may correspond to an evolutionary stage intermediate between other birds of paradise and *A. macgregoriae*. Their adult male plumage is more ornamented than that of any bowerbird: iridescent breast shield, wirelike ornamental feathers protruding from the head or tail. Unlike other birds of paradise, these two genera construct terrestrial display courts that deserve the name "bower," but that lack ornamentation and are simpler than the bower of any species of Ptilonorhynchidae.

The spatial arrangement of bowers is relevant to the possible role of arena behavior in bowerbird evolution (*2*). Arena behavior, evolved independently by numerous species of birds, mammals, frogs, and insects, means the clustering of displaying males at traditional display courts, to which females come for insemination and where males are in visual or vocal contact with each other. At least one population of bowerbird (*Archboldia papuensis sanfordi*) clearly has its bowers clumped in arenas, but this appeared to me not true of *Amblyornis flavifrons*. I found bowers along both ridges that I climbed, the bowers or sets of bowers were about equally spaced along the ridges, and the distance between bowers was such that I could not hear the calls of one bower-owning male from the next bower.

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6. The live appearance of adult male *A. flavifrons* is as follows: stocky build; tail slightly notched, extending 4 cm beyond the folded wings; bill entirely black, legs and iris dark; upper parts, head, and upper breast dark brown, contrasting with the warm, orange ochraceous lower breast and belly; crest originating at the base of the bill and extending over the whole forehead and crown to cover the upper back; crest yellow viewed from the side, orange-yellow viewed from other angles. The crest is more orange in living birds than in the 1895 specimens, partly because of differences in arrangement of the feathers (underfeathers more orange and less yellow than superficial ones), and partly because of postmortem fading and yellowing, as documented for *A. macgregoriae* and *A. subalaris* [E. T. Gilliard and M. LeCroy, *Bull. Am. Mus. Nat. Hist.* **123**, 1 (1961); (*5*), p. 343; R. Schodde and J. L. McKean, *Emu* **73**, 51 (1973)]. The subadult male acquires the orange underfeathers of the crest before the superficial yellower feathers. The previously unknown female, and probably immatures of both sexes, resemble the adult male, except for lacking the crest. *A. macgregoriae* differs in that the underparts are dirty olive-brown with no hoodlike contrast between upper and lower breast, the lower mandible is pale horn rather than black, the tail is rounded rather than notched, and the crest of the adult male arises from the middle of the crown rather than from the base of the bill and is more orange to red-orange (less yellow). Specimens of *A. flavifrons* were not collected as this is forbidden: *A. flavifrons* is on Indonesia's list of protected species, and the Foja Mountains are part of a national park. Copies of my tapes of the vocalizations have been deposited with the Cornell Laboratory of Ornithology.
7. I thank H. Makabory for collaboration in the fieldwork, M. LeCroy for suggestions, and the National Geographic Society, World Wildlife Fund, and Lievre Fund for support.

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Selective, Naloxone-Reversible Morphine Depression of Learned Behavioral and Hippocampal Responses

Abstract. *Morphine administered intravenously causes immediate and complete abolition of a simple learned response (classically conditioned nictitating membrane extension in rabbit) and of the associated learning-induced increase in hippocampal neuron activity. Both effects are completely reversed by low doses of naloxone. Morphine has no effect at all on behavioral performance of the unconditioned reflex response.*

Currently there is widespread interest in the effects of opiates and endogenous opioids on learning and memory processes (*1, 2*). At present, these effects are complex and not well understood (*3*). Indeed, the effects of the original opiate—morphine—on learning and memory processes are not clear (*2, 4*). A major source of difficulty is that, in most learning experiments, drug effects on memory and on performance cannot easily be distinguished. Classical conditioning has the advantage of permitting relatively direct and independent measurement of drug effects on the learned response—the conditioned response (CR)—and on performance—the unconditioned response (UR). If a drug abolishes the CR but does not affect the UR, performance variables relating to the execution of the behavioral response can be excluded. We now report such a selective action of morphine on a simple conditioned response.

