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Halothane Suppression of Spinal Sensory Neuronal Responses to Noxious Peripheral Stimuli Is Mediated, in Part, by Both $GABA_A$ and Glycine Receptor Systems

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Background: **A major effect of general anesthesia is lack of response in the presence of a noxious stimulus. Anesthetic depression of spinal sensory neuronal responses to noxious stimuli is likely to contribute to that essential general anesthetic action. The authors tested the hypothesis that γ-aminobutyric acid receptor type A ($GABA_A$) and strychnine-sensitive glycine receptor systems mediate halothane depression of spinal sensory neuronal responses to noxious stimuli.**

Methods: **Extracellular activity of single spinal dorsal horn wide dynamic range (WDR) neurons was recorded in decerebrate, spinal cord transected rats. Neuronal responses to noxious (thermal and mechanical) and nonnoxious stimuli were examined in the drug-free state. Subsequently, cumulative doses (0.1–2.0 mg/kg) of bicuculline ($GABA_A$ antagonist) or strychnine (glycine antagonist) were administered intravenously in the absence or presence of 1 minimum alveolar concentration (MAC) of halothane.**

Results: **Halothane, 1.1%, depressed the response of WDR neurons to both forms of noxious stimuli. Antagonists, by themselves, had no effect on noxiously evoked activity. However, bicuculline and strychnine (maximum cumulative dose, 2.0 mg/kg) partially but significantly reversed the halothane depression of noxiously evoked activity. Similar results were seen with most, but not all, forms of nonnoxiously evoked activity. In the absence of halothane, strychnine significantly increased neuronal responses to low threshold receptive field brushing.**

Conclusion: **Halothane depression of spinal WDR neuronal responses to noxious and most nonnoxious stimuli is mediated, in part, by $GABA_A$ and strychnine-sensitive glycine systems. A spinal source of glycine tonically inhibits some forms of low threshold input to WDR neurons.**

THE ability of general anesthetic agents to depress the responses of spinal sensory neurons to noxious peripheral receptive field (RF) stimulation is likely to contribute to anesthetic depression of movement to a noxious stimulus (immobility) and to a reduction of sensory messages sent to supraspinal regions of the central nervous system (CNS; analgesia). Cutaneous nociceptors synapse exclusively within the spinal dorsal horn[1–4] and communicate with the CNS as a result of that initial synapse with spinal second order neurons.[5] Spinal sensory neurons, therefore, are the only pathway through which the majority of information about a noxious somatic stimulus may be processed to initiate a reflex response or a sensation.

Anesthetic-induced immobility in the presence of a noxious stimulus is the result of, mainly, anesthetic actions at the level of the spinal cord,[6–9] and it has been reported recently that isoflurane acts in the spinal cord to blunt the transmission of noxious inputs to the thalamus and cerebral cortex.[10,11] It is therefore likely that anesthetic depression of spinal sensory neuronal responses to noxious peripheral stimuli contributes to anesthetic-induced immobility in the presence of a noxious stimulus and to reduced transmission of noxious information to supraspinal regions of the CNS.

Halothane has been shown to suppress noxiously evoked activity of neurons in the spinal cord,[12,13] including wide dynamic range (WDR) neurons[14] that play a central role in spinal transmission of nociceptive information. Gamma-aminobutyric acid receptor type A ($GABA_A$) and glycine receptor systems are thought to be the major inhibitory systems in the CNS. The spinal cord contains $GABA_A$ and glycine receptors,[15,16] and volatile anesthetic agents enhance currents at $GABA_A$ and glycine receptors[17–21] in a way that is thought to be important to the production of general anesthesia.[22,23] Inhibition of $GABA_A$ and strychnine-sensitive glycine systems has been shown to antagonize halothane effects in several model systems,[24–28] resulting in a hypothesis that halothane depression of spinal WDR neuronal responses to noxious thermal stimulation of peripheral receptive fields is mediated, in part, by $GABA_A$ or glycine receptor systems. The primary purpose of this study was to examine the effects of $GABA_A$ or glycine receptor antagonists on halothane depression of noxiously evoked activity of spinal WDR neurons. We also examined drug effects on the responses of WDR neurons to nonnoxious receptive field stimulation.

