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Ventral Posterior Thalamic Neurons Differentially Responsive to Noxious Stimulation of the Awake Monkey

Abstract. *Of 76 cutaneously activated neurons recorded from the ventral posterior thalamus of awake, behaving monkeys, nine were weakly excited by innocuous skin stimulation and responded maximally only when noxious mechanical cutaneous stimuli were delivered within small, contralateral receptive fields. These results show that neurons capable of encoding the spatial and temporal features of noxious stimuli are located in the ventral posterior thalamus of the awake primate.*

Neurons of the ventral posterior lateral (VPL) and ventral posterior medial (VPM) nuclei of the thalamus receive somatic sensory input from the body and face, respectively, and precisely encode the location and timing of cutaneous stimuli. These ventral posterior (VP) neurons are organized somatotopically and respond to innocuous tactile stimuli such as movement of hair or light pressure on the skin (*1–3*). Little information is available, however, about the thalamic mechanisms for encoding the spatial and temporal features of noxious stimuli. Neurons recorded from the posterior group nuclei of the anesthetized cat (*4*) and the posterior ventrobasal complex of the anesthetized rat (*5*) respond exclusively or differentially to noxious stimuli, but these cells differ from the tactile VP neurons in having larger, often bilateral, receptive fields and occasionally responding to sensory stimuli of other modalities. In the primate, there is substantial anatomical and physiological evidence that spinothalamic and trigeminothalamic neurons project to VP and that a significant fraction of these projection neurons either respond exclusively to noxious stimuli (NS neurons) or have a wide dynamic range (WDR) of response that is graded in intensity as stimulus strength increases from innocuous to noxious (*6*). Nonetheless, extensive surveys of single neuron responses in the VP thalamus have failed to reveal NS or WDR neurons in either the anesthetized or unanesthetized intact monkey (*2, 3, 7*). Even when tactile input to the thalamus was markedly reduced by extensive dorsal spinal cord lesions, Perl and Whitlock (*8*) found, in the anesthetized monkey, that 52 VP neurons responded maximally to innocuous mechanical stimuli, whereas only two were exclusively nociceptive. Recently, however, Kenshalo *et al.* (*9*) found 73 NS and WDR neurons among thousands of tactile-responsive cells recorded from the VPL of monkeys anesthetized with pentobarbital and chloralose. The NS and WDR VP neurons recorded from these anesthetized animals had small contralateral receptive fields and typically responded to noxious thermal as well as mechanical cutaneous stimuli. Similar results in the anesthetized cat have been reported recently (*10*).

Although the anesthetics that have been used in studies of VP neurons do not generally depress neuronal responses to tactile stimuli, it is possible that anesthesia reduces the range of cutaneous stimuli exciting some neurons with both tactile and nociceptive inputs so that they appear to respond differentially to noxious stimuli. Small doses of pentobarbital produce this effect on medial thalamic neurons of awake squirrel monkeys (*11*). It is essential, therefore, to determine if there are nociceptive VP neurons in the awake, intact primate. Some neurons responding to pinprick have been recorded from the VPL of awake monkeys, but the proportion of such neurons and their differential responses to noxious stimuli were not documented (*12*). We recorded the differential responses of VP neurons to innocuous and noxious somatic stimuli delivered to awake, behaving squirrel monkeys.

Eight squirrel monkeys had a skull-mounted microdrive (*13*) and electronic headstage implanted during anesthesia under sterile surgical conditions. In some animals, bipolar stimulating electrodes were placed in the midbrain trajectory of the spinothalamic tract (*14*). These stimulating electrodes were used to deliver single pulses (0.2 msec, 0.1 to 1.0 mA at 1.0 Hz) to activate VP neurons not otherwise spontaneously active or not activated by continual testing of the body surface with natural somatic stimuli. The midbrain stimulation produced no obvious behavioral effect. Natural innocuous somatic stimuli included brushing the hair without touching the skin and cutaneous stimuli such as touch, pressure, tapping, and gentle squeezing of the skin. The noxious stimuli included pinching the skin with fingers or forceps, pinprick, and touching with a metal rod that had been heated to approximately 50°C. Stimuli were not sufficiently intense to produce skin damage. Noxious stimuli were used only toward the end of a study of a single neuron, were applied for 5 seconds or less, and were applied repeatedly (typically no more than five times) only when initial testing clearly suggested that the response to noxious stimulation exceeded the response to innocuous stimulation. Whenever possible, innocuous electrical stimulation was

