

Naloxone Fails to Antagonize the Righting Response in Rats Anesthetized with Halothane

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The righting responses of 75 Wistar rats during exposure to halothane, 0.5 per cent, 10 min after subcutaneous injection of naloxone, 10 or 20 mg/kg, or saline solution were examined. There was no difference in recoveries of the righting responses among the three groups. It is concluded that naloxone does not antagonize the loss of righting response produced by halothane anesthesia in the rat. (Key words: Anesthetics, volatile: halothane. Antagonists, narcotic: naloxone.)

IT HAS BEEN SUGGESTED that naloxone may antagonize the action of general anesthetics.¹ Berkowitz *et al.*,² using the phenylquinone writhing test in mice, found that naloxone decreased the analgesic action of nitrous oxide. This group subsequently reported that naloxone antagonized the anesthetic effects of cyclopropane, halothane, and enflurane, as evidenced by increased responses to tail clamping and changes in electroencephalographic patterns to those consistent with lighter anesthesia.

However, the tail-clamping and writhing tests measure pain responses but do not measure the effects of general anesthesia, which by definition also includes loss of consciousness. Accordingly, a study was made of the ability of naloxone to reverse in rats the loss of righting reflex produced by halothane, which is not reliant solely on the analgesic factor of halothane.

Methods

Seventy-five male Wistar rats (250–350 g) were exposed to halothane, 0.5 per cent, 10 min after lower abdominal subcutaneous administration of either naloxone HCl, 10 or 20 mg/kg, or saline solution and their righting responses measured. Each animal served as its own control, so the righting response was determined twice, once after injection of naloxone and again on a separate occasion after injection of saline solution, in equal volumetric proportions. Half the animals received injections of saline solution first and half received naloxone first. The choice of exposure to naloxone or saline solution was random, but the behavioral observer was unaware of the type of injection each animal had received.

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Immediately after the injection, a rat was placed into each of five compartments (23 × 14 cm) of a cylindrical wire mesh cage, which was rotated horizontally on its axis at 4 rpm. The cage was then placed in a close-fitting air-tight plexiglass box and connected to a gas-recirculating system. A gas-mixing Venturi mixer, driven by low-pressure air at 5 l/min, forced air from the box through a halothane vaporizer and back into the box. Any excess pressure in the system was vented through a shallow bubbler. The halothane concentration in the box was monitored constantly using a Perkin Elmer 1100 mass spectrometer.

After the box was sealed, the concentration of halothane was increased to a constant level, at which it was maintained for 10 min, at the end of which time the rats were tested. The cage was then rotated for 1 min, *i.e.*, four revolutions, and all rats observed for loss of righting response, which was the point at which an animal rolled onto its back and completely over. This usually occurred during the first 5 sec of the exposure.

Control studies were carried out first to determine the RR₅₀ halothane dose, *i.e.*, the concentration of halothane that will cause 50 per cent of a group of rats to lose their righting responses. Twenty-five rats, in groups of five, made 60 exposures to concentrations of halothane between 0.3 and 0.8 per cent (fig. 1), and it was found by probit analysis that an RR₅₀ with halothane in air occurred after 10 min to the nearest 0.1 per cent at halothane, 0.5 per cent.

Accordingly, 75 animals were exposed in three groups of 25, Groups A, B, and C (table 1). Groups A and B were given naloxone HCl, 10 mg/kg, or saline solution, and Group C, 20 mg/kg or saline solution, each animal serving as its own control. Five of the rats in Group A were eliminated from the study due to preexisting respiratory illness. For this reason, the same procedure was repeated for 25 rats in Group B. However, the Group A results are given minus those for the five sick rats.

