学 位 論 文 の 要 旨

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学 位 論 文 名	5-HT_3 RECEPTORS PARTIALLY MEDIATE HALOTHANE DEPRESSION OF SPINAL DORSAL HORN SENSORY NEURONS
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論 文 内 容 の 要 旨

INTRODUCTION

The mechanisms of general anesthesia have been investigated for many years. Recently it was reported that the spinal cord was an important site of anesthetic action. We reported that halothane depression of spinal low- threshold dorsal horn neurons is dependent, in part, on γ-aminobutyric acid type A ($GABA_A$)- and strychnine-sensitive glycine inhibitory neurotransmitter systems. Although there are many other inhibitory neurotransmitter systems in the spinal cord, the fact that the serotonin subtype 3 system is a member of the same superfamily of fastacting ligand-gated ion channels as $GABA_A$ and glycine makes it a likely candidate for an additional system that could mediate halothane depression of spinal neurons. On the basis of these reports, we hypothesized that 5-HT receptor systems help to mediate halothane depressive effects on spinal dorsal horn neurons.

The aim of this study was to test that hypothesis and to define the 5-HT receptor subtypes that may be involved in those anesthetic-induced modulations.

MATERIALS AND METHODS

This protocol was approved by the institutional animal care and use committee. Electrophysiological experiments were performed with rats.

Under general anesthesia, all rats were intubated and mechanically ventilated for the remainder of the experiment. All animals were spinally transected at the third thoracic level and were rendered decerebrate by aspiration of cranial contents. A laminectomy (T12-13) was performed to expose the lumbar where the recordings were made.

After recovery from general anesthesia, the extracellular activity of a single dorsal horn neuron was isolated and its response profile to peripheral receptive field stimulation was examined.

After isolation of a single neuron, the receptive field within which the stimulus always elicited a response was carefully determined and marked on the shaved skin (baseline). After that, the most sensitive portion of it was stimulated by brushing with a paintbrush. Unit activity was fed to a computer and analyzed. Group 1 rats then received IV injections of an antagonist. After each injection, the receptive field area and brush-induced activity were reevaluated. In Group 2, after baseline determinations, 1.1% halothane was administered, and the receptive field area and brush-induced activity were reevaluated. Then, with continuing halothane anesthesia, rats received a 5-HT receptor antagonist in a dose-dependent manner, and the measurements were again reevaluated. The antagonists were as follows: methysergide, a nonspecific 5-HT receptor antagonist; methiothepin, a 5-HT_1 receptor antagonist; ketanserin, a 5-HT_2 receptor antagonist; and tropisetron, a 5-HT_3 receptor antagonist.

RESULTS AND DISCUSSION

In a decerebrate, spinal cord-transected animal, halothane caused a reduction

in receptive field size that was partially reversed by the IV administration of methysergide. Because methysergide is a nonspecific antagonist, we next examined antagonists for identified 5-HT receptor systems in the rat spinal cord.

The 5-HT_3 receptor antagonist tropisetron produced a small and partial, but statistically significant, reversal of the halothane-induced reduction in receptive field size. Tropisetron, in the absence of halothane, produced no change in the receptive field size. Neither ketanserin (5-HT_2 antagonist) nor methiothepin (5-HT_1 antagonist) had any effect on the receptive field size in the presence or absence of halothane.

It has been reported that halothane enhanced 5-TH_3 receptor function when homomeric receptors were expressed in oocytes. We therefore hypothesized that halothane-induced reductions in spinal dorsal horn neuronal responses to receptive field stimulation were mediated, in part, by spinal serotonergic systems. It was also reported that the administration of bicuculline ($GABA_A$ antagonist) and strychnine (glycine antagonist), in the presence of 1.1% halothane, occurred a significant but incomplete reversal of the receptive field size to approximately 78% of the control. The reversal of inhibition by methysergide or tropisetron was approximately 10%-15% of the control value. Although this is a relatively small amount, it fits well with the remaining 22% depression when $GABA_A$ and glycine antagonism are accounted for.

CONCLUSION

In summary, 5-HT_3 receptor systems help to mediate halothane depression of spinal dorsal horn neurons. The results of this study support the hypothesis that anesthetics modulate sensory transmission by influencing the action of multiple neurotransmitter systems.