Materials and Methods

Surgical Preparation

The protocol was approved by the Yale University Institutional Animal Care and Use Committee. Male Sprague-Dawley (Harlan Sprague-Dawley, Inc., Indianap-

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olis, IN) rats (weight, 350–450 g) were used in these studies. Anesthesia for surgical preparation of the animals was induced by 4% halothane in 100% oxygen. After loss of the righting reflex, anesthesia was maintained by 2 to 3% halothane in 100% oxygen delivered through a tightly fitting mask. The left external jugular vein and carotid artery were cannulated to allow for drug and fluid administration and blood pressure monitoring, respectively. After tracheostomy, the trachea was intubated, and animals were mechanically ventilated. Animals were paralyzed with intravenous doses of pancuronium bromide, 0.2 mg, to avoid motor activity that could result from noxious stimulation in the presence of bicuculline or strychnine. End-tidal P_{CO_2} and rectal temperature were monitored and maintained within physiologic ranges. End-tidal halothane concentrations were also monitored (MULTINEX, Datascope Co., Montvale, NJ). Decerebration by aspiration of cranial contents rostral to the mesencephalon allowed us to discontinue halothane anesthesia. The spinal cord was transected at T2–T3 *via* a small laminectomy to eliminate descending modulatory influences on the neurons under study. The lumbar spinal cord (L2–L5) was exposed by a separate laminectomy. The dura of the lumbar spinal cord was opened and retracted to form a well that was filled with mineral oil.

Data Collection

For the recording of single unit activity, a tungsten microelectrode (impedance 10 Mohm, FHC Inc., Brunswick, ME) was inserted using a hydraulic micromanipulator into the lumbar enlargement of the dorsal horn of the spinal cord until activity of a single neuron could be isolated and distinguished from background activity. WDR neurons were identified by the depth of the microelectrode (about 500–1000 μm from surface of the dorsal surface of the spinal cord) and by their characteristic response profiles. WDR neurons were identified as those neurons that were excited by nonnoxious light brush, noxious pinch, and noxious radiant heat (51°C) stimulation. Traditionally, a WDR neuron is one that has an increased firing frequency to increasing stimulus intensity, with the maximum response occurring when an intense noxious stimulus is presented to the neuron's RF.

After isolation and characterization of a single WDR neuron, the baseline low threshold RF was mapped on the skin, and the responses of the neuron to all stimuli were recorded as control values. RFs were typically located on the hindquarters of the animals, usually the hip, thigh, or back. The edge of the RF area was determined as those points where light touch with a von Frey hair (5.15 g) elicited a response 50% of the time. Mechanical stimuli and radiant thermal stimuli were applied to the center of each neuron's RF. A thermocouple (diameter = 1 mm) was positioned within the receptive field to provide feedback to the stimulus controller so that the each stimulus temperature could be maintained precisely. Low-intensity stimuli included brushing the receptive field with a small artist brush 10 times with a 3-s interstimulus interval and applying radiant heat at 41°C for 4 s. Noxious stimuli included the application of noxious pinch to the center of the RF and radiant heating at 46 and 51°C. Thermal stimuli were applied to an area approximately 8 mm in diameter. A hand-held forceps with tip diameter of 3 mm was used to produce noxious mechanical pinch. The skin was pinched for 5 s while strain gauges mounted on the forceps monitored pressure. The pressure was maintained for that 5-s period at a level that was considered noxious by the experimenter when applied to his skin. Similar pressures were applied for each stimulus presentation in any one animal, but they varied between animals depending on receptive field accessibility. The action potentials evoked by each stimulus and appropriate pre- and poststimulus activity rates were recorded for subsequent off-line analysis. Only one neuron was examined in each animal to avoid cumulative effects of repeated drug administration and to maintain statistical independence among the neurons tested.

