phenacaine and the phosphodiesters show the importance of hydrogen bonding in the interaction between the constituents of the complex. The formation of a hydrogen-bonded complex is a feature common to the functioning of useful local anesthetics, although apparently it is not obligatory that a drug be a potential hydrogen bond donor in order to block nerve conduction. Furthermore, the formation of a hydrogen-bonded complex as a significant feature in the mode of action of local anesthetics is compatible with several current theories of nerve conduction.

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16. Propanidid, {4-[(diethylcarbamoy)methoxy]-3-methoxyphenyl} acetic acid propyl ester, is an experimental short-acting intravenous anesthetic. This compound has the aromatic rings and side chains normally present in local anesthetics, but the diethylamide group is not a hydrogen bond donor at physiological *p*H.
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Nalorphine: Increased Sensitivity of Monkeys Formerly Dependent on Morphine

Abstract. *Three rhesus monkeys* Macaca mulatta, *formerly dependent on morphine, had increased sensitivity to nalorphine's effect of suppressing operant responding for food, as compared with two monkeys with no history of morphine exposure. Within the dose range employed, nalorphine injections produced emesis, salivation, and hyperirritability in formerly morphine-dependent monkeys but not in controls.*

An injection of nalorphine, a potent antagonist of morphine, immediately elicits an abstinence syndrome in morphine-dependent organisms which resembles, in nearly all aspects, the syndrome associated with the abrupt withdrawal of morphine. Because low doses of nalorphine have few effects on nondependent organisms, this drug is used extensively to determine the presence and magnitude of opioid physical dependence. A period of chronic exposure to morphine in man, or exposure to a single dose of morphine in rats, results in a decreased sensitivity (tolerance) to certain of morphine's effects which persist for several months (*1*). However, the possibility that organisms formerly dependent on morphine might show significant changes in sensitivity to drugs other than morphine has not yet been explored. We here demonstrate that rhesus monkeys formerly dependent on morphine have an increased sensitivity to nalorphine that appears to be the result of long-lasting physiological changes developed during periods of morphine dependence.

Prior to this experiment three monkeys were maintained for 2 months on 12 mg of morphine sulfate per kilogram (body weight) per day, given as

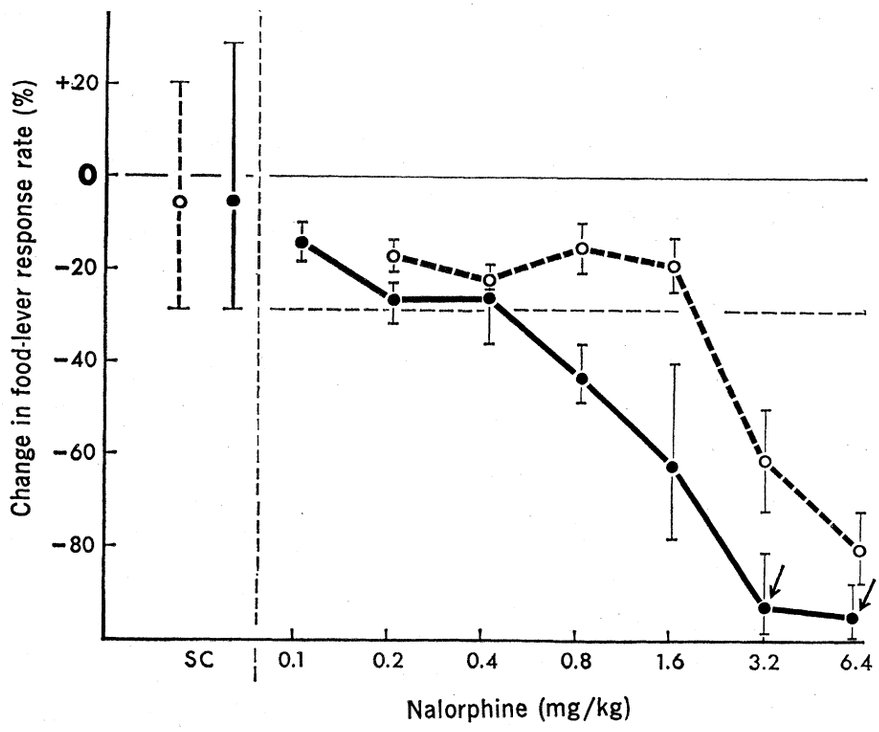

Fig. 1. Average percentage change in rate of food-lever response from the 5-minute period preceding the intravenous injection of saline or nalorphine to the 5-minute period after the injection of saline or nalorphine. The two points at the far left represent the average and the brackets represent the range of four saline control (*SC*) sessions. The horizontal dotted line indicates the lower limit of the range on saline control sessions. At each of the doses of nalorphine the points represent the average percent change in rate of food-lever response and the brackets represent the range. Arrows indicate the observation of emesis, excessive salivation, and hyperirritability. (Open circles) Control monkeys (no history of dependence on morphine), $N = 2$; (solid circles) monkeys withdrawn for 3 months from morphine dependence, $N = 3$.

a subcutaneous injection of 3 mg/kg every 6 hours, and were then completely withdrawn from morphine for 3 months. These formerly dependent monkeys had never received nalorphine prior to this study. Two nondependent monkeys that had never been exposed to morphine or nalorphine served as controls.