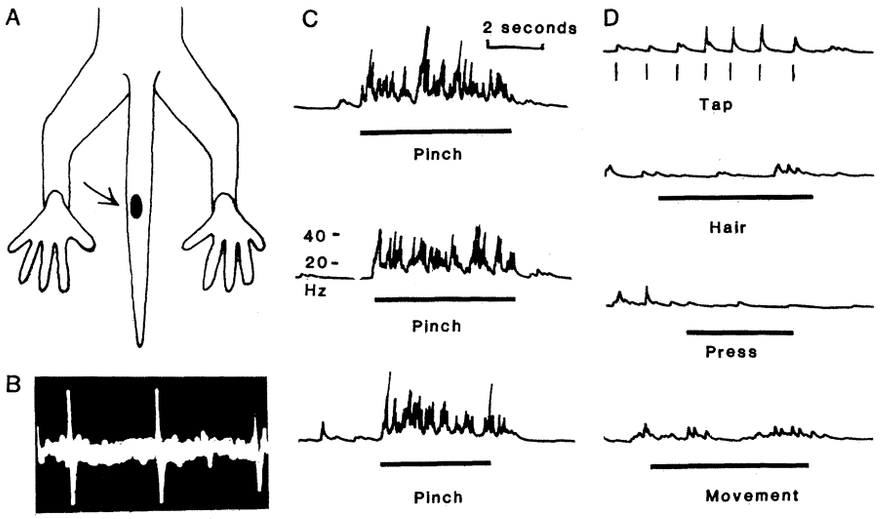

Fig. 1. Thalamic VP neuron that is differentially responsive to noxious pinch of tail skin within (A) the receptive field shown by the black spot. (B) A 100-msec sweep of spontaneous activity of this neuron (peak-to-peak action potential amplitude, 400 μV). Records of spike frequency show the maximal responses of this cell to noxious pinch (C) of sufficient intensity to elicit vigorous withdrawal movements. Records of responses to innocuous stimuli (D) show lower responses to brisk but innocuous tapping of skin, but no responses to movement of hair, light pressure on the skin, or vigorous active movement of the tail.

applied within the neuron's receptive field to determine the latency of neuronal responses.

During all testing, the monkeys were seated in a primate chair with the limbs and tail unrestrained. Each recording session was limited to approximately 2 hours. The occasional testing of noxious stimuli did not produce agitated behavior that might have interfered with the experiment. The monkey's level of consciousness ranged from aroused waking to quiet drowsiness evidenced by both behavior and electroencephalographic activity recorded from skull screws. While the monkey was quiet, receptive fields could be mapped in detail and a wide range of somatic stimuli could be tested.

The monkey's movements were detected by spring-mounting a piezoelectric device to the top of the restraining chair. The output of this device was led to one channel of a pen recorder. This arrangement allowed us to detect and record any visible movements of the head, trunk, tail, and distal parts of limbs except for the fingers and toes.

Stainless steel microelectrodes (5 to 10 megohms impedance at 300 Hz) were lowered into the VPL nucleus of the thalamus while the effect of somatic and central stimulation was tested. Extracellularly recorded action potentials that were easily discriminated from the background activity triggered electronic pulses that were led into a frequency-to-voltage converter with an output to a pen recorder. Somatic stimuli did not produce changes in the amplitude of the action potential (*11*). Recording stability was sufficient to permit the study of individual neurons for at least 2 hours.

Recording positions were marked by passing anodal d-c current (20 μA for 20 seconds) through the microelectrode. Electrode tracks were reconstructed by drawings taken from 50-μm frozen sections of the brain stained with cresyl violet.

