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Physical Dependence on Morphine Fails to Develop During the Hibernating State

Abstract. *Physical dependence on morphine occurs in a typical fashion during the active state of the mammalian hibernator* Citellus lateralis, *but does not occur when morphine exposure is confined to the hibernating state. Morphine exposure during hibernation can produce stereotyped behavior, thus demonstrating partial responsiveness of the central nervous system to opioids during this natural state.*

In the mammalian central nervous system (CNS), the development of physical dependence is a direct consequence of prolonged opioid action. This phenomenon, commonly characterized by a constellation of autonomic and behavioral signs that appear after abrupt or antagonist-precipitated withdrawal of the opioid agent (*1*), has been observed in response to various opioid doses, durations of exposure, routes of administration, and environmental conditions (*2*).

We now report that, rather than being an inevitable consequence of prolonged exposure of the CNS to opioids, physical dependence may be a state-dependent phenomenon. It develops in a typical fashion in the mammalian hibernator when morphine is administered during the euthermic (nonhibernating) state—that is, while brain activity is comparable to that of mammals that do not hibernate. However, no physical dependence is apparent when morphine exposure is confined to deep hibernation, a state that is initiated and maintained by the CNS (*3*) and that is characterized by striking changes in brain electrophysiological and neurochemical parameters (*4*).

California golden-mantled ground squirrels (*Citellus lateralis*) of both sexes, with no previous exposure to drugs, were studied. During the euthermic state, two 75-mg morphine sulfate pellets (*5*) were implanted in the interscapular region while the animals were lightly anesthetized with ether. After a 72-hour exposure to morphine in their home cages, the animals were transferred to a plexiglass test chamber (17.5 by 21.5 by 24.5 cm; floor covered with wood shavings and cotton nesting material) for determination of the abstinence syndrome. A 20-minute period was allowed for behavioral observation and acclimation. The abstinence syndrome was precipitated with naloxone HCl (1 mg/kg, subcutaneously), and the signs displayed after the naloxone injection were recorded for 30 minutes.

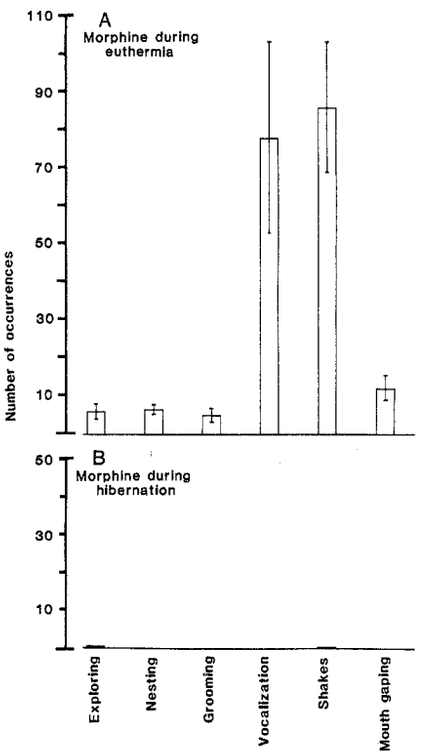

Fig. 1. Quantified signs of abstinence precipitated by naloxone during the nonhibernating (euthermic) state in ground squirrels implanted with morphine pellets. (A) Strong abstinence syndrome (N = 10). (B) No abstinence syndrome (N = 6). Exploring and body shakes were present in negligible amounts. Brackets denote standard error of mean.

Hibernating animals received the same drug treatment as the euthermic animals. The morphine pellets were implanted during the early phase of the animals' hibernation bout (individual period of hibernation); 72 hours later, they were transferred to the plexiglass test chamber and handled briefly to stimulate full arousal from hibernation (*6*). Immediately after reaching the euthermic state, the animals were observed for 20 minutes before naloxone injection (1 mg/kg, subcutaneously) and for the 30-minute period after precipitation of the abstinence syndrome, as described above.

Control animals (euthermic and hibernating) received implants of two placebo pellets (*5*); they were tested 72 hours later with naloxone (1 mg/kg, subcutaneously). All experiments were conducted during the winter season, with the animals maintained throughout at an ambient temperature of 5°C in dim illumination. The onset and offset of illumination paralleled the natural light cycle. All animals in this study had been cycling in and out of hibernation bouts in a normal fashion. Experiments on the effects of morphine exposure during euthermia were conducted in animals that were naturally in this phase of the hibernation cycle at the time of testing.