Drug Administration

The first series of drug experiments involved control studies of the effects of bicuculline ($GABA_A$ antagonist) and strychnine (glycine antagonist) (Research Biochemicals, Inc., Natick, MA) administered in the absence of halothane. Cumulative (.01, .03, 0.6, 1.0, 2.0 mg/kg) doses up to 2 mg/kg were administered intravenously. Bicuculline was dissolved in 0.01 M citric acid, and strychnine was dissolved in saline. Fresh solutions were prepared for each experiment. A maximum dose of 2 mg/kg was chosen because we previously observed peak antagonism of halothane effects at that dose.

The second series of experiments involved an examination of the ability of bicuculline and strychnine to reverse halothane-induced depression of the activity of WDR neurons evoked by receptive field stimulation. After determining control values without halothane, 1.1% halothane (1 minimum alveolar concentration [MAC] for rats) was administered. Thirty minutes later, neuronal activity was again recorded followed by the administration of cumulative doses of bicuculline or strychnine. Five minutes after each dose of antagonist, the neuron's responses to receptive field stimulation were again determined followed by the next dose of antagonist. The time between each dose was approximately 10 min. When neuronal responses were determined after the last dose of antagonist, halothane was discontinued, and animals were monitored until end-tidal halothane was 0% (approximately 15–20 min). Neuronal activity was then recorded one last time to determine the degree of recovery.

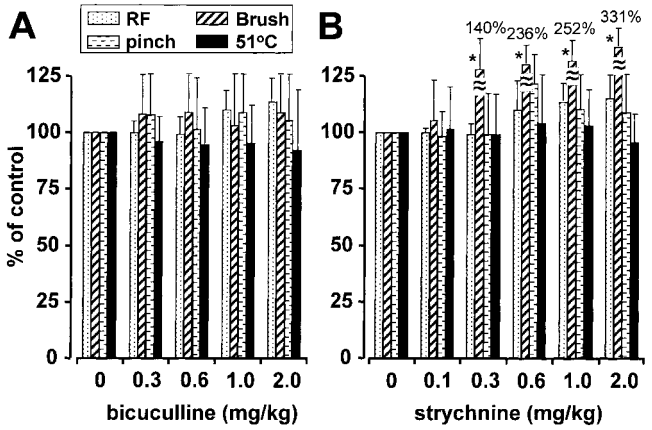

Fig. 1. Effects of bicuculline (*A*) and strychnine (*B*) on wide dynamic range (WDR) neurons in the absence of halothane are shown. Cumulative doses of intravenous bicuculline did not significantly change the mean neuronal response to receptive field stimulation by either low-intensity (receptive field [RF], brush) or noxious (pinch, 51°C) stimuli. Strychnine also failed to alter the mean response to noxious stimuli and the RF size. However, strychnine did increase the mean neuronal activity evoked by brush stimulation. Data are presented as mean ± SD. *$P < 0.05$ *versus* 0 mg/kg; (n = 9–11).

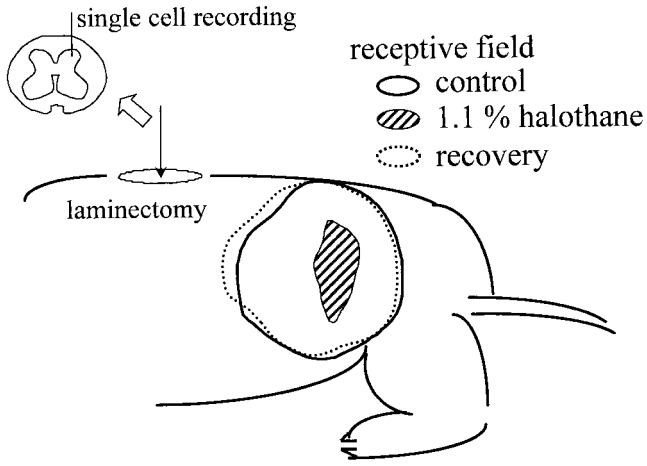

Fig. 2. A typical example of a change of receptive field (RF) size in response to halothane is shown. The RF was mapped on the skin of the hindquarter. One MAC of halothane significantly decreased the RF size to 3.5 cm^2 from the control value of 13.2 cm^2. With discontinuation of halothane inhalation, the RF recovered to the control value (13.4 cm^2).

