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12. This may have been one of the reasons why Gross *et al.* (*3*), in a previous study, utilizing somewhat different methods, had failed to find any receptive fields for inferotemporal neurons.
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17. Supported by NIH grant MH-14471 and NSF grant GB-6999. We thank D. Schweitzer-Tong and Mrs. G. Seiler for assistance.

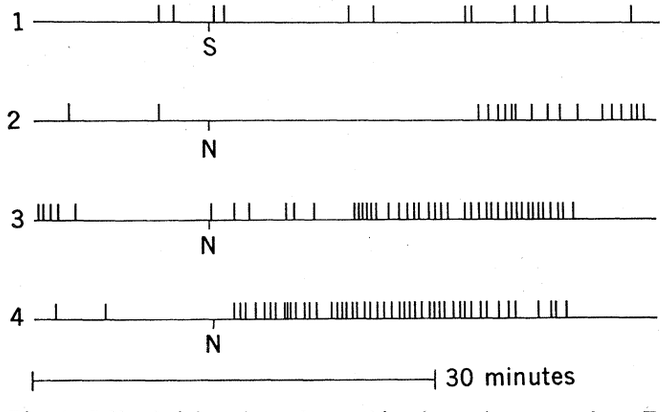
14 July 1969; revised 26 August 1969 ■

Morphine: Conditioned Increases in Self-Administration in Rhesus Monkeys

Abstract. *Operant responding in three monkeys was maintained by intravenous presentations of morphine. Nalorphine produced reliable increases in morphine-reinforced responding. With successive daily nalorphine injections there was a decreased latency of self-administration responding for morphine, and substituted saline injections produced conditioned increases in morphine-reinforced responding.*

Nalorphine counteracts many pharmacological and behavioral effects of morphine. In organisms dependent upon morphine, nalorphine induces a severe withdrawal syndrome, which includes restlessness, piloerection, vomiting, salivation, body tremors, and general irritability. Certain of these changes induced by nalorphine can be elicited by stimuli associated with withdrawal, for example, a mock injection (*1*), which suggests that components of the morphine-withdrawal syndrome are susceptible to classical conditioning. Wikler proposed that relapse of narcotic addicts to drug taking after treatment may be due in part to the failure of treatment programs to extinguish previously conditioned environmental stimuli associated with withdrawal distress and its relief by administration of a narcotic (*2*). In rats, both a classically conditioned morphine-abstinence phenomenon (increased "wet dog" shake frequencies) and increased oral consumption of an opioid (Etonitazene) can persist for many months after withdrawal of morphine (*3*). However, such behavior is independent of whether the environmental-conditioned stimuli had been temporally contiguous with relief from morphine-withdrawal distress (*3*). We now report that presentation of previously neutral environmental stimuli to morphine-dependent rhesus monkeys following repeated nalorphine-induced withdrawal episodes results in large conditioned increase in self-administration of morphine.

Three rhesus monkeys *Macaca mulatta* were placed in cubicles and adapted to stainless steel restraining arms and a metal catheter-protection harness. After this adaptation period chronic jugular catheters were surgically implanted. Each cubicle contained a lever, which when depressed delivered 1.0 mg of morphine sulfate per kilogram of body weight (*4*). Once the monkeys began to respond, the morphine dosage was reduced gradually to 0.1 mg/kg per injection. Responding increased and stabilized within 1 to 2 months. After stability was reached, the monkeys administered 110 to 180 injections per day (11 to 18 mg/kg per day). At this point the monkeys were assumed to be strongly dependent on morphine (*5*). On this base line of self-administration, nalorphine (0.1 mg/kg) was administered intravenously once on



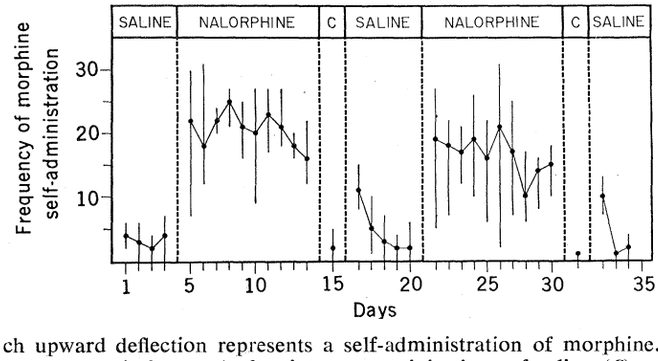


Fig. 1. Self administration of morphine in a rhesus monkey. Each upward deflection represents a self-administration of morphine. Days 1 to 4 indicate the frequency of morphine self-administration responses before and after intravenous injections of saline (*S*) or nalorphine (*N*) (0.1 mg/kg). Fig. 2. Frequency of self-administration of morphine in the 30-minute period following the intravenous injection of saline or morphine (0.1 mg/kg) during conditioning in three morphine-dependent rhesus monkeys. Each point represents the average frequency of self-administration in the three monkeys, and the vertical bars represent the range. Injections of saline or nalorphine were omitted on the control days (*C*).