The monkeys were surgically prepared with chronic jugular catheters (*2*) and they were then trained to press a lever for food; every tenth response was reinforced with a pellet of food (a fixed-ratio of 10 schedule of reinforcement). Each monkey worked on this schedule for 1 hour a day. Four daily sessions were conducted in which saline was given intravenously through the catheter during the food period. After these control sessions, a series of nalorphine doses, administered through the catheter, was tested in ascending order in successive daily sessions during the food period.

Changes in responding, when observed after injections of nalorphine, usually persisted for only several minutes. Only after the 6.4-mg dose of nalorphine (per kilogram of body weight) was given were longer lasting changes in responding observed (Fig. 1). Doses of nalorphine from 0.2 mg/kg to 1.6 mg/kg produced no change in the response rate of the two nondependent monkeys compared to response rate after saline injection. Suppression of their responding was first observed at a dosage of 3.2 mg of nalorphine per kilogram. The three monkeys formerly dependent on morphine showed no change in their response rate after doses of nalorphine from 0.1 to 0.4 mg/kg. Unlike the nondependent monkeys, however, the 0.8 mg/kg and 1.6 mg/kg doses of nalorphine suppressed their response rate. A dose of 3.2 mg/kg of nalorphine, which only partially suppressed the response rate of nondependent monkeys, almost completely suppressed responding of the three formerly dependent monkeys. In addition, emesis, excessive salivation, and hyperirritability were observed in the three formerly dependent monkeys after the 3.2- and 6.4-mg injections of nalorphine per kilogram. In contrast, none of these signs were observed in the nondependent monkeys.

Rhesus monkeys formerly dependent on morphine, with no previous history of nalorphine-induced abstinence, show an increased sensitivity to nalorphine when compared with nondependent monkeys with no history of exposure to morphine or nalorphine. After complete withdrawal of morphine from dependent organisms, certain signs of the morphine-abstinence syndrome persist for many months. This phenomenon has been observed in both animals and man in studies of physical dependence and has been called a secondary abstinence syndrome (*3*). Altered sensitivity to the effects of nalorphine and morphine could be considered part of this secondary abstinence syndrome, and may have implications for the treatment of formerly dependent patients.

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Neuronal Network Triggering a Fixed Action Pattern

Abstract. *Bursts of impulses in groups of brain cells of the nudibranch* Tritonia *trigger prolonged swimming that is identical to the natural escape response. The cells in which the activity occurs form two bilaterally symmetrical groups of at least 30 cells in each pleural ganglion. These neurons are interconnected by pathways that have a low electrical resistance, both within a ganglion and across the brain. Together they form a network that determines whether a swimming escape response will occur or not by filtering out weak neural activity yet responding with a burst of impulses to intensive specific input to either group.*

It is not yet known what kind of central neuronal events initiate stereotyped behavioral acts, such as fixed action patterns, but the results of ethological studies suggest that the first event is a triggerlike process (*1*). A single brief event lasting no more than a second causes a whole behavioral sequence to occur, and this response may greatly outlast the stimulus. Nothing is known about the neurophysiological basis of this triggering process because of the inaccessibility and lack of knowledge concerning the location of the relevant neurons. In vertebrate animals, a number of instances of elicitation of complex motor acts or sensory experience following stimulation of selected hypothalamic or cortical regions are known (*2*), but these are too complex to permit analysis at the cellular level. Interneurons that drive relatively complex, coordinated movements (*3*) are known in invertebrates, but they must be continually active in order to be effective and do not meet the criteria required of decision-makers. In the intact animal the initiation of activity must have been made ahead of these interneurons, since the stimulus to activity may be a single, brief event.

We located a group of neurons in the brain of the nudibranch mollusk *Tritonia gilberti* which seems to meet the criteria. The cells control the initiation of a fixed action pattern (*4*) of moderate complexity—the swimming escape response. This consists of several sequential, coordinated activities: (i) reflex withdrawal of the oral veil, rhinophores, and branchial tufts; (ii) elongation by contraction of circular body wall muscles and expansion of oral veil and tail; (iii) a series of from one to eight cycles of dorsal and ventral flexions of the body wall musculature; and (iv) one to four spasmodic dorsal flexions. The response is elicited naturally by epidermal contact with certain species of starfish, or it can be evoked by certain surface active agents and salts. Activity of brain cells during the execution of these movements was monitored with intracellular glass micropipettes placed in identified cells of the cerebral-pleural-pedal ganglion complex with the use of an intact animal preparation similar to that described earlier (*5*), except that immobilization of the brain has been improved. In the newer procedure the connective tissue surrounding the brain was pinned to a small wax-covered table held on the end of a rigid arm, placed beneath the brain.

The cells whose coordinated activity triggers swimming are located in two groups [numbered 10 and 21 in earlier