Euthermic animals (N = 10) displayed heightened locomotor activity during the first 12 hours of morphine exposure that resulted in destruction (flattening) of their normally well-maintained nest. This was followed for the rest of the 72-hour period by a depressed phase that was typified by quiet, sedentary behavior. No animal entered hibernation during this period. Injection of naloxone after the 72-hour administration of morphine precipitated a vigorous abstinence syndrome incorporating a constellation of 14 signs. Six of these signs (exploratory behavior, nesting behavior, grooming, vocalization, body shakes, and a yawn-like gaping of the mouth) were counted each time they occurred (Fig. 1A). The other eight signs, tabulated simply as present or absent during the 30-minute postnaloxone period, included chewing, milky dacryorrhea, digging, dyspnea, eye twitch, flattened posture, ptosis, and a forward thrust of the tail. Vocalization (consisting of a mixture of trilling and chirping sounds) and body shakes (head or trunk) were the most prominently displayed of the counted

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signs (Fig. 1A). In all animals, signs began to appear 1 to 2 minutes after naloxone administration and continued throughout the subsequent 30-minute observation period.

Control animals ($N = 2$) displayed no signs after naloxone injection, remaining quiet in the test chamber throughout the observation period.

After being tested with naloxone, the animals were anesthetized, the morphine pellets were removed, and the animals were returned to their home cages for a 30-day period. Morphine pellets were then implanted as before, and 72 hours later, naloxone was administered. The animals once again displayed a pronounced abstinence syndrome that showed no differences from that displayed after the initial morphine treatment.

Hibernating animals ($N = 6$) that had been exposed to morphine for 72 hours displayed uniform, normal behavior throughout the period of deep hibernation (rolled into a ball-like posture, little or no movement except for respiration), as well as during and after the arousal from hibernation caused by handling, when alert posture, attentiveness to the environment, and locomotor activity were evident. Naloxone injection during the immediate postarousal euthermic state failed to evoke an abstinence syndrome (Fig. 1B). The mean ± standard error of the number of occurrences of signs displayed after arousal and naloxone injection (exploring, 0.5 ± 0.5; body shakes, 0.2 ± 0.2; nesting, grooming, vocalization, and mouth gaping, 0) was significantly reduced (t-test, $P < .05$) from that observed in animals exposed to morphine during euthermia (Fig. 1A). Control hibernating animals, aroused to the euthermic state and tested with naloxone, displayed no significant differences from animals exposed to morphine during hibernation. In companion control experiments ($N = 2$), a single injection of naloxone (1 mg/kg, subcutaneously) during hibernation produced no overt behavioral effects or changes in hibernation state.

To exclude the possibility that changes in the blood-brain barrier or cardiovascular parameters during hibernation (*7*) might prevent subcutaneously administered morphine from reaching the brain in adequate quantity and thus preclude the development of physical dependence, we conducted another series of experiments in which morphine was infused directly through an implanted cannula into the lateral cerebral ventricle of 19 euthermic and hibernating animals (*8*). Nine euthermic animals received morphine intracerebroventricularly for 18 to 72 hours. Intracerebroventricular administration, like morphine pellet implantation, produced an initial phase of heightened behavioral activity, followed by one of quiet, sedentary behavior. In all animals, naloxone (1 mg/kg, subcutaneously) precipitated a strong abstinence syndrome indistinguishable from that produced by the 72-hour morphine pellet implantation. Administration of naloxone to control animals ($N = 3$) that had been given 0.9 percent NaCl intracerebroventricularly for 48 to 72 hours resulted in no overt abstinence signs.

