

# Suppression of Impulse Transmission in the Cat's Dorsal Horn by Inhalation Anesthetics

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Effects of halothane and nitrous oxide on impulse transmission through the dorsal horn were tested in decerebrate cats. Unit discharge rates of dorsal horn (lamina IV) neurons at rest and during maximal natural stimulation (stroking of skin hairs) were recorded with extracellular microelectrodes. Halothane inhibited these discharge rates in dose- and time-related fashion, depressing spontaneous activity slightly more and sooner than the response to tactile stimulation. Nitrous oxide had little effect on neuronal firing rates. These findings agree with earlier observations in spinal cats, and point to suppression of impulses of cutaneous origin in the dorsal horn as one means whereby general anesthetics may obtund sensation. (Key words: Theories of anesthesia; Spinal cord; Dorsal horn; Halothane; Nitrous oxide.)

ON THEIR WAY to the brain, impulses from the skin traverse the dorsal portion of the spinal cord. Early in the journey, impulses destined to travel the extralemniscal route encounter one or more synaptic crossings in the grey matter of the dorsal horn. Recently we showed this synaptic region to be readily depressed by halothane.<sup>1</sup>

In that study we transected the cervical spinal cord to render the animal unaware of pain. But transection, whatever the level, is

bound to alter the normal cohesive functioning of the central nervous system and so could possibly modify the response to anesthetics. To evaluate the latter we repeated the experiments in decerebrate cats, leaving midbrain and hindbrain connections to the cord intact.

## Methods

**Preparation.** Thirty-four healthy cats (average weight 4.1 kg) anesthetized with nitrous oxide and halothane were decerebrated. Insensibility assured, anesthesia was discontinued and the lungs ventilated mechanically with oxygen so as to keep the end-expiratory CO<sub>2</sub> tension at 4.0 ± 0.2 per cent. We replaced fluid losses with 5 per cent glucose in lactated Ringer's solution and large blood losses with heparinized cat blood or dextran. Esophageal temperature was kept near 38 C with a warming blanket. When needed, a 10-mg dose of gallamine prevented reflex muscle contraction.

After immobilization of the vertebral column in a rigid frame, the spinal cord was exposed through a wide lumbar laminectomy. The dura was slit longitudinally and the pia-arachnoid overlying the left fifth lumbar segment carefully teased apart. A warm gel of agar in saline solution poured over the cord prevented cooling and drying.

A metal-filled microelectrode, the tip plated with a 2- to 4- $\mu$  diameter ball of platinum black<sup>2</sup> and having an impedance of about 250 kOhm at 1 kHz, was mounted on a hydraulic micro-drive. The electrode was inserted into the dorsal horn at a location halfway between the midline of the cord and the entrance zone of the fifth lumbar dorsal root. The extracellularly recorded action potentials were amplified and monitored conventionally. An electronic gate passed only signals between preselected upper and lower voltage limits, counted

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their rate per second, printed the count, and displayed the shaped impulses as bright dots on the oscilloscope.

Correlation between position of the electrode tip in the dorsal horn and electrical events is so good that we elected to rely on physiologic responses for localization.<sup>3-6</sup> As described before,<sup>1</sup> progress of the electrode through dorsal column axons and into the grey matter of the dorsal horn can be gauged by the waveforms and firing patterns of the various neural elements. Units in the midportion of the lumbar dorsal horn (corresponding to Rexed's lamina IV) have a small cutaneous receptive field on the foot or ankle, fire spontaneously at a slow and irregular rate, are driven by light touch or puffs of air, and respond maximally with little accommodation when skin hairs are stroked. Rarely, in these decerebrate cats, did pinching the skin cause more rapid firing than stroking; in fact, the converse was more often the case.

Control records of the spontaneous firing rate of the cell and of the maximal response to natural stimulation of the skin were made at intervals for 15 to 30 minutes. One or two per cent halothane vapor in oxygen or 80 per cent nitrous oxide with oxygen was then delivered to the inspiratory side of the nonrebreathing system. The spontaneous and maximally stimulated firing rates were recorded every minute for the first five minutes and at least every five minutes thereafter.