Data Analysis

Wide dynamic range neuronal recordings, the digital output of an amplitude discriminator, and the output of the thermocouple for the radiant heat stimulator were converted to digital signals (CED 1401 plus, Cambridge Electronic Design Ltd., Cambridge, UK) and stored in a computer. All data were subsequently analyzed using the Spike 2 software program (Spike 2, Cambridge Electronic Design Ltd., Cambridge, UK). The variables were expressed as percentage of control values. Effects of drugs, dose dependence, and time course were analyzed by one-way and two-way analysis of variance (ANOVA) for repeated measures, followed by *post hoc* comparisons using Scheffé F test. Differences were determined to be significant with $P < 0.05$. All data are shown as mean ± SD.

Results

Effects of Bicuculline and Strychnine in the Absence of Halothane Anesthesia

The purpose of these control studies was to determine if either antagonist caused changes in the neuronal activity under study in the absence of halothane. As seen in figure 1, bicuculline, at a maximum cumulative dose of 2 mg/kg, produced no significant change in the mean response of the neurons to either low-intensity (RF, brush) or noxious (pinch, 51°C) stimulation of their peripheral receptive fields. We also see in figure 1 that the maximum cumulative dose of strychnine had no effect on the mean response of the neurons to noxious stimuli, although it did produce a significant increase in the neuronal response to receptive field brushing. We assumed from these data that any antagonist effect on halothane-induced depression of responses to noxious stimuli could be attributed to an interaction between the anesthetic and the receptor system under study rather than nonspecific drug effect.

Effects of Bicuculline and Strychnine on Halothane-induced Reduction in Neuronal Activity

The ability of halothane to depress evoked activity of WDR neurons is shown in figures 2 and 3. In figure 2, the low threshold receptive field area was reduced from 13.2 cm^2 to 3.5 cm^2 by 1 MAC of halothane with subsequent recovery to baseline values (13.4 cm^2) after discontinuation of the anesthetic agent. In figure 3, we see that the response of a WDR neuron to receptive field brushing, noxious pinch, and noxious heat were all depressed by 1 MAC of halothane. It was this observed halothane depression of neuronal responses against which bicuculline and strychnine were tested.

Noxiously Evoked Activity

Table 1 presents the mean control values for responses elicited by each of the forms of stimuli used in studies of bicuculline and strychnine reversal of halothane effects as seen in figures 4 and 5.

Figure 4 presents mean data for halothane depression of WDR neuron responses to noxious pinch and noxious thermal stimulation. One MAC of halothane produced a significant reduction in the response to all three noxious stimuli, with the least noxious, 46°C, being depressed to the greatest extent. Increasing cumulative doses of bicuculline (fig. 4A) and strychnine (fig. 4B) produced a significant, but only partial, reversal of the halothane depression. As an example, halothane reduced the response to 51°C to 32 ± 18% (fig. 4A) and 34 ± 11% (fig.