Intracerebroventricular infusion of morphine in ten hibernating animals for 24 to 72 hours produced no changes in overt behavior during deep hibernation. Subsequent naloxone administration (1 mg/kg, subcutaneously) during the euthermic state immediately after arousal from hibernation failed to elicit an abstinence syndrome in any of these animals. Five of the ten animals began to arouse spontaneously 24 to 72 hours after the onset of morphine infusion, and all showed stereotypy at the earliest stages of arousal, while still curled in the typical hibernating posture. By contrast, only one of the five deliberately aroused animals showed stereotypy. The stereotypy consisted initially of dorsolateral head movements directed to the right and, as the arousal progressed, also included jerking of the right forelimb, circling, and licking and biting of the cotton nest material and chamber walls. It continued into the euthermic state and was not blocked by naloxone. Control experiments ($N = 3$) in which intracerebroventricular administration of 0.9 percent NaCl for 48 to 72 hours was followed by deliberate arousal and subsequent naloxone injection produced no abstinence signs or stereotypy. A second group of control experiments ($N = 3$) with 0.9 percent NaCl administered intracerebroventricularly for 24 to 72 hours showed that a single naloxone injection (1 mg/kg, subcutaneously) during deep hibernation produced no overt effects on behavior or on hibernation state.

After a 1-month cessation of intracerebroventricular morphine infusion, three animals from the euthermic group and seven from the hibernating group were retested with morphine administered intracerebroventricularly while in the euthermic state. All animals displayed the same kind of vigorous naloxone-precipitated abstinence syndrome that is illustrated in Fig. 1A.

During the active state, ground squirrels develop physical dependence on morphine, but transition to the hibernating state suppresses the development of this phenomenon. Nevertheless, the appearance in some animals of morphine-induced stereotypy closely resembling that described in morphine-tolerant rats (*9*) indicates that the CNS does respond to morphine during hibernation, though in an altered fashion.

We believe that our results are the first demonstration of a natural mammalian state that produces resistance to the development of physical dependence on morphine. A related phenomenon, natural resistance (tolerance) to the acute effects of morphine in a lagomorph, the Afghan pika, has been described (*10*). Although we cannot presently specify which features of the CNS are responsible during hibernation for the lack of physical dependence, four possibilities merit attention. (i) During hibernation the distribution pattern of morphine in the CNS may differ from that in the euthermic state, resulting in a modified response. (ii) Tolerance to morphine failed to develop in cultured mouse spinal cord at 20°C, whereas it did develop at 35°C (*11*). Thus, a temperature-dependent mechanism may contribute to the blocking of physical dependence. (iii) Administration of the CNS tripeptide thyrotropin-releasing hormone modified the characteristic development of morphine physical dependence in mice (*12*). Our observations could thus be due to changes in neurotransmitter (or neuromodulator) parameters during hibernation, perhaps involving release of endogenous opioids. (iv) The density or binding characteristics of opiate receptors in the CNS may be different in the hibernating and the nonhibernating states, with consequent differences in the responsiveness to morphine.

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5. Morphine pellets were formulated by the method of R. D. Gibson and J. E. Tingstad [*J. Pharm. Sci.* **59**, 426 (1970)]. Placebo pellets contained only the base material, that is, lactose, 0.075 g; Avicel, 0.075 g; Cab-o-Sil, 0.00075 g; and calcium stearate, 0.0015 g.
6. Arousal from hibernation typically requires approximately 2 hours. During this time, internal temperature increases from hibernating levels (near ambient temperature, 5°C) to 36° to 38°C, and behavioral activity ensues.
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8. Euthermic animals were anesthetized (Nembutal, 65 mg/kg, intraperitoneally), and pellets were implanted stereotaxically under aseptic conditions with a unilateral cannula guide (22-gauge, stainless steel tube). The tip of the guide was positioned 1 mm above the right lateral ventricle at coordinates AP, 7.1; L, 1.8; H, 9.5 [as given in S. A. Joseph, K. A. Knigge, L. M. Kalejs, R. A. Hoffman, P. Reid, *Edgewood Arsenal Special Publication 100-12* (1966)]. After at least 1 week of recovery from surgery, morphine sulfate (55 μg/μl in sterile 0.9 percent NaCl) was infused into the lateral ventricle with a miniature osmotic pump (Alza model 2001) connected to an injection cannula (26-gauge stainless steel tube) by a short length of PE-20 polyethylene tubing. The tip of the injection cannula projected 1 mm beyond the tip of the guide tube into the ventricular space. Morphine was delivered at a rate of 1 μl/hour for a period of up to 72 hours. For experiments on euthermic animals, the pump was implanted subcutaneously in the interscapular region, with the animals under light ether anesthesia; in hibernating animals, it was not implanted in the animal but rather was immersed continuously in a container of 0.9 percent NaCl maintained at 37°C to provide sustained pumping at a rate equal to that in euthermic animals. After the conclusion of each experiment, the infusion site was verified by injecting India ink through the injection cannula, killing the animal with a Nembutal overdose, and examining thionine-stained, serial coronal sections cut at 20 μm.
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Induced Hearing Deficit Generates Experimental Paranoia