each successive day (Fig. 1). The monkey administered morphine to himself at a low rate both before and after a saline injection. On day 2 an injection of nalorphine (0.1 mg/kg) produced little initial change in self-administration, but after a 20- to 25-minute delay a large increase in responding appeared which continued for 20 to 30 minutes. With repeated presentations of this dose of nalorphine the delay in appearance of increased self-administration diminished. By day 4, the increased rate of self-administration responding appeared within 2 minutes of the nalorphine injection. The other two monkeys showed similar responses. The change in responding observed with repeated administration of nalorphine might have been due to the novelty of the drug effect. We would expect, however, that a novelty effect would have been demonstrated as a decrease in the number of administrations of morphine after repeated injections of nalorphine, rather than an increase. If we assume that the administration of nalorphine to morphine-dependent monkeys produces aversive stimulation which can be reduced by administration of morphine, then the decreased self-administration response latencies after repeated nalorphine injections may reflect the development of conditioned escape or avoidance responding. Nalorphine may not be unique in this regard—rats self-administer certain barbiturates at a higher relative rate shortly after the brief presentation of electric shock (*6*). In our second set of observations, we explored the possibility that previously neutral environmental stimuli can elicit conditioned changes in the pattern of morphine self-administration after repeated withdrawal episodes.

After the initial injections of nalorphine, a form of classical conditioning was begun. A stimulus (flashing red light) was presented once a day at the same time for 10 minutes before and 30 minutes after an intravenous injection of saline or nalorphine. After four pairings of light and saline injection, the light was presented once a day in association with an intravenous injection of 0.1 mg of nalorphine per kilogram of body weight. The light and the stimulus associated with the injection procedure might thus be viewed as conditioned stimuli (CS) and the nalorphine injection as an unconditioned stimulus (US). After ten pairings of light and nalorphine injection, a control trial was conducted by omitting the light-injection pairing. The control trial was followed by five daily test trials with light–saline injection pairings.

No change in the number of administrations of morphine was produced by intravenous saline injections during the initial trials (days 1 to 4) (Fig. 2). During conditioning trials (days 5 to 14), intravenous injections of nalorphine (0.1 mg/kg) increased the frequency of administration of morphine in the 30-minute period following the injection. After the tenth conditioning trial (day 14), a control trial, without a light-injection pairing was conducted and the rate of self-administration was similar to that of days 1 to 4. Thus, conditioning had not altered the base-line performance of the monkeys. The first test (pairing of light and saline injection, day 16), after the tenth conditioning trial, resulted in large increases in the number of self-administrations of morphine during the 30 minutes following the saline injection. The self-administration rate of the three monkeys after the injection was three to five times greater than that seen after the initial light–saline injection trials (days 1 to 4). With repeated pairings of light and saline injection (days 16 to 20), this conditioned response rapidly disappeared. Reconditioning training was then conducted (days 21 to 30) and results closely paralleled those in the initial conditioning sessions. On the first day of the subsequent test (days 32 to 34) the animals showed a large increase in the number of self-administrations of morphine.

We noted (*2*) that pairing of a red light CS with a nalorphine US suppressed food-reinforced lever pressing during the interval between CS onset and US onset. No change in self-administration was seen in the present study, however, during the 10-minute interval between CS onset and injections of saline or nalorphine.

That the monkeys increased their responding to saline injections although they did not increase their responding to the light CS preceding the injections indicates that the stimuli associated with injections had acquired the property of increasing self-administration of morphine. A stimulus complex consisting of pairing of light and saline injection acquires conditioned reinforcing properties after a number of response-contingent pairings of light and morphine injection. During extinction conditions, response-contingent presentations of this stimulus complex produces large, but transitory, increases in response rate previously reinforced with morphine (*7*). Thus, stimuli associated with either the nalorphine-induced withdrawal syndrome or with morphine reinforcement can acquire conditioned properties which result in their playing an important role in the control of self-administration of drugs.

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11 August 1969; revised 22 September 1969

Olfactory Stimuli and the "Pseudo-Extinction" Effect

Abstract. *Continuously rewarded rats show a decrease in running speed on a runway recently traversed by other rats undergoing experimental extinction. This "pseudo-extinction" effect is caused by discriminable odors emitted by extinction subjects. These odors could be confounding variables in studies using forms of aversive stimulation.*

The influence of olfactory stimuli on the albino rat in a variety of situations has been studied. The results are inconsistent with several experiments demonstrating patterned responding within differential conditioning, single and double alternation, and straight runway situations (*1*). The hypothesis has been advanced that discriminable odors elicited by certain specifiable conditions rather