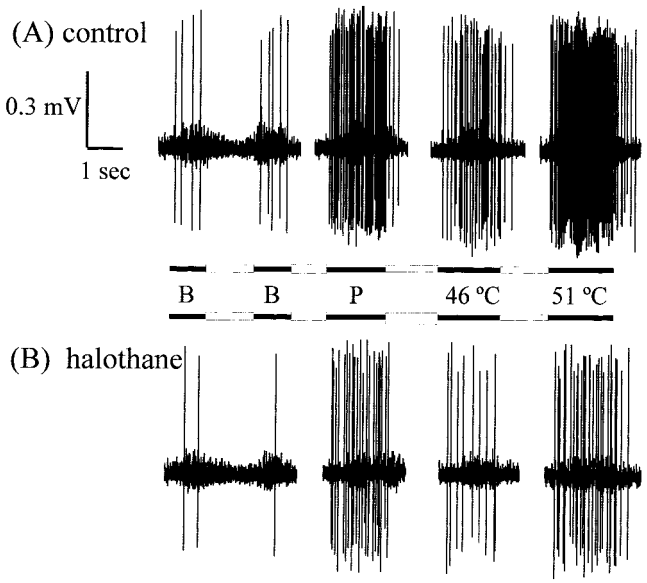

Fig. 3. Typical responses of a wide dynamic range (WDR) neuron to receptive field (RF) stimuli (B = brush, P = pinch) are shown. Each large vertical line represents the occurrence of one action potential. As was seen with change of RF size in figure 2, the number of action potentials evoked by nonnoxious brush decreased from the control by 1 MAC of halothane (from 4–6 action potentials per stimulus to 1–3 per stimulus). Note the characteristic WDR increase in response as the stimulus intensity is increased with a maximum response seen at the highest intensity. The number of action potentials evoked by noxious stimuli (pinch, 46 and 51°C) also decreased from the control by 1 MAC of halothane (72, 33, from 68 to 27, 10, 25).

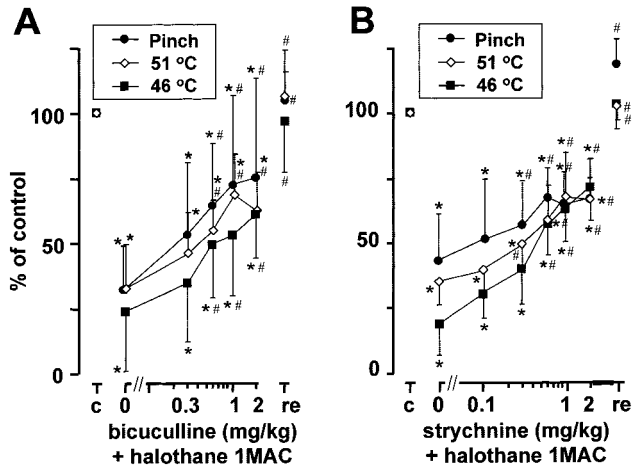

Fig. 4. Effects of bicuculline and strychnine on halothane depression of noxiously evoked activity are shown. Bicuculline (*A*) and strychnine (*B*) partially but significantly reversed the halothane depression of mean noxiously evoked activity. Data are presented as mean ± SD. **P* < 0.05 *versus* control; #*P* < 0.05 *versus* bicuculline or strychnine, 0 mg/kg, with halothane. C = control; Re = recovery; n = 9–11.

4B) of control. Bicuculline, 2 mg/kg, reversed that value to 63 ± 15% of the control, whereas 2 mg/kg of strychnine reversed it to 67 ± 16% of control. After the end of anesthetic administration, recovery to control values was seen for all stimuli.

Low-intensity Stimuli

Figure 5 summarizes the effects of bicuculline and strychnine on halothane depression of mean WDR neuron responses to low-intensity stimuli. Note that the mean responses evoked by nonnoxious stimuli were depressed to a greater extent than the responses evoked by noxious stimuli as seen in figure 4. As an example, 1 MAC of halothane reduced RF size to 11 ± 10% (fig. 5A) and 11 ± 13% (fig. 5B) of the control value, respectively. The intravenous administration of cumulative doses of bicuculline or strychnine (2.0 mg/kg) significantly, but partially, reversed those reductions up to 48 ± 13% and 63 ± 12% of the control values, respectively. Similar changes were seen on the mean response to the nonnoxious 41°C stimulation.

Drug effects on mean neuronal response to RF brushing were somewhat different. Bicuculline reversal of halothane depression exhibited a pattern that was similar to the other two forms of nonnoxious stimuli. However, neuronal activity evoked by tactile brush stimulation was restored by 0.6 mg/kg of strychnine and significantly increased by 2 mg/kg of strychnine even during halothane anesthesia. Although this appears to be a reversal of halothane depression, in light of the direct action of strychnine in the absence of halothane (fig. 1), we consider this effect to be nonspecific to the presence of halothane.