Anesthetic administration was discontinued either when the cell stopped firing or after 30 or 60 minutes of exposure to the anesthetic. The spontaneous and maximally stimulated firing rates, with appropriate rest periods between, were recorded until the unit recovered or until no further changes were observed. Contact with the cell often dropped off during recovery and could not always be restored by repositioning the electrode.

## Results

### CONTROLS

The mean control systolic pressure was 124.5, diastolic 91.1, torr. Mean electrode depth at the start of recording was 1,375  $\mu$  below the dorsal cord surface. At this depth, dorsal horn neurons fired spontaneously at an

irregular rate of 9.7 discharges/sec on the average (range 0 to 26). The maximal response of the neuron, at a mean rate of 53.0 discharges/sec (range 16 to 150), was elicited by stroking of skin hairs. The receptive field on the skin of the foot was small and irregularly shaped, so we were unable to delineate precisely the regions of greater and lesser excitability within it.

### HALOTHANE

*Administration.* Quantitative differences between the cells at rest and when the skin was stimulated were observed. Their spontaneous activity was depressed faster and more profoundly than the response to tactile cutaneous stimulation during administration of 1 or 2 per cent halothane. Figures 1 and 2 summarize the findings. Observe the brief initial rise in rate of discharge and the subsequent decrease, becoming more profound the longer halothane was administered. Note further that the firing of unstimulated neurons tended to accelerate during the first few minutes of halothane, whereas the discharge rate of cells responding maximally to cutaneous stimulation did not increase.

These figures, representing averaged results, do not tell the full story, however. In twelve of 31 cells 2 per cent halothane completely suppressed spontaneous firing in less than 15 minutes, whereas it fully suppressed the response to tactile stimulation in only 15 of 29 cells in that period.

In five experiments, the arterial concentration of halothane rose from an average of 0.02 per cent just before, to 0.93 per cent at five minutes, and to 1.09 per cent at ten minutes after addition of 2 per cent halothane to the inflowing gas.

*Recovery.* Difficulties in maintaining electrical contact during recovery notwithstanding, return of the firing rates towards control values was documented for the majority of cells in the crucial first few minutes. Statistically relevant data were obtained for recovery from the effects of 2 per cent halothane and are shown in figure 3. Observe the quick rally, especially of the more severely depressed response to tactile stimulation, with near-normal responses restored within 15 minutes.

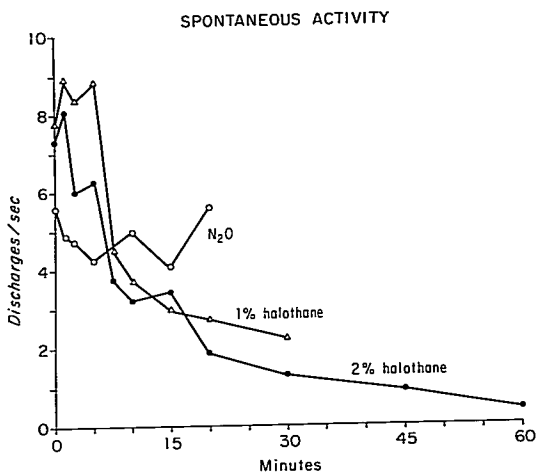


FIG. 1. Effects of halothane and nitrous oxide on mean discharge rate of spontaneously firing dorsal horn cells. Points represent averages of five to 31 experiments.

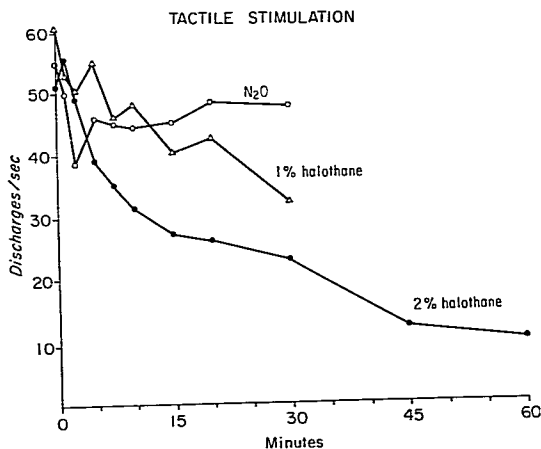


FIG. 2. Effects of halothane and nitrous oxide on mean discharge rate of dorsal horn cells responding maximally to stroking of skin hairs. Points represent averages of five to 18 experiments.

