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Title : CEREBELLAR DEAFFERENTATION--A CENTRAL EFFECT OF HALOTHANE

Authors : L. Triner, M.D., Ph.D., M. Verosky, B. A., Y. Vulliemoz, Ph.D., M. Alpert, B.A.

Affiliation: Department of Anesthesiology, Columbia University College of Physicians & Surgeons, New York, NY 10032

Introduction. Halothane, at low concentration (0.3 vol %, ED_{50} loss of righting reflex being 0.61 vol%) causes a marked decrease (> 50%) of cerebellar cortex cGMP content, which represents the nucleotide level of cerebellar Purkinje cells (Pc) and reflects their activity; higher Pc activity is accompanied by an increase of cGMP and diminished activity by a decrease. A balance between excitatory and inhibitory inputs converging on Pc determines their activity; excitatory inputs from other brain regions and periphery reach Pc through climbing and mossy fibers, while the inhibitory input is provided by a network of cerebellar neurons (stellate, basket and golgi cells) and is transmitted on Pc by GABA. Consequently, the halothane-induced decrease in cerebellar cGMP could be due to (1) an effect on the Pc rendering it less responsive to excitatory stimuli, (2) facilitation of the GABA inhibition of Pc, or (3) reduction of excitatory firing reaching Pc due to (a) decreased generation of proprioceptive and other peripheral signals secondary to diminished motor activity induced by anesthesia, (b) decreased synaptic transmission at the spinal level and/or (c) at the supraspinal level in pathways transmitting excitatory signals to the cerebellar cortex.

Action of halothane was examined by measurement of cerebellar cGMP as a marker of Pc activity in vitro, to determine a direct effect on Pc or on cerebellar inhibitory processes, and in vivo, using drugs acting at different levels of the excitatory pathways reaching Pc.

Methods. Sherman male rats weighing 200-250 g were housed at 22° C and kept on a 12-h light, dark cycle. Under ethyl ether anesthesia, a 16-G x 2" Abbocath was placed in the trachea and ventilation instituted by a small animal respirator set at a tidal volume of 1.5 ml 100^{-1} g and a frequency rate of 80 min^{-1} to maintain normal arterial blood gases. Drugs given iv were injected through a 22-G x 1" Deseret Angiocath placed in a tail vein. Rats were sacrificed by microwave radiation focused to the head for 5 sec. The cGMP content of the cerebellar cortex was determined by radioimmunoassay. Halothane concentration in the inspired gas was measured continuously with a Beckman Medical Gas Analyzer LB-2.

Results. In vivo, halothane decreased cerebellar cGMP in a concentration-related fashion; 0.92 vol% diminished the cGMP content by 80%, from a control value of 2.74 ± 0.57 pmol mg^{-1} protein. However, cGMP content in slices of cerebellar cortex exposed to halothane (3 vol %) for 30 min, 3.32 ± 0.65, was the same as in controls, 3.42 ± 1.23 pmol mg^{-1} protein, indicating that the effect of halothane is not exerted directly on Pc or cerebellar inhibitory processes. Since both excitatory and inhibitory inputs determine the activity of Pc and the content of cGMP in cerebellar cortex, the effect of halothane on excitatory pathways to Pc was examined. Halothane (0.92 vol%) caused a similar decrease of cerebellar cGMP (by 88%) in rats with complete neuromuscular blockade (0.3 mg kg^{-1} d-tubocurarine iv) as in control rats, indicating that the effect of halothane on cerebellar cGMP is not secondary to a reduction of excitatory firing to Pc due to a lack of generation of proprioceptive and other peripheral stimuli resulting from diminished motor activity. While 0.3 mg kg^{-1} iv of d-tubocurarine did not change the nucleotide content, a high dose (3 mg kg^{-1} iv) caused a significant decrease in cerebellar cGMP, by 78% (as previously reported), the mechanism of which is not clear at present. The stimulation of the afferent pathways to Pc at the spinal level, as manifested by an increase of cerebellar cGMP (by 724%), caused by strychnine (which inhibits glycine receptors in the spinal cord), was abolished by halothane, indicating that the transmission in the afferent pathways at the spinal and/or at more central sites is inhibited by halothane. The inhibition of a central afferent pathway to Pc by halothane is demonstrated by a 50% decrease of cerebellar cGMP response to harmaline, which selectively activates the climbing fibers originating in the inferior olive nucleus.

cGMP Content in Rat Cerebellar Cortex (pmol mg^{-1} protein)

Treatment	None	Halothane 0.92 vol%
Saline (control)	2.74 ± 0.57	0.49 ± 0.03**
d-tubocurarine 0.3 mg kg^{-1} iv	2.68 ± 0.50	0.31 ± 0.03**
d-tubocurarine 3.0 mg kg^{-1} iv	0.61 ± 0.21*	-
Strychnine 1 mg kg^{-1} sc	22.58 ± 4.07*	0.56 ± 0.18**
Harmaline 6.4 mg kg^{-1} iv	5.56 ± 0.62*	2.69 ± 0.58**

Values are means ± SEM.
*Significantly different ($P < 0.01$) from control rats.
**Significantly different ($P < 0.01$) from treated rats not receiving halothane.

Conclusion. The results indicate that the decrease in cerebellar cGMP content caused by halothane is due to an action at the spinal and supraspinal levels, resulting in diminished excitatory firing reaching Pc. It is proposed that this effect of halothane causes a deafferentation of the cerebellar cortex, resulting in decreased Pc activity and, consequently, motor activity. It is possible that similar deafferentation caused by halothane may occur in other regions of the central nervous system.