In previous work, we have decribed a learning-induced increase in hippocampal unit activity that develops in simple learning situations and that invariably predicts behavioral learning. This response is independent of performance and relates only to the learned response: over a wide range of conditions that influence the development, maintenance and extinction of the learned behavioral response, alteration of the learning-induced hippocampal response precedes and accurately predicts subsequent alteration of the learned behavioral response (*5, 6*). In short, the hippocampal response seems to have the properties of a relatively direct measure of the inferred processes of learning and memory retrieval in the brain. The present experiment provides a further test of this hypothesis.

Methods of training and recording have been described in detail (*5*). Rabbits are restrained and given classical conditioning training with paired tone conditioned stimulus (CS) (1 kHz, 85 dB, 350 msec) and corneal airpuff unconditioned stimulus (US) (210 g/cm pressure, 100 msec, coterminating with CS) trials at a rate of approximately one per minute, eight paired trials and one CS-alone test trial per block, 13 blocks per day. Control animals are given the same number of stimuli but explicitly unpaired in a pseudorandom sequence with an interstimulus interval of approximately 30 seconds. The nictitating membrane extension response is measured with a micropotentiometer attached to the membrane and digitized for computer analysis. Multiple unit and isolated single unit activity is recorded from the CA1 pyramidal cell layer of the dorsal hippocampus using permanently implanted microelectrodes (or a permanently implanted microdrive system). The largest unit discharges (multiple unit recording) or all unit discharges (single unit recording) are detected with a discriminator circuit and stored in the computer in 3-msec time bins for each trial for analysis. Standard scores of the conditioned increase in unit activity are computed from the background and CS period activity.

In the present experiments, animals were trained to a criterion of eight CR's in any nine successive trials, given two blocks of additional training, and then injected with morphine intravenously (ear vein). A rough dose response was determined in pilot animals injected with 1, 5, or 10 mg of morphine per kilogram of body weight in constant volume (0.25 ml/kg). The 1.0 mg/kg dose had no effect on the learned behavioral response and served as a vehicle control. The 5 and 10 mg/kg doses both had profound effects on behavior. In these experiments, morphine doses were as follows: 13 paired

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animals were given 5 mg/kg; six paired animals, 10 mg/kg; and four unpaired control animals, 5 mg/kg. Naloxone (0.1 mg/kg) was injected five blocks later, and two additional blocks of training were given. Two additional animals were given paired training with unit recording electrodes in the central nucleus of the inferior colliculus and injected with 5 and 10 mg of morphine per kilogram, followed by naloxone.

Figure 1A shows the behavioral data for the 5 mg/kg dose of morphine. The CR was immediately and completely abolished, but the UR did not change at all. The CR's recovered slightly over the five blocks, and then immediately returned to initial level after naloxone. This morphine effect on the CR is statistically significant [$F(7, 84) = 30.50$, $P < .001$]. There was no effect on the UR [$F(7, 84)$, $P < 1$]. Results for the 10 mg/kg paired animals were identical except that the CR was even more profoundly depressed. This dose had no effect on the UR. The unpaired control animals permitted independent determination that morphine had no effects on the UR [$F(7, 21) = 1.58$, not significant]. The powerful effect of morphine on memory retrieval was for a task that had just been learned. The animals had been trained to a high level of conditioned responding but had not been overtrained—the memory is recent, not old.

For hippocampal unit recording, only those animals with electrode tips localized to the CA1 pyramidal cell layer and with acceptable unit recordings (*5*) were analyzed ($N = 6$). The effect of morphine on the learned hippocampal response (standard scores) for this group is shown in Fig. 1B. As with the learned behavioral response, the learned increase in hippocampal unit activity was immediately and completely abolished [$F(7, 35) = 3.51$, $P < .05$]. The recovery of this response is greater than and in fact predicts the recovery of the learned behavioral response. Naloxone immediately restores the learned hippocampal unit response to its initial level. An individual example of the action of morphine on the simultaneously recorded behavioral and hippocampal unit responses is shown in Fig. 2. Morphine had no effect on the number of tone CS evoked unit discharges in the inferior colliculus. That the marked morphine depression of the learned behavioral and hippocampal responses is immediately reversed by a low dose of naloxone suggests that it is due to a specific receptor action, possibly on the μ receptors, which preferentially bind morphine and for which naloxone has its highest affinity (*7*).