**Blood Pressure.** Adding 1 or 2 per cent halothane to the ventilating gas lowered the arterial blood pressure. The rate of fall was steepest in the first 5 to 10 minutes, then

leveled off to stabilize at 15 to 20 minutes. The average systolic pressures were 77 and 57 per cent of control values after 30 minutes of 1 and 2 per cent halothane, respectively.

Mean arterial pressures of animals ventilated with 2 per cent halothane in oxygen are shown in figure 4 (left).

Arterial pressure recovered rapidly, particularly after 1 per cent halothane, with 95 per cent or better recovery in 15 minutes. Recovery from the effects of 2 per cent halothane, especially if administered for 30 minutes or longer, tended to be slower and more gradual (fig. 4, right), with 95 per cent return to normal pressure after 45 minutes. In two cats the pressures did not rise above 60 per cent of control values.

#### NITROUS OXIDE

**Administration.** Unlike halothane, which has profound depressant effects, nitrous oxide caused little deviation from normal discharge rates and firing patterns of dorsal horn cells. After a brief initial period of moderately reduced activity, cells soon regained most of the ability to fire spontaneously and to increase the rate of discharge when skin hairs were stroked (figs. 1 and 2).

**Recovery.** Normal discharge rates and patterns were restored within 7½ minutes after discontinuation of nitrous oxide.

**Blood Pressure.** Systolic blood pressure, too, reacted differently to nitrous oxide than to halothane, rising to a maximum of 119 per cent of control value at five minutes, then falling slightly to a plateau of 110 per cent of control value. Blood pressure recovered from the effects of nitrous oxide equally promptly, returning to near-control values within 2½ minutes.

#### Discussion

Recent work by Wall,<sup>7</sup> Galindo,<sup>8</sup> Kitahata *et al.*,<sup>9</sup> and our own work<sup>1</sup> have demonstrated the pronounced depressant effects of general anesthetics on components of the cutaneous afferent pathways. The present investigation has built on that experience, seeking information about events with the greater portion of the CNS left intact.

In brief, we found that halothane suppresses the transmission of tactile impulses in the dorsal horn of decerebrate cats. This suppression was dose- and time-dependent, and was reversed upon discontinuation of halo-

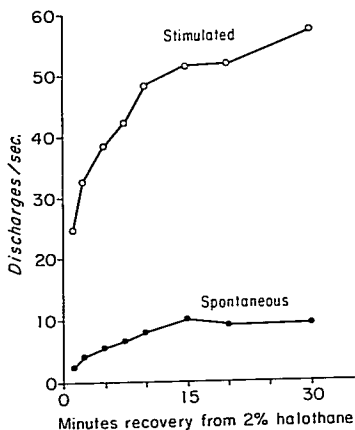


FIG. 3. Recovery from the depressant effects of 2 per cent halothane. Mean discharge rates of spontaneously firing and maximally excited dorsal horn cells are compared. Points represent averages of eight to 14 experiments.

thane. Nitrous oxide, conversely, had little effect on the firing rate of dorsal horn neurons, whether the latter were discharging spontaneously or responding to stroking of skin hairs.

Were the results due to the central actions of halothane? We think so, for we eliminated most factors known to affect neuronal performance.<sup>9, 10</sup> Further, we believe that halothane-induced hypotension contributed little to neuronal depression, as the time courses of the two events were altogether dissimilar. More directly, even when the cardiovascular actions of halothane are bypassed, the anesthetic still depresses synaptic transmission.<sup>9</sup> Last, other afferent cells, those responding to joint movement, for instance, continue to discharge at near-normal rates during halothane-induced hypotension.<sup>1, 11</sup>

The findings presented here are similar to those reported earlier in studies of spinal cats<sup>1</sup> and decerebrate monkeys.<sup>11</sup> Nevertheless, some dissimilarities which could bear on the mode of action of anesthetics have come to light. We attribute them to experimental and species differences, as discussed below.