Abstract. *The development of paranoid reactions was investigated in normal people experiencing a temporary loss of hearing. In a social setting, subjects made partially deaf by hypnotic suggestion, but kept unaware of the source of their deafness, became more paranoid as indicated on a variety of assessment measures. The results support a hypothesized cognitive-social mechanism for the clinically observed relationship between paranoia and deafness in the elderly.*

Clinical observation has uncovered a relationship between deafness and psychopathology (*1–3*). In particular, when deafness occurs later in life and the hearing loss is relatively gradual, paranoid reactions are often observed (*4–14*). Delusions of persecution and other paranoid symptoms, first noted by Kraepelin (*6*) in 1915, seem especially prevalent among the hard-of-hearing elderly (*7–9*). Audiometric assessment of hospitalized, elderly patients (with age and other selection factors controlled statistically) has revealed a significantly greater degree of deafness among those diagnosed as paranoid than among those with affective disorders (*10–12*).

Maher (*15*) suggested that one process by which deafness may lead to paranoid reactions involves an initial lack of awareness of the hearing defect by the person, as well as by interacting others. Paranoid thinking then emerges as a cognitive attempt to explain the perceptual anomaly (*16*) of not being able to hear what people in one's presence are apparently saying. Judging them to be whispering, one may ask, "about what?" or "why me?" Denial by others that they are whispering may be interpreted by the hard-of-hearing person as a lie since it is so clearly discrepant with observed evidence. Frustration and anger over such injustices may gradually result in a more profound expression of hostility.

Observers, without access to the perceptual data base of the person experiencing the hearing disorder, judge these responses to be bizarre instances of thought pathology. As a consequence, others may exclude the hard-of-hearing person, whose suspiciousness and delusions about their alleged plots become upsetting (*17*). Over time, social relationships deteriorate, and the individual experiences both isolation and loss of the corrective social feedback essential for modifying false beliefs (*18, 19*). Within a self-validating, autistic system, delusions of persecution go unchecked (*20*). As such, they eventually become resistant to contrary information from any external source (*21*). In this analysis, paranoia is sometimes an end product of an initially rational search to explain a perceptual discontinuity, in this case, being deaf without knowing it.

We now report an experimental investigation of the development of paranoid reactions in normal subjects with a temporary, functional loss of hearing. Across a variety of assessment measures, including standard personality tests, self-reports, and judgments of their behavior by others in the situation, these subjects became significantly more paranoid than did subjects in two control conditions. The effect was transient and limited to the test environment [by the specificity of the instructions, by extensive postexperimental interviews (debriefing procedures), and by the healthy "premorbid" status of each participant]. Nevertheless, qualitative observations and objective data offer support for the role of deafness-without-awareness as a causal factor in triggering paranoid reactions. Although the subjects were young and had normal hearing, these results have obvious bearing on a possible cognitive-social mechanism by which deafness may eventuate in paranoia among the middle-aged and elderly.

Participants were 18 college males selected from large introductory classes. In the selection process, each student (i) demonstrated that he was highly hypnotizable according to the Harvard Group Scale of Hypnotic Susceptibility (*22*) and the Stanford Scale of Hypnotic Susceptibility, form C (*23*); (ii) evidenced posthypnotic amnesia; (iii) passed a test of hypnotically induced partial deafness; (iv) scored within the normal range on measures of psychopathology; and (v) attended at least one of two hypnosis training sessions before the experiment.

Six participants were randomly assigned to the experimental treatment in which partial deafness, without awareness of its source, was hypnotically induced. The remaining participants were randomly assigned to one of two control groups. In one of these groups, partial deafness with awareness of its source was induced to demonstrate the importance of the knowledge that one's difficulty in understanding others is caused by deafness. In the other control group, a posthypnotic suggestion unrelated to deafness was experienced (a compulsion to scratch an itchy ear) along with amnesia for it, to establish whether merely carrying out a posthypnotic suggestion with amnesia might be sufficient to yield the predicted results. Taken together, these two groups provide controls for experimental demand characteristics,

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