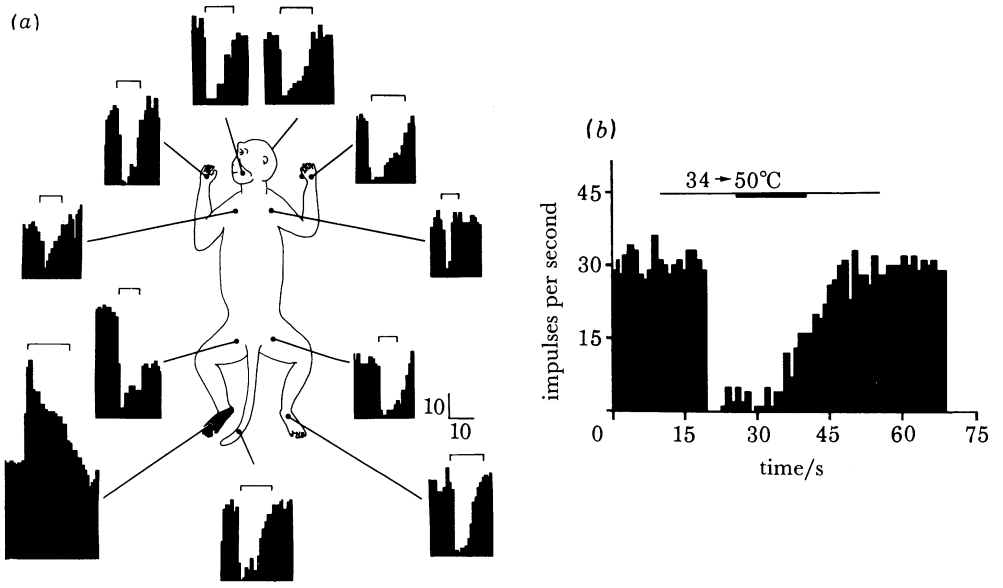


FIGURE 7. Inhibitory receptive fields of an s.t.t. neuron. In (*a*), the excitatory receptive field of a 'wide dynamic range' or 'multireceptive' s.t.t. cell is shown on the left foot (blackened area). A segment of a single-pass peristimulus time histogram shows the excitation of this cell when the skin was squeezed with forceps. The other histogram segments show the reduction in background activity that resulted from squeezing the skin at the indicated points. In (*b*), the background activity of the same neuron is shown to be inhibited when a noxious heat stimulus was applied to the right foot. (From Gerhart *et al.* (1981).)

in the monkey, cat and rat (Abols & Basbaum 1981; Chaouch *et al.* 1983; Kevetter & Willis 1983; Kevetter *et al.* 1982). The cells in all of these species tend to be concentrated in laminae VII and VIII of Rexed, although some cells are also found in more superficial layers of the cord grey matter (figure 8*b*). Many of the s.r.t. cells are ipsilateral to the site of HRP injection in the reticular formation, although others are contralateral. In the monkey, the proportions of crossed and uncrossed projections are about equal for the cervical enlargement but most of the s.r.t. cells of the lumbosacral enlargement give rise to crossed projections (Kevetter *et al.* 1982). Interestingly, some s.r.t. cells are also s.t.t. cells; that is, some spinal neurons give rise to axons that project to both the reticular formation and the thalamus (Giesler *et al.* 1981; Kevetter & Willis 1983 ).

Recordings have been made from s.r.t. neurons identified by antidromic activation in monkeys, cats and rats (Fields *et al.* 1975, 1977; Haber *et al.* 1982; Maunz *et al.* 1978; Menétrey *et al.* 1980). Many of these cells are nociceptive. However, the receptive fields are often larger and more complex than are those of s.t.t. cells. Presumably, these cells account for the nociceptive responses of neurons in the medial reticular formation (Casey 1969, 1971; Guilbaud *et al.* 1973; Wolstencroft 1964).

### (*c*) *Spinomesencephalic tract*

The spinomesencephalic tract could be regarded as a component of the s.r.t. However, there are sufficient organizational differences to warrant retention of a separate name.

The spinomesencephalic tract (s.m.t.) projects to the mesencephalic reticular formation and the lateral part of the periaqueductal grey, as well as to other sites in the midbrain (figure 9*a*; Mehler *et al.* 1960). The cells of origin of the s.m.t. have been demonstrated by the HRP

