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Title : STIMULATION OF THE PERIAQUEDUCTAL GRAY AREA REDUCES ANESTHETIC REQUIREMENT

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Introduction. Electrical stimulation of the periaqueductal gray region at the level of the posterior commissure relieves intractable pain in patients and increases CSF β -endorphin levels. Naloxone antagonizes this effect. In the rat, accumulation of norepinephrine and serotonin occurs in the same periaqueductal gray area during anesthesia with either of two diverse agents, halothane or cyclopropane. Destruction of the main norepinephrine nerve fibers supplying this terminal region in the rat brain decreases anesthetic requirements, as does destruction of a serotonergic nucleus near this region. Therefore, anesthetic agents may produce anesthesia by selectively stimulating or inhibiting specific brain regions; stimulation of the periaqueductal gray region should reduce anesthetic requirement. On the other hand, pain suppression by periaqueductal stimulation in both human subjects and animals is highly specific: most patients report no effects of stimulation other than analgesia, i.e., no drowsiness, no projected sensation, no loss of skin sensation, no seizures, and no motor signs.^{1,2} Thus, anesthetic requirements may not be affected by such stimulation.

Methods. To determine whether stimulation of the periaqueductal gray area affects anesthetic requirement, we studied the minimal alveolar concentration (MAC, the amount of anesthetic needed to prevent movement in response to skin incision in 50% of patients) of halothane and 60% nitrous oxide in 23 patients (29-65 years of age). These patients had electrodes that were previously implanted in the periaqueductal gray area and were undergoing a total of 24 procedures for electrode internalization. Patients had not used their stimulators for 24 hr or received any sedative, hypnotic, or analgesic agent for 12 hr prior to surgery. Informed consent and approval of the Committee on Human Research had been obtained. Patients randomly received ($n = 12$) or did not receive ($n = 12$) electrode stimulation 1 hr prior to surgery. Anesthesia was induced with halothane and 60% nitrous oxide in oxygen, or with 1 mg/kg of thiopental intravenously, at least 25 min before skin incision. The trachea of each patient was intubated after the larynx was sprayed with 160 mg lidocaine/70 kg without the use of other drugs. Anesthesia was then continued with 60% nitrous oxide and a variable amount of halothane in oxygen. Ventilation was controlled. The MAC value for halothane was determined by a modification of the Dixon "up-and-down method,"³ and by Waud's analysis.⁴ End-tidal halothane concentration was monitored using analysis of expired gas by ultraviolet analyzer (Cavitron).

Results. MAC (mean \pm SEM) of halothane combined with 60% nitrous oxide for patients stimulated immediately before surgery was $0.13 \pm 0.08\%$, values that were significantly less than $0.49 \pm 0.03\%$, the MAC

for patients in the unstimulated group. Ventricular CSF β -endorphin levels (pgm/ml) measured in one patient were 276 before stimulation, 966 at 15 min, and 1065 at 60 min after stimulation.

Discussion. Anesthetic requirements are reduced by periaqueductal gray stimulation. Thus, either the specific pain pathways inhibited by stimulation of the periaqueductal gray area are involved in decreasing the sensation of skin incision; are closely involved in the mechanism of anesthesia; or exert a non-specific effect that decreases anesthetic requirement. Since so few of the non-pain-reducing effects of opiates occur after stimulation of the periaqueductal gray area, it is unlikely that electrical stimulation of this area reduces anesthetic requirements by a non-specific effect. Since skin sensation is preserved after periaqueductal gray stimulation, it is unlikely that electrical stimulation of this area reduces anesthetic requirements by decreasing the sensation of skin incision. Thus, the most likely mechanism by which periaqueductal gray stimulation reduces anesthetic requirement is stimulation of a pathway involved in the mechanism of anesthesia. Although elevation of CSF β -endorphin levels is associated with periaqueductal gray stimulation, the effect of this stimulation on anesthetic requirements may have nothing to do with β -endorphin levels. This hypothesis is supported by the minimal (if any) effect of naloxone as an antagonist of general anesthesia. The periaqueductal gray area is rich in both serotonergic and adrenergic innervation; changes in periaqueductal gray amine levels are also associated with altered anesthetic requirements. Thus, reduction of anesthetic requirement by periaqueductal gray stimulation may be less dependent on increasing CSF β -endorphin levels than on stimulation of a specific pathway.

References

1. Hosobuchi Y, Adams JE, Linchitz R: Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. *Science* 197:183-186, 1977
2. Richardson DE, Akil H: Pain reduction by electrical brain stimulation in man. Part 2: Chronic self-administration in the periventricular gray matter. *J Neurosurg* 47:184-194, 1977
3. Dixon WJ: Quantal-response variable experimentation: The up-and-down method, *Statistics in Endocrinology*. JW MacArthur, T Colton (eds), Cambridge, Massachusetts, MIT Press, 1970, pp 251-267
4. Waud DR: On biological assays involving quantal responses. *J Pharmacol Exp Ther* 183:577-607, 1972