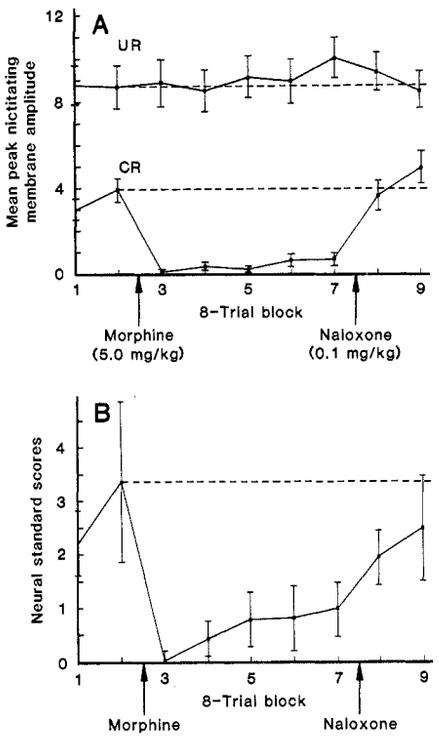

Fig. 1. (A) Mean ($N = 13$) nictitating membrane response peak amplitude during the conditioned stimulus period (for CR) and unconditioned stimulus period (for UR). Dashed lines represent the baseline before morphine was given. (B) Mean hippocampal unit standard scores during the conditioned stimulus period. Dashed line represents the baseline.

Important recent evidence suggests that some effects of administered brain opioids on memory may be mediated in part peripherally (*8*). We have completed preliminary studies with morphine and naloxone analogs administered both peripherally and intracerebrally that indicate strongly a direct, central action of morphine. The selective and reversible abolition of the CR by morphine provides a potentially useful tool for identifying the neuronal circuitry that codes the learned response—the memory system—as well as for understanding of the mechanisms of action of morphine. The absence of morphine action on neurons in the central nucleus of the inferior colliculus argues that the essential neuronal plasticity coding the learned response does not develop in the CS pathway—the primary auditory relay nuclei (*9*). By the same token, the UR is unaffected by morphine. Consequently, the reflex pathways that generate the UR are not a part of the essential neuronal plasticity coding memory.

The action of morphine on the learning-induced hippocampal response parallels its action on the learned behavioral response. Two effects of hippocampal unit activity support the general hypothesis that the learning-induced hippocampal unit response is a relatively direct measure of learning and memory processes in the brain. (i) It recovers more rapidly from the effects of morphine than the learned behavioral response does, and (ii) it predicts the recovery of the behavioral response over trials. It cannot be argued, however, that the effect of morphine on the learned behavioral and hippocampal responses is due to a direct action on the hippocampus. Although this is possible, it is also possible that morphine exerts its primary effects on other structures and circuits in the brain. Some portion of the neuronal circuitry essential for the learned response—for memory retrieval of a simple, classically

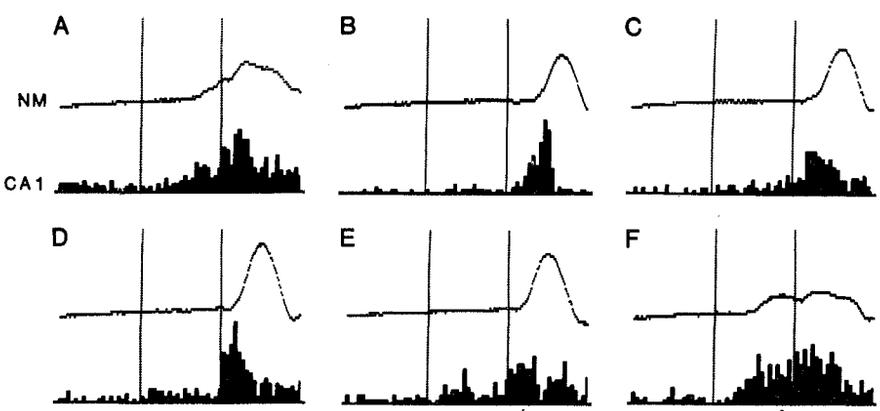

Fig. 2. Examples of eight-trial averaged behavioral nictitating membrane (*NM*) responses (upper trace) and associated multiple unit histograms of hippocampal activity (lower trace, 12-msec time bins) for a single animal. The early vertical line indicates tone onset, and the later line, airpuff onset. Total trace length equals 750 msec. (A) Block of eight trials immediately preceding the injection of morphine. Note the (conditioned) increase in hippocampal activity in the CS period (CS-US interval), which is completely absent immediately after the injection of morphine (B). The unit increase begins to redevelop in the later blocks 3 to 5 (C to E). Both the behavioral and unit conditioned responses recover fully after an injection of naloxone (F).

conditioned response to an aversive US—is impaired by morphine. It may be that conditioned aversiveness or fear is an essential component of learning and memory in this task. Considerable evidence implicates morphine as acting on conditioned fear (*10, 11*).