Results

There was no difference in the RR₅₀'s among the three groups. With naloxone, 43 of the 69 rats showed loss of righting responses (table 1), whereas with saline solution, 42 of the 69 rats showed loss of righting responses. Thus, it is concluded that naloxone

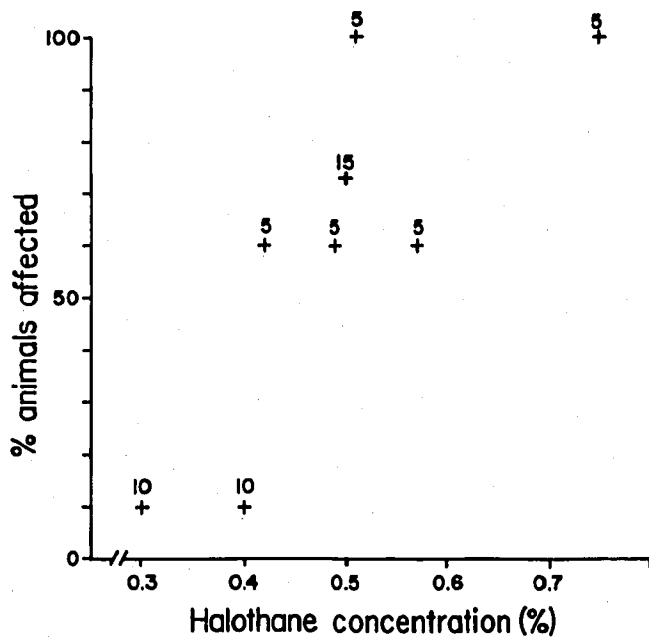


FIG. 1. Percentages of halothane to the nearest 0.1 per cent that caused 50 per cent of the exposed rats to roll over (RR_{50}) when placed in a cylindrical cage revolving at 4 rpm. 5, 10, and 15 indicate numbers of rats tested per data point.

did not antagonize the RR_{50} effect produced in rats by exposure to halothane.

Discussion

These results demonstrate that the antagonism of general anesthesia found by earlier researchers using tail-clamping and writhing responses may relate only to the analgesic properties of the anesthetics. This may be due to the anesthetic's causing release of endogenous morphine-like substances in the central nervous system that bind to central opiate receptors, which naloxone inhibits.³⁻⁵ The wider effects of general anesthesia leading to loss of consciousness, as evidenced by loss of the righting response, are unaffected by naloxone. This might be expected considering contemporary concepts of mechanisms of general anesthesia,⁶ which relate to specific

changes in the dimensions of bilayers, their dipole charges, and increased ion conductance across membranes, which are not related to an action on specific morphine receptors.

Furst, Folders and Knoll⁷ reported that naloxone, 1 mg/kg, administered subcutaneously or intravenously at the same time as pentobarbital, 35 mg/kg, and by the same route, delayed the development and decreased the duration of the loss of righting response in rats. Naloxone also antagonized the toxicity of pentobarbital, 50-125 mg/kg, administered intraperitoneally, and increased the LD_{50} of pentobarbital from 59 to 101 mg/kg. On the other hand, Dayton and Blumberg⁸ found that hypnosis and light anesthesia, as measured by loss of righting response, due to pentobarbital, 50 mg/kg and to pentobarbital, 12.5 mg/kg, plus oxymorphone, 0.5 mg/kg, were equal in the two experimental situations but after 30 min halothane, 1 mg/kg, subcutaneously, antagonized the action of the pentobarbital-oxymorphone combination only. Similarly, pentobarbital, 200 mg/kg, caused 90 per cent mortality in 61.5 min, and pentobarbital, 50 mg/kg, plus oxymorphone, 4 mg/kg, 80 per cent mortality in 59.1 min. Again, naloxone, 4 mg/kg, subcutaneously, prevented the deaths with the latter combination only.

Like the results of the present study, these results agree with an interpretation that naloxone acts only as a specific antagonist of narcotic analgesics. The work to date has involved the use of very large doses compared with human application and various means of administration at different levels of anesthesia, all of which could explain the differences in results among the various groups.

The present results indicate that naloxone may not antagonize the effects of general anesthesia. Further, they emphasize that although local anesthetics, narcotics, and general anesthetics may, as reported by Kendig and Cohen,⁹ block conduction by an action on a common pressure-sensitive membrane site, many differences between the mechanisms of action of such narcotics and local and general anesthetics remain.

TABLE 1. Effects of Naloxone and Saline Solution on the Righting Responses (RR_{50}) of Rats Exposed to 0.5 Per Cent Halothane

	Group A (20 Rats)		Group B (25 Rats)		Group C (25 Rats)	
	Naloxone, 10 mg/kg	Saline Solution	Naloxone, 10 mg/kg	Saline Solution	Naloxone, 20 mg/kg	Saline Solution
Number of rats that rolled over	11	15	17	14	15	13

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