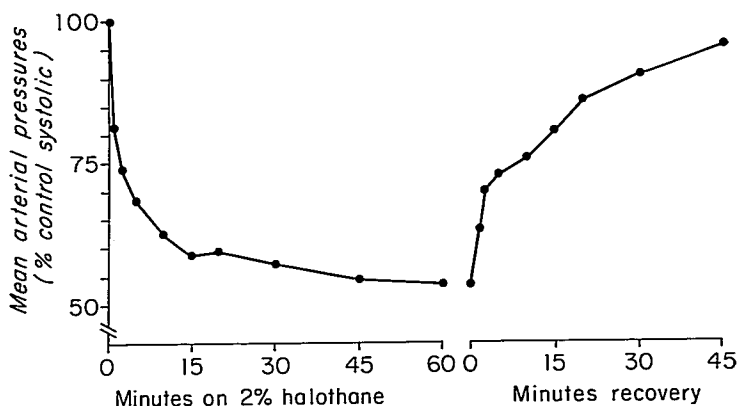


FIG. 4. Effects of 2 per cent halothane on mean systolic arterial pressure and subsequent recovery. Points represent averages of 11 to 23 experiments.

Discrimination between tactile and noxious stimuli was one function where spinal and decerebrate cats clearly differed. In spinal cats noxious stimulation (pinching a fold of skin) raised the firing rate of dorsal horn cells notably more than tactile stimulation (stroking of hairs). In decerebrate cats, conversely, tactile stimulation produced as intense a reaction as noxious stimulation. The response range to inputs of varying intensity evidently was greater in spinal cats, possibly for want of supraspinal restraint over dorsal horn relays. These findings are in line with studies that show inhibition of dorsal horn neurons along bulbospinal pathways and release from inhibition when the cord is isolated from the hindbrain by cooling.<sup>6</sup>

The excitability of dorsal horn neurons is influenced measurably by descending supraspinal impulses.<sup>6, 12, 13</sup> Since pentobarbital (Nembutal) enhances supraspinal inhibitory control over dorsal horn neurons,<sup>13</sup> we wondered whether inhalation anesthetics likewise would inhibit dorsal horn transmission more profoundly in animals with hindbrain and midbrain intact than in spinal animals. As shown, this was not the case. If anything, the

depressant effect was somewhat less in decerebrate than in spinal cats. From this we conclude that the observed effects of inhalation anesthetics on afferent transmission are attributable in the main to direct intraspinal drug action. This conclusion is supported by Galindo's work on cuneate neurons, demonstrating locally mediated inhibition in the course of perfusion with halothane.<sup>8</sup>

It is worth recalling that nitrous oxide depresses transmission of noxious but not of innocuous impulses in spinal cats.<sup>1</sup> This moderately potent analgesic evidently selectively affects certain cutaneous sensations. Halothane, conversely, appears to be less selective. One might speculate that this selectivity, or lack of it, corresponds to pharmacologic properties such as analgesia. Experiments with a potent inhalation analgesic (diethyl ether, for instance) might provide an answer.

Anatomic,<sup>14</sup> electronmicroscopic,<sup>15</sup> and physiologic<sup>16</sup> evidence speaks strongly for axodendritic and axoaxonal interaction in the region of the substantia gelatinosa of the dorsal horn. This region then suggests itself as a possible site where inhalation anesthetics might block the ascent of cutaneous impulses.

One way to visualize this action is in terms of the important interplay between impulses arriving along A-fibers and C-fibers in the dorsal horn.<sup>17</sup> Conceivably, general anesthetics, much like local anesthetics, could affect small fibers more profoundly than large fibers.<sup>18</sup>

While differences between various preparations and species clearly exist, similarities, nevertheless, are more striking. In fact, studies of long-term electrode-implanted rats show surprisingly little difference in dorsal horn activity on comparison of high spinal and intact animals.<sup>19</sup> Our experiments on spinal and decerebrate cats thus may be expected to yield qualitatively similar results in intact animals.

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### Drugs

**TETANUS** A syndrome of hyperactivity of the sympathetic nervous system has been found in patients who have severe tetanus. Chlorpromazine did not provide satisfactory control, and general anesthesia for a prolonged period was thought to be too toxic. A combination of propranolol and bethanidine (action at postganglionic nerve endings) was used in three patients to block adrenergic effector mechanisms, and proved successful in controlling the hypertension, tachycardia, and cardiac dysrhythmias. (*Prys-Roberts, C., and others: Treatment of Sympathetic Overactivity in Tetanus, Lancet* 1: 542 (March) 1969.)