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Editorial Views

The Spinal Cord Dorsal Horn

IN YEARS PAST, the spinal cord served as a testing ground for ideas concerning the mode of action of anesthetics. Anesthetic effects on synapses in reflex arcs and on motoneuron membrane properties were studied, but the brain was considered to be the primary site of anesthetic action. Then, in 1965, Melzack and Wall [1] postulated that pain may be controlled by a gating mechanism located in the dorsal horn of the spinal cord ("gate control theory"), and hinted that cells in this region might be a target of anesthetic drugs.

The pain theory of Melzack and Wall tied together the anatomic and physiologic evidence that sensory information processing begins at the first dorsal horn relay. Let's examine some of this evidence. First, a look at the dorsal horn's microanatomy.

Suitable magnification reveals that the dorsal horn has six cell layers (fig. 1). These were first described by Bror Rexed,[2] a Swedish anatomist, who observed that spinal gray matter resembles multilaminated cerebral cortex. The lamination is similar in all higher mammals. Lamina I (only recently associated with perception of pain) is a thin veil capping the dorsal part of the spinal gray matter. Laterally, the first layer (and the second and third, too) bends around the apex and extends for a short distance over the lateral side of the dorsal horn. Lamina I has small, medium and fairly large cells, which on planar view range in size from 5×8 μ to 25×30 μ.

Lamina II, while much thicker than the first layer, maintains the same spatial relationship to the dorsal horn. It consists of tightly packed, small cells measuring between 5×5 μ and 10×10 μ, with the majority somewhere in between. Laminae III and IV occupy the larger part of the head of the dorsal horn. The third layer does not bend over laterally as sharply as the second layer. Cells in lamina III are generally larger and less closely packed than those in lamina II. The smallest cells measure 5×7 μ, the majority about 8×12 μ, and the largest 12×18 μ.

The nerve cells of lamina IV give the impression of being loosely scattered through the layer. The greater number of nerve fibers and the variation in cell sizes contribute to the impression of less compactness in comparison with the third layer. Cell size varies more in lamina IV than in preceding laminae. The smallest cells are about 7×10 μ and the largest around 35×45 μ. Between these extremes are all intermediary sizes, but most cells are about 10×15 μ. The very large cells are few in comparison with the others, but they are more conspicuous because of their size, which gives a general impression of a layer with large cells.

Lamina V extends straight between the medial and lateral sides of the dorsal horn. It has fewer cells than laminae I to IV, and more and thicker nerve fibers run through it. In the lateral part of lamina V, the fiber bundles are large and numerous, giving the section a reticulated appearance. The smallest cells in lamina V are about 8×10 μ and the largest, 30×45 μ.

Lamina VI is a voluminous layer in the cervical and lumbosacral enlargements, but it is much reduced or even nonexistent in other regions of the cord. It occupies the base of the dorsal horn and has a slightly curved ventral surface. In lamina VI, the smallest cells come

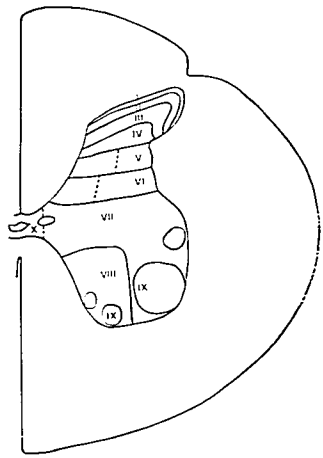

FIG. 1. Schematic drawing of the lamination of the spinal cord gray matter of the fifth lumbar segment of the adult cat. (VII–X indicate Rexed laminae outside the dorsal horn. In the main, these laminae subserve association and motor functions. From Rexed.[4])

down to 8×8 μ, but most cells are about 12×15 μ.

When a recording electrode is driven from the surface of the dorsal horn towards the ventral horn, distinct zones of electrical activity are detected. In more than half such penetrations, single unit activity is recorded when the electrode approaches the border of the gray and white matter. The spikes increase in amplitude, rapidly reach a maximum when the tip of the electrode is within lamina I, and then decrease as the tip goes into deeper layers. In laminae II and III there is relative silence. Presumably, the cells in this area are too small for microelectrode study (but we do not know whether the small cells even generate nerve impulses!). Deeper in the cord there are regions with unique properties corresponding approximately to Rexed's laminae IV, V, and VI. Cells in lamina IV have small cutaneous receptive fields and respond as though many different types of specific cutaneous afferents converge on them. Cells in lamina V respond as though many cells in lamina IV converge on them. The latency of response of lamina VI cells to peripheral stimulation is slightly longer than that of lamina V cells. But receptor modalities of lamina VI cells differ from the modalities of lamina IV and lamina V cells.