Figure 6 is a comparison of the mean response of WDR neurons to brush and pinch in the presence of increasing cumulative doses of strychnine in the absence of halothane. Firing frequency was normalized to the duration of each stimulus. Note that the highest doses of strychnine significantly increased the mean firing rate to a level comparable with that produced by noxious pinch. In the absence of strychnine, there was a significant difference between brush- and pinch-evoked activity.

Table 1. Mean Control Values of Responses to Receptive Field (RF) Stimulation

	Pinch (IPS)	51° (IPS)	46°C (IPS)	41°C (IPS)	Brush	RF
Control values for bicuculline study	60 ± 24	94 ± 63	65 ± 51	27 ± 33	13 ± 21	11 ± 7
Control values for strychnine study	77 ± 23	77 ± 37	40 ± 24	20 ± 10	11 ± 75	15 ± 9

Data for pinch, 51°C, 46°C, and 41°C are mean impulses per second ± SD. Data for brush are mean impulses per brush stroke ± SD. Receptive field area is mean area in cm^2 ± SD.

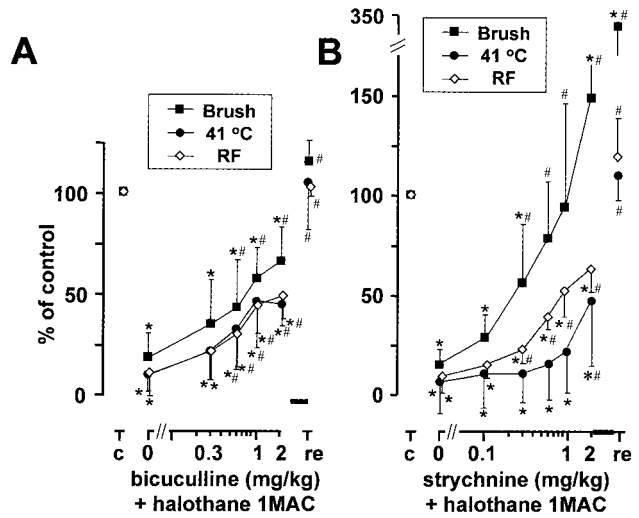

Fig. 5. Effects of bicuculline and strychnine on halothane depression of nonnoxiously evoked activity are shown. (*A*) Bicuculline significantly but only partially reversed the halothane depression of the mean responses. (*B*) Strychnine also only partially reversed the halothane depression of receptive field (RF) size and response to 41°C stimulation. The strychnine effects on brush response are considered to be nonspecific to halothane. Data are presented as mean ± SD. **P* < 0.05 *versus* control and #*P* < 0.05 *versus* bicuculline or strychnine, 0 mg/kg, with halothane. C = control; Re = recovery; n = 9–11.

Discussion

The results of this study support the hypothesis that halothane depression of spinal WDR neuronal activity is mediated, in part, by $GABA_A$ and strychnine-sensitive glycine systems. They also indicate that there is tonic glycine modulation of low threshold input to WDR neurons in decerebrate, spinal cord–transected animals. Reversal of that tonic input and the subsequent increase in neuronal activity could be the basis for the production of allodynia in awake rats after spinal intrathecal strychnine administration.

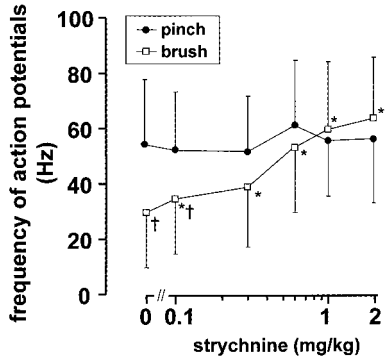

Fig. 6. Effects of strychnine on frequency of action potentials evoked by pinch or brush stimulation without 1 MAC halothane are shown. Strychnine increased the frequency evoked by brush to the same value of the frequency evoked by pinch. Data are presented as mean ± SD. **P* < 0.05 *versus* control; †*P* < 0.05 *versus* pinch; n = 9–11.