The receptive field and adequate (maximally effective) stimulus was determined for 76 single neurons recorded from VPL and VPM. These neurons discharged irregularly at rates of 1 to 20 Hz in the absence of stimuli presented by the experimenter. In monkeys with stimulating electrodes in the midbrain spinothalamic tract, all VP neurons responsive to natural somatic stimuli were excited by central stimulation at latencies of 0.7 to 3.0 msec. Most neurons (N = 67) responded maximally to innocuous somatic stimuli such as movement of hair (N = 36) or mechanical contact with the skin (N = 29). Neurons requiring contact with the skin for activation did not respond to hair movement. Conversely, neurons responding to hair movement were not independently excited by skin stimulation. Noxious cutaneous stimulation elicited no greater response from these neurons than innocuous stimuli. All neurons had receptive fields that covered a small fraction of a limb, the tail, trunk, or face contralateral to the recording site.

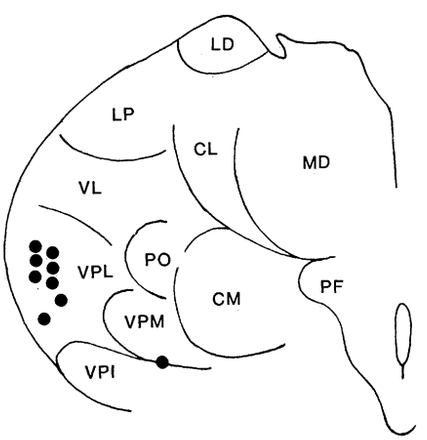

Fig. 2. Thalamic location of the nine neurons (black dots) that responded differentially to noxious mechanical stimulation of the skin. Thalamic nuclei: *CL*, centralis lateralis; *CM*, centre median; *LD*, lateralis dorsalis; *LP*, lateralis posterior; *MD*, medialis dorsalis; *PF*, parafascicularis; *PO*, pulvinar oralis; *VL*, ventralis lateralis; *VPI*, ventralis posterior inferiorus; *VPL*, ventralis posterior lateralis; *VPM*, ventralis posterior medialis.

The remaining nine neurons, all recorded from the lateral posterior part of the VPL or the ventral posterior part of the VPM, required noxious mechanical stimulation of the skin to attain maximal discharge. These cells discharged irregularly at rates of 2 to 10 Hz in the absence of applied stimuli. Innocuous mechanical stimulation of the skin evoked a low-frequency discharge from each of these neurons, but hair movement was ineffective. The most effective stimulus in each case was a strong skin pinch sufficiently intense to elicit withdrawal movements and occasionally vocalization (Fig. 1). Noxious heat was no more effective than innocuous pressure to skin.

The receptive fields of these nociceptive VP neurons were on the contralateral trunk, hindlimb, or tail and were roughly circular areas (20 to 80 mm^2) well within the size range of the receptive fields of tactile VP cells. It was not possible to test the effect of electrical stimulation within the receptive field of each neuron. Innocuous electrical stimuli delivered to the tail receptive field of one WDR cell, however, regularly evoked thalamic discharge at a latency of 17 to 19 msec. Two tactile VP neurons with receptive fields on the tail had discharge latencies of 12 to 15 msec after electrical stimulation.

Although the noxious mechanical stimuli invariably elicited movement, the movement did not elicit the neuronal discharge. Chart records of unit activity and movement showed that the neural responses preceded the movement by at least 100 msec. Furthermore, passive movements, joint manipulations, and muscle palpation did not evoke unit responses. Evoked neural activity did not

reflect the activation of central motor pathways, because active movements that occurred independent of the stimulus were not associated with unit discharge (Fig. 1D). It is unlikely that we failed to recognize neuronal activity related to active movement, because we were easily able to recognize neurons with discharges preceding limb movement in recordings from the adjacent ventrolateral (VL) thalamic nucleus. All VPL and VPM neurons we studied could be excited in the absence of movement by adequate stimulation applied only to discrete cutaneous receptive fields. The discharges of these nine VPL neurons, therefore, must signal the occurrence of noxious cutaneous mechanical stimuli. The anatomical location from which these neurons were recorded is shown in Fig. 2.