Anatomically, lamina II and lamina III cells relate closely to arriving cutaneous afferent fibers and to dendrites of deeper-lying cells. The intimate association of cells in laminae II and III with afferent terminals and dendrites from deeper layers hints at extensive presynaptic control over afferent impulses. Thus, we come back to the pain theory of Melzack and Wall.

This theory asserts that a "gate" in the dorsal horn governs the flow of messages from sensory nerves to spinal pathways. According to the theory, tactile stimulation (hair movement, light touch, etc.) causes laminae II and III (substantia gelatinosa) neurons to depolarize the terminals of small fibers that transmit pain signals. When depolarized, the terminals cannot relay impulses carried by their axons to the cord on to the brain—*the spinal gate is closed!* In the absence of obvious stimulation, the gate is relatively open. Impulses that pass through the gate bombard trigger (T) cells, which project the signals on to higher CNS structures. Originally, Melzack and Wall placed the T cells in lamina IV, but they now locate them in lamina V. Perhaps T cells are in both laminae, for both project to pain pathways.

Investigators quickly realized that whether or not Melzack and Wall's pain theory held, the sum of the spinal cord's dorsal horn anatomy and its cells' physiologic properties indicated that this area is a potentially important target of general anesthetic agents. Extracellular recording techniques (such as described by Kitahata *et al.* in this issue) were used to examine this tenet. Anesthetic-induced changes in cell firing were taken to reflect changes in the functional state of synapses linking dorsal horn cells to primary afferents. All general anesthetics tested—halothane, ether, N_2O, thiopental, pentobarbital—depressed both spontaneous and evoked discharges of neurons in laminae IV, V and VI. (Little physiologic information about lamina I cells at hand;

they were not studied.) Lamina V neurons were usually the most severely depressed. The depression was time- and dose-dependent, could be demonstrated in several animal species, and paralleled the clinical course of anesthesia. Analgesic agents such as morphine, in contrast, had little or no effect on dorsal horn structures (unpublished observations).

What is the significance of these findings in relation to anesthesia—after all, a patient with high spinal section can be fully alert. If it is accepted that all primary afferent relays in the nonspecific core of the central nervous system —brain *and* spinal cord—are subject to gate control (and there is evidence that this is so), it is plausible that some or all general anesthetics keep pain signals from the brain by diffusely shutting down primary relays.

At the very least, the findings may open the way to better understanding of integrative processes in the CNS. Such an understanding is needed to determine the validity of using physical means such as acupuncture for controlling pain. Already a "two-gate" hypothesis has been put forth to explain how acupuncture works,[3] and variations on this theme are sure to follow.

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Obstetrics

KETAMINE FOR DELIVERY Ketamine was studied in 14 pregnant subjects and 18 nonpregnant controls. Approximate clearances calculated indicated reduced clearance in pregnant subjects. Side-effects included 30–40 per cent increases in systolic and diastolic blood pressures, increases in pulse rates and respiration, salivation, and nausea, and vivid but usually pleasant dreams. Although fetal *p*H decreased slightly after induction of anesthesia, it remained in the normal range, along with P_{CO_2} and P_{O_2}. Intrauterine tone increased, and there were changes in fetal heart rate, but none that could not have been attributed to advancing labor. The first five pregnant patients (high-dose) received 2.2 mg/kg/min. The mean induction-to-delivery interval was 26.6 minutes. The last nine pregnant patients (low-dose) received 1.5 mg/kg, followed by continuous infusion of 0.08 mg/kg/min. The mean induction-to-delivery interval time was 17.7 minutes. Of the five high-dose patients, two became apneic and needed positive-pressure breathing. Four of five infants delivered of mothers who received the high dose had one-minute Apgar scores of 2 to 4. Four of the nine infants of mothers who received the low dose had one-minute Apgar scores of 1 to 6. An unaccountable increase in the infant serum bilirubin concentration was found. Mothers and babies were all discharged from the hospital at the expected time postpartum, in apparent good health. Additional detailed studies are needed before the drug can be recommended as an obstetric anesthetic agent. (*Little, B., and others: Study of Ketamine as an Obstetric Anesthetic Agent, Am. J. Obstet. Gynecol. 113: 247–260, 1972.*)