Mechanisms of Halothane Depression

Our primary focus in this study was on the mechanisms by which halothane could depress responses of WDR neurons to noxious stimulation of their peripheral receptive fields. We hypothesized that halothane effects on $GABA_A$ and strychnine-sensitive glycine inhibitory receptor systems mediate part of the depression. Both receptor types exist in the spinal cord[15,16] and, when activated, cause decreased excitability of the neurons in which they exist. Antagonism of $GABA_A$ and glycine receptor systems has been reported to reverse halothane effects.[24–26] Of particular relevance to this study, Zhang *et al.*[27] have recently reported that the spinal intrathecal administration of $GABA_A$ or glycine antagonists increased, by about 40%, the MAC value of isoflurane in rats. In the present study, we observed an approximate 50% reversal of halothane depression at 51°C (32–63% for bicuculline; 34–67% for strychnine).

Wide dynamic range neurons are one of only two types of spinal sensory neurons through which information about noxious peripheral stimuli can be processed. At the spinal level, a reflex withdrawal from a noxious stimulus is dependent, at least in part, on input from WDR neurons.[29] Supraspinally, perception of the noxious stimulus is dependent, at least in part,[30] on input from spinal WDR neurons. Halothane depression of the response of spinal WDR neurons to noxious peripheral RF stimulation is likely to contribute to immobility in the presence of a noxious stimulus and to a reduced afferent input to the CNS. Those significant effects of general anesthesia are mediated in part by halothane interactions with $GABA_A$ and glycine inhibitory systems. However, as recently reported,[31] it is likely that some degree of immobility is caused by volatile anesthetic effects directly on spinal motor neurons.

Strychnine Induced Increase in WDR Neuronal Responses to RF Brushing

The spinal intrathecal administration of strychnine has been shown to produce an allodynic state in awake rats.[32] Those animals were reported to respond to gentle brushing of the affected dermatome as if there was a noxious stimulus being applied. Subsequent studies confirmed that strychnine-induced allodynia is generated by light tactile stimulation of large diameter primary afferents that are not normally associated with signaling of nociceptive information.[33–35] The hypothesized mechanism of action is a blockade of tonic glycinergic inhibition on primary afferents that are sensitive to low-intensity brushing of receptor fields. The results of the present study provide evidence for that tonic glycinergic inhibition and also suggest that it is derived from spinal sources because it is evident in spinally transected animals. The results of this study also partially address a question raised by Sorkin and Puig[35] concerning the site of the inhibition. Because strychnine by itself only en-

hanced responses to brushing, we can assume that the glycine inhibition is not directly on the WDR neurons but is presynaptic to the input from brush-sensitive primary afferents.

Investigators have also reported a bicuculline-induced tactile allodynia, suggesting tonic GABA modulation of primary afferents.[32,36,37] The absence of evidence for tonic GABA modulation in the present study of spinal cord–transected animals suggests that the tonic GABA modulation is derived from supraspinal sources rather than from spinal sources as with glycine.

Spinal WDR neurons have been shown to play a central role in the transmission of pain information. Some investigators have proposed that WDR activation is adequate for the production of the sensation of pain.[38] It is therefore possible that the data shown in figure 6 explain how spinally administered strychnine could cause allodynia. As proposed by other investigators, by increasing the firing rate elicited by brushing to a level comparable with that seen when a noxious pinch is presented, it is likely that the brush stimulus is interpreted to be noxious.

In conclusion, the results of the current study support the hypothesis that halothane depression of noxiously evoked activity of spinal WDR neurons is mediated, in part, by $GABA_A$ and strychnine-sensitive glycine receptor systems. Because WDR neurons are central to the processing of information about noxious stimuli, it is likely that important spinal actions of anesthetic agents share that mechanism of action.

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