In previous studies, neurons differentially responsive to noxious stimuli have not been found in the VP thalamus of unanesthetized primates (*3, 11*). It is possible that nociceptive VP neurons were missed because of an inadequate search procedure or because of an inadequate sample size. Indeed, the report by Kenshalo *et al.* (*9*) suggests that nociceptive neurons may constitute a very small proportion of all VP cells. We found no NS neurons, but our failure may be due to our small sample of nociceptive cells and the fact that, in the awake animal, noxious stimuli cannot be applied continually while searching for neuronal responses. It is also possible that nociceptive neurons were not evenly distributed throughout the VP or that, relative to cells responding to innocuous stimuli, a higher proportion of nociceptive neurons may be found in regions dominated by spinothalamic rather than dorsal column nuclear input (*15*). The cells we recorded were in fact found in the posterior and lateral part of VP in an area described by Berkley (*15*) as receiving a relatively high proportion of spinothalamic tract fibers.

It may be significant that the WDR neurons we recorded are different from those described in recordings from medullary and spinal dorsal horn since none of the cells we recorded responded to hair movement; all required mechanical stimulation of the skin. This finding suggests that the less intensive hair-elicited discharges of spinal or medullary WDR neurons projecting in the spinothalamic tract may not produce the postsynaptic temporal and spatial summation necessary to discharge VP neurons. Additional experiments will be necessary to resolve this issue.

Neurons of the medial and intralaminar thalamus and of the posterior group of thalamic nuclei respond differentially to noxious stimuli in cats, rats, and monkeys (*4, 16*). Because these neurons typically have wide receptive fields that may include both ipsilateral and contralateral portions of the body surface, their role in pain mechanisms is uncertain. Neurons of the VPL and VPM thalamus, however, precisely encode the location and time of somatic stimuli and project specifically and somatotopically to the somatosensory cortex. This suggests that the VP nociceptive cells we have recorded could subserve the sensory-discriminative component of pain (*17*). This hypothesis would gain support if future experiments show that VP nociceptive neurons encode intensity within the noxious range and if their responses are selectively modified during analgesia produced by brain stimulation (*18*), analgesic drugs, or behavioral methods.

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Alcohol Self-Administration Disrupts Reproductive Function in Female Macaque Monkeys

Abstract. *Female macaque monkeys self-administered high doses of alcohol (2.9 to 4.4 grams per kilogram per day) for 3 to 6½ months. Amenorrhea, atrophy of the uterus, decreased ovarian mass, and significant depression of luteinizing hormone levels were associated with chronic alcohol intoxication. Reproductive system failure in female primates following self-induced dependence on alcohol parallels the results of clinical studies of alcoholic women.*

Alcoholism in women is often associated with several derangements of reproductive function, including amenorrhea, infertility, and spontaneous abortions (*1, 2*). The mechanism of amenorrhea in alcoholic women is unknown, and there are conflicting opinions as to whether reproductive system dysfunction primarily reflects toxic effects of alcohol on the ovary (*3*) or at the hypothalamic pituitary level (*1*). Moreover, since alcoholic women are often malnourished and have liver disease, it has been difficult to determine the relative contribution of alcoholism and of these related disorders to the spectrum of reproductive system derangements (*1*). Either malnutrition associated with profound weight loss (*4*) or hepatic dysfunction can disrupt menstrual cycle regularity (*1*). These clinical findings indicate that an animal model of alcoholism is necessary to systematically evaluate the effects of alcohol dose and exposure duration on female reproductive function under controlled conditions. Since the reproductive physiology of female macaque monkeys is similar to that of human females, and since the neuroendocrine regulation of primate reproductive function has been studied extensively (*5*), we chose this species to develop such a model. We found that self-induced alcohol dependence led to reproductive system dysfunction in these female monkeys.

Five sexually mature female macaques