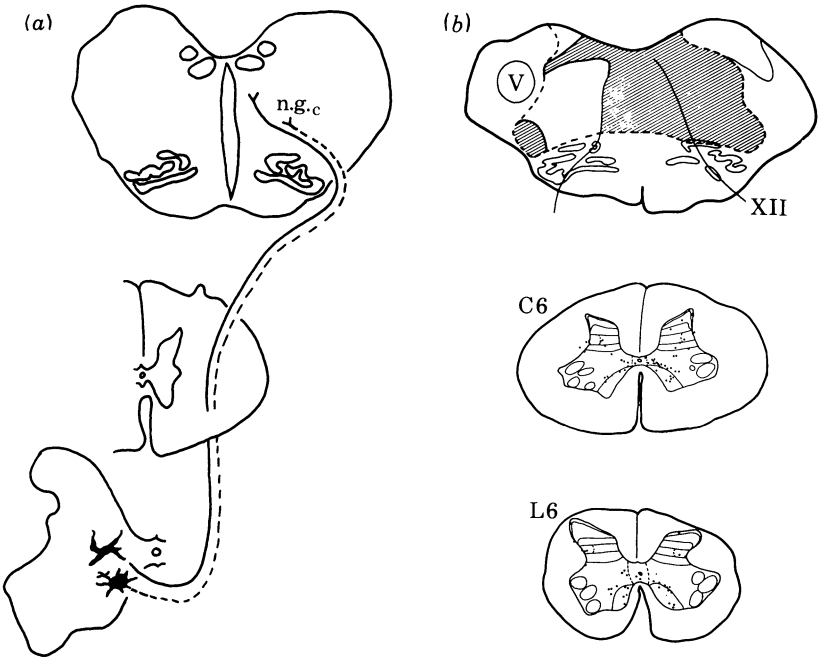


FIGURE 8. The cells of origin and the course of the primate spinoreticular tract are shown schematically in (*a*). The spinoreticular neurons are in the ventral horn (Rexed's laminae VII and VIII), and they are shown to project axons through the contralateral ventral lateral funiculus to the medial part of the medulla, with endings in such nuclei as the nucleus gigantocellularis (n.g.$_c$). However, spinoreticular neurons are also found in other spinal cord laminae, and they may project ipsilaterally as well as contralaterally. In (*b*) are shown the cells of origin of the primate spinoreticular tract as demonstrated by retrograde transport of HRP. The injection site is shown in the drawing at the top, and the distribution of the spinoreticular neurons in the cervical and lumbar enlargements in the lower drawings. The injection was a large, bilateral one, and so the laterality of the projections could not be determined in this experiment. (From Kevetter *et al.* (1982).)

technique in the monkey, cat and rat (Menétrey *et al.* 1982; Trevino 1976; Wiberg & Blomquist 1981; Willis *et al.* 1979). The cells have a distribution like that of the s.t.t. neurons that project to the lateral thalamus and not like that of s.r.t. cells projecting to the rhombencephalon (figure 9*b*). Price *et al.* (1978) were able to activate some s.t.t. cells both from the v.p.l. nucleus and from the vicinity of the lateral periaqueductal grey, suggesting a collateral projection to both of these sites.

Besides the study of Price *et al.* (1978) in the monkey, the only other investigation of the response properties of neurons of the s.m.t. done from the perspective of pain mechanisms is that of Menétrey *et al.* (1980) in the rat. Many of the s.m.t. cells observed by Menétrey *et al.* were nociceptive.

### (*d*) *Spinocervical tract*

Of the two pathways that ascend in the dorsal part of the spinal cord that are most likely to contribute to nociception, the best studied is the spinocervical tract. This pathway originates from neurons located in the dorsal horn, and it synapses in the lateral cervical nucleus, an isolated group of cells that is found just adjacent to the dorsal horn in the upper two segments of the cervical spinal cord (see reviews by Brown 1981 and by Willis & Coggeshall 1978). Neurons of the lateral cervical nucleus send their axons across the midline, where they ascend at first in the ventral funiculus of the spinal cord and then with the medial lemniscus in the




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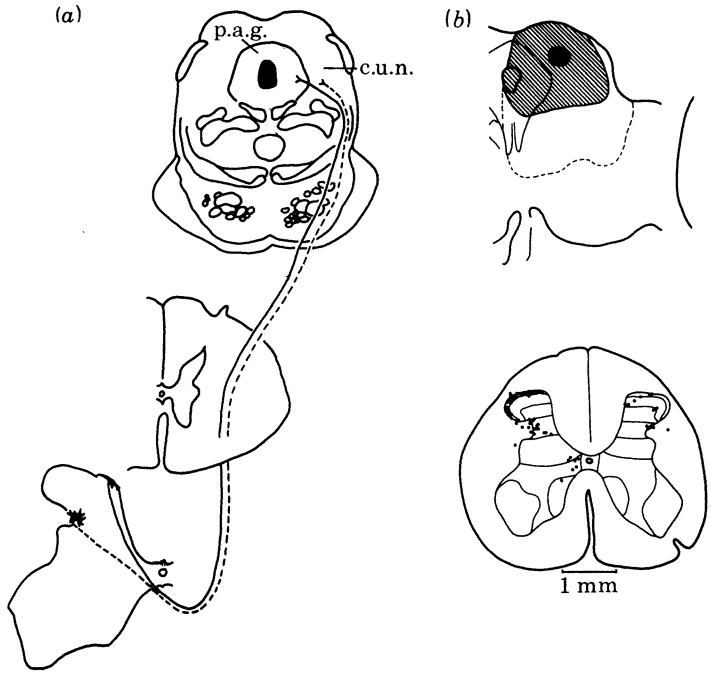