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Heroin "Overdose" Death: Contribution of Drug-Associated Environmental Cues

Abstract. *A model of "overdose" deaths among heroin addicts is proposed which emphasizes recent findings concerning the contribution of drug-associated environmental cues to drug tolerance. Results of animal experiments performed to evaluate this model suggest that conditioned drug-anticipatory responses, in addition to pharmacological factors, affect heroin-induced mortality.*

Substantial tolerance generally develops to the effects of opiates; the drug-experienced individual can survive a dose many times greater than that which would kill the drug-inexperienced individual (*1*). Despite such tolerance, about 1 percent of U.S. heroin addicts die each year, mostly from the so-called overdose (*2*). In urban areas with substantial numbers of addicts, drug overdose is among the leading causes of death in people aged 15 to 35 (*3*). Postmortem examination of these victims routinely reveals pulmonary edema (*4*), which usually is attributed to hypoxia resulting from drug-induced respiratory depression (*5*).

Although mortality attributed to drug overdose is a major public health problem, its mechanisms are unclear. Some fatalities result from pharmacological overdose (*6*), but many experienced drug users die after a dose that should not be fatal in view of their tolerance (*7, 8*). Indeed, some die following a heroin dose that was well-tolerated the previous day (*8*). Some fatalities may result from a synergism between the opiate and other drugs concomitantly administered or from adulterants (especially quinine) in the heroin, but many do not result from such drug interactions (*7, 8*).

We suggest that drug "overdose" may frequently result from a failure of tolerance. That is, the opiate addict, who can usually tolerate extraordinarily high doses (*4, 9*), is not tolerant on the occasion of the overdose. A recently proposed model of tolerance based on the principles of Pavlovian conditioning (*10*) suggests conditions that favor such a failure of tolerance. The model is based on Pavlov's (*11*) suggestion that drug administration constitutes a conditioning trial, with the conditioned stimulus consisting of environmental cues present at the time of administration and the unconditioned stimulus consisting of the systemic effects of the drug. According to this interpretation of tolerance, as the drug is administered with increasing frequency, with the same environmental cues signaling each pharmacological stimulation, an association is established between these cues and the central effects of the drug. This association may be revealed in a subject with a history of drug abuse by administering a placebo in the drug administration environment. Conditioned pharmacological responses revealed in this manner are often the converse of the unconditioned drug effects (*10, 12*). Such anticipatory responses attenuate the drug effects and contribute to tolerance. Accordingly, environmental signals of impending pharmacological stimulation are important because they enable the organism to make compensatory conditioned responses in anticipation of the unconditioned effects.

Table 1. Rat mortality after the injection of heroin at 15 mg/kg.

Group	Number of rats	Mortality (%)
ST	37	32.4
DT	42	64.3
Control	28	96.4

On the basis of this model, a failure of tolerance should occur if the drug is administered in an environment that has not, in the past, been associated with the drug. Indeed, several studies have demonstrated such dependence of opiate tolerance on environmental cues. For example, if the last of a series of morphine injections is given in the presence of cues that have not previously signaled the drug, rats and humans display less tolerance than if this injection were given in the presence of the usual drug-associated cues (*13*). Although these studies establish a role for learning in morphine tolerance, primarily small drug doses were used. There is evidence, however, that the conditioning model of tolerance applies to the pernicious effects of very high doses of opiate (*14*). Thus, one contributing factor in death from the so-called opiate overdose might be the absence of a conditioned compensatory pharmacological response.

The results of the study described below indicate that heroin-induced mortality in heroin-experienced rats is higher when the drug is injected in an environment not previously associated with the drug than when it is injected in the usual drug-administration environment. The experimental design used provided a methodologically rigorous demonstra-

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