An Inquiry into the Neurophysiological Basis for Pain*

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"Tremendous as the part is which pleasure and pain play in our psychic life, we must confess that absolutely nothing is known of their cerebral conditions. It is hard to imagine them as having special centres; it is harder still to invent peculiar forms of process in each and every centre to which these feelings may be due. And let one try as one will to represent the cerebral activity in exclusively mechanical terms, 1, for one, find it quite impossible to enumerate what seems to be the facts and yet to make no mention of the psychic side which they possess."

With these words, written in 1890, William James summarized three of the major questions regarding the physiology of pain. First, does pain involve special centers or pathways; second, does a special code or pattern of neuronal activity occur; and third, what is the influence of psychic factors on the perception of pain? This study is devoted to the first two questions, with special emphasis upon the ways in which painful stimuli might be recognized by the organism.

We chose the medial mesencephalon as the locus of recording for the following reasons. First, the anterolateral quadrant of the spinal cord projects to this area and has been recognized as important in the transmission of painful stimuli since the time of Gowers (1878), a fact frequently confirmed when anterolateral cordotomy is performed to relieve pain. Second, stimulation of the smaller fibers in the peripheral nerve results in activity in this region, and the smaller fibers are of critical importance in the perception of pain. Finally, the larger fibers of the dorsal column have been found to terminate lateral to this region, and interaction between these two systems may be important in those central events following peripheral stimuli that lead to pain perception.

In our study we have been concerned not only with the presence or absence of a response in a given unit, but in its response pattern, which may correlate with information about intensity, as increasing peripheral electrical or physiological stimuli are applied through gradations considered non-noxious to reach noxious levels.

**Methods**

**Experimental Preparation.** Adult cats, anesthetized with halothane and nitrous oxide, were paralyzed with gallamine triethiodide and artificially ventilated. Each animal was placed in a Pfeiffer stereotaxic instrument and both superficial radial nerves were isolated and placed on distal recording and proximal stimulating platinum electrodes, 10 cm apart. The nerves were cut distally to obtain a monophasic action potential and were covered with a mixture of mineral oil and petroleum jelly. A bilateral pneumothorax was performed to reduce brain movement. After a transthalamic brain section or decortication was performed, the anesthetic was discontinued. The transthalamic brain section was performed through bilateral trephines placed at Horsley-Clarke coordinates anterior 7.0 to 11.0. An adequate transthalamic brain section was determined grossly in each case when the brain was studied postmortem. Trephine sites were filled with bone wax and the skull openings for recording were filled with 4% agar, to further diminish brain movement. Blood pressure was continuously monitored throughout the experiment on a Sanborn instrument (pressure transducer model 267B, carrier pre-amplifier model 350–3000; write-out on 2-channel recording system.

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model 296) and animals undergoing decortication received blood transfusions in amounts necessary to maintain normal blood pressure and pulse rate. Body core temperature was maintained between 37° and 39°C.

Recording System. Unit responses were recorded with glass-insulated tungsten microelectrodes (tip diameter less than 1 μ), attached to a Bak unity gain pre-amplifier, and led through a Tektronix 2A61 amplifier to a Tektronix 565 dual beam oscilloscope and loudspeaker. The peripheral nerve monophasic action potentials (obtained from the cut distal end) were led through a Tektronix 122 pre-amplifier and Type 2A63 amplifier and also monitored oscilloscopically. Both unit and peripheral nerve responses were recorded on magnetic tape.

Anatomy. The region studied extended within these Horsley-Clarke coordinates: anterior 2.0 to 4.0; lateral 1.0 to 2.0; depth 2.0 to −4.0. This included periaqueductal gray and ventral tegmentum (Fig. 1). At the conclusion of the experiment either a DC current or radiofrequency current was passed through the electrode at the estimated Horsley-Clarke coordinates anterior 3.0; lateral 1.0; depth 0.0 in order to verify the electrode positions histologically. Trypan blue was then injected intravenously for easier identification of the electrode tracks and lesion. The animal was killed with an overdose of intravenous sodium pentobarbital, and the brain was perfused with 10% formalin.

Stimulation. Supramaximal trains of electric stimuli were applied at 3- to 5-sec intervals to the pads of the forepaws alternately as the electrode was being advanced down a track. Any unit responding to this stimulus was then examined, providing the spike duration was greater than 200 μsec. Stimulation was then applied to the superficial radial nerve, and recordings were obtained in the following manner: 100 consecutive 0.5-msec stimuli just above A-beta (A large), just above A-beta-gamma-delta (A large and small), and just above A + C thresholds were applied at 4.25-sec intervals. The 100 responses of the peripheral nerve and central unit at each level of stimulation were recorded on magnetic tape. Physiological stimulation was usually applied in separate experiments, but occasionally in the same experiment with the distal exposed nerve left intact. Touch and rub were considered nonnoxious, while strong electric shock, pinch, and heat were considered noxious. Pinch was applied with a hemostat, and heat was applied with a focused flood lamp. Physio-

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Fig. 1. Electrode tract shown in section at Horsley-Clarke anterior 4.0. The region of periaqueductal gray and ventral tegmentum studied is at the level of the superior colliculus and red nucleus.