FIGURE 9. The cells of origin and the course of the primate spinomesencephalic tract are depicted schematically in (*a*). The spinomesencephalic neurons are shown to be in laminae I and V of Rexed. Their projections include the periaqueductal grey (p.a.g.) and the midbrain reticular formation (including nucleus cuneiformis, c.u.n.). The locations of spinomesencephalic neurons in the primate spinal cord as demonstrated by retrograde transport of HRP are shown in (*b*). The injection site is indicated at the top, and a plot of the distribution of the cells at the bottom. (From Willis *et al.* (1979).)

brainstem. The terminations of these axons are in the v.p.l. and posterior medial nuclei of the thalamus and in several midbrain nuclei (Berkley 1980; Blomqvist *et al.* 1978; Boivie 1970, 1980).

The cells of origin of the spinocervical tract have been demonstrated by retrograde labelling with HRP (Brown *et al.* 1980; Craig 1976, 1978). The cells are found chiefly in laminae III, IV and V.

Many spinocervical tract cells in the cat are responsive just to tactile stimuli. However, other spinocervical tract cells are activated not only by tactile but also by noxious stimuli (Brown & Franz 1969; Cervero *et al.* 1977; Kniffki *et al.* 1977). Thus the spinocervical tract in the cat may well be in part a nociceptive pathway. However, a difficulty with this hypothesis is that there has been little evidence for nociceptive responses in recordings from neurons of the lateral cervical nucleus in the cat (Craig & Tapper 1978; Horrobin 1966; cf. Giesler *et al.* 1979).

Little has been reported about the response properties of spinocervical tract cells in primates (Byran *et al.* 1974). However, there is good anatomical evidence that such a pathway exists, at least in monkeys (Boivie 1980) and probably also in man (Truex *et al.* 1965).

### (*e*) *Postsynaptic dorsal column pathway*

In addition to the well-known direct projection of primary afferent fibres to the medullary dorsal column nuclei, the dorsal funiculus of the spinal cord contains the axons of neurons whose cell bodies are located in the dorsal horn. These neurons collectively form the postsynaptic dorsal




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column pathway. They were discovered by Uddenberg (1968) and further characterized functionally by Angaut-Petit (1975). The projection is to the nuclei gracilis and cuneatus, and there is a somatotopic arrangement (Giesler *et al.* 1984; Rustioni 1973, 1974; Rustioni *et al.* 1979). The pathway has been demonstrated in the cat, rat and monkey.

The locations of the cell bodies of neurons giving rise to the postsynaptic dorsal column pathway have been mapped by the HRP technique (Bennett *et al.* 1983; Brown & Fyffe 1981; Giesler *et al.* 1984 ; Rustioni *et al.* 1979; Rustioni & Kaufman 1977). The cells are concentrated in laminae III and IV, although some are in other layers as well.

As in the case of the spinocervical tract, most neurons of the postsynaptic dorsal column pathway respond selectively to innocuous mechanical stimuli or to these and to noxious stimuli as well (Brown *et al.* 1983; Lu *et al.* 1983; Uddenberg 1968). However, a few purely nociceptive responses have also been reported (Angaut-Petit 1975).

## 4. Conclusions

The most significant nociceptive pathways in primates, including man, ascend from the spinal cord to the brain in the anterolateral quadrant. Because of this, it has been possible for neurosurgeons to alleviate pain by anterolateral cordotomy. However, cordotomies may result in only a transient analgesia, with pain recurring after some months or years. It is not clear why pain recurs, but one possible explanation is the presence of alternative nociceptive pathways that were not interrupted by the cordotomy.

The ascending tracts in the anterolateral quadrant of the spinal cord that seem most likely to mediate pain are the spinothalamic, spinoreticular and spinomesencephalic tracts. Neurons belonging to these pathways project chiefly contralaterally, and recordings in animal experiments have demonstrated the presence of nociceptive neurons among the cells of origin of all of these pathways. A reasonable working hypothesis based on electrophysiological investigations is that the sensory aspects of pain are mediated primarily by the spinothalamic tract and that the motivational-affective aspects result from activity in all three of these pathways.

Alternative nociceptive pathways include the components of these same three tracts that ascend on the side of the spinal cord ipsilateral to the area to which a noxious stimulus is applied and also several pathways that ascend in the dorsal part of the spinal cord, such as the spinocervical tract and the postsynaptic dorsal column pathway. A multisynaptic pathway through chains of interneurons is still another possibility.

In addition to activating brain mechanisms that are involved in sensing and reacting to noxious stimuli, it should be kept in mind that another role of the ascending nociceptive pathways is likely to include engagement of descending control systems that will in turn modify nociceptive transmission. A full appreciation of the detailed mechanisms of operation of these ascending and descending systems should lead not only to a better understanding of a major sensory apparatus but may also contribute further to practical applications in the sphere of pain control.

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