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15. The order of presenting drug (D) and placebo (P) conditions on each of the 2 days of testing (four sessions) was counterbalanced by assigning eight subjects in the hyperactive group (and four subjects in the control group) to each of the four possible order combinations (DPDP, DPPD, PDPD, and PDDP). A warm-up test of four items was presented in each of the four sessions before data collection started to minimize practice or warm-up effects.
16. An alternative partition of the 3 degrees of freedom associated with the four learning-retention conditions may be derived from an analysis of variance incorporating the two main effects, learning state and retention state, and their interaction. For example, in such an analysis (which included a factor to evaluate counterbalancing procedures), the only significant effects were retention state [$F(1,28) = 18.5$] and the interaction of learning state and retention state [$F(1,28) = 15.5$]. The three planned comparisons discussed in the text are preferable because they incorporate a test for bidirectional state dependency, which the regular analysis of variance lacks.
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19. The reasons why these nine hyperactive children failed to show drug facilitation on day 1 but showed a large effect on day 2 are obscure. Hypotheses not testable from our data are (i) for these individuals, drug facilitation will occur in difficult tasks (for example, 24-item lists) but not in easy tasks (6-item lists), (ii) for these individuals, the hyperactive state was normalized on day 1 without medication as a result of the novel situation, the stress experienced, or both. Of these nine children, six received the drug condition the morning of the first day, so perhaps the result was partially due to an effect of practice or of the time of day.
20. Given the trend of our data for the control group, we expect a larger dose of methylphenidate would effectively produce a behavioral difference by imparing performance in the drug state relative to the placebo state, and that under such conditions the group of normal children would show state dependency similar to that reported for adults (*12*).
21. Supported by the Research Foundation of the Hospital for Sick Children (J.M.S.) and the Connaught Foundation (M.K.). We thank A. R. Hart, who scheduled and managed subjects, Dr. W. Roberts, who performed the neurological examinations of the subjects and interviewed parents, and M. Hiscock and B. Caplan, who helped test subjects.

9 December 1975; revised 25 March 1975

Analgesia Mediated by a Direct Spinal Action of Narcotics

Abstract. *Narcotic analgetics administered directly into the spinal subarachnoid space of the rat via a chronically inserted catheter produce a potent analgesia that can be antagonized by naloxone. The narcotics, acting only at the spinal level, changed cord function to block not only spinal reflexes but also the operant response to painful stimuli.*

Morphine, acting within the mesencephalic central gray matter alone, can significantly elevate the nociceptive (pain) threshold (*1*). This observation suggests that narcotic analgesia may be principally mediated by a unique action of the drug upon this supraspinal structure. We now present evidence, however, that the direct injection of narcotics into the spinal subarachnoid space, producing an action limited entirely to the spinal cord, can also produce a well-defined, dose-dependent analgesia in the intact and behaving animal.

To permit the long-term administration of drugs into the spinal subarachnoid space, polyethylene catheters (*2*) were inserted through a slit made in the cisternal membrane of the anesthetized rat. The catheter was cut to extend to the level of the lumbar enlargement and was affixed to the back of the skull with stainless steel screws and dental acrylic. After a 2-week recovery period, 5 μl of drug solution (*3*) was injected by a gear-driven pump (5 μl of vehicle was given immediately to wash the catheter). We assessed the pain threshold with both a spinally mediated response, the tail flick (*4*), and responses that have a supraspinal component, namely, the hot-plate response (*5*) and the squeak-escape response (*6*).

Narcotics administered into the subarachnoid space of the spinal cord elevated the analgetic thresholds (Fig. 1). All elevated thresholds produced by these narcotics could be antagonized by naloxone injected either intraperitoneally (0.5 to 2.0 mg per kilogram of body weight), or directly into the spinal catheter (0.1 to 3.0 μg). The time of onset of the analgesia varied with the drug; fentanyl produced marked changes within 2 to 3 minutes, but morphine, codeine, and ethylmorphine required about twice as long. Similarly, the duration of action was drug- and dose-dependent, with the effects of fentanyl lasting 20 to 30 minutes and those of morphine lasting as long as 2 hours.

The withdrawal-squeak response to hindpaw pinch was attenuated with the same time course as that observed in the hot-plate test. In contrast, the forelimbs and, particularly, the face remained normally sensitive to pinch. After 40 to 60 minutes, however, with the higher dose of morphine, the forepaws would also begin to lose their responsiveness. The face, however, never became insensitive.

To further verify that the change in the thresholds represented a change in the animal's perception of stimulus intensity, we performed experiments using the operant shock titration procedure (*7*). In these experiments, fentanyl (5 μg) and morphine (15 μg) produced a uniform elevation in the level of tolerated shock to between two and three times the threshold in the absence of drugs.

We were concerned that the intrathecally injected narcotics were moving rostrally to supraspinal structures either by diffusing through the subarachnoid

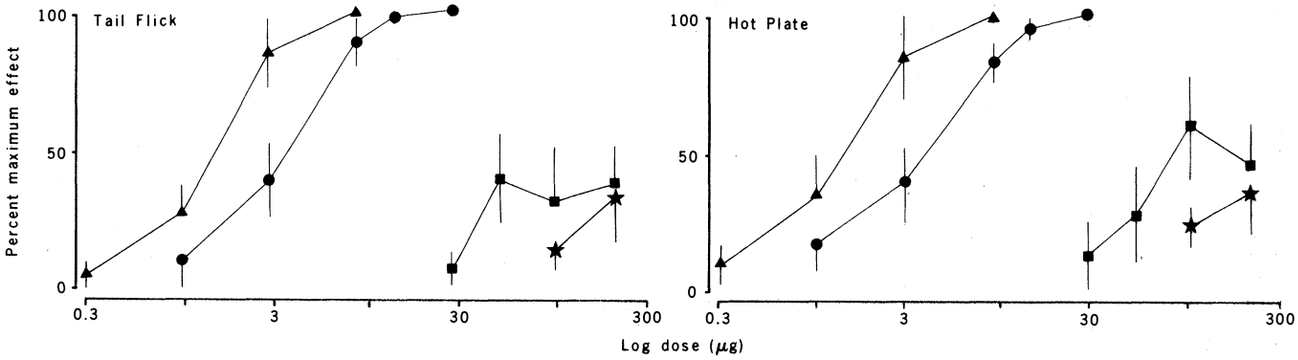

Fig. 1. Log dose–response curves for fentanyl citrate (▲), morphine sulfate (●), codeine alkaloid (■), and ethylmorphine hydrochloride (★) obtained on the tail-flick and hot-plate tests. The vertical bars are standard errors of the mean. Each point is the mean response of at least four animals, plotted in terms of the percentage of maximum effect (*15*).

space or by moving into blood and thence to other sensitive structures. With regard to the first alternative, injections of dye (10 μl, 5 percent bromophenol blue) showed intense staining limited to spinal segments not more than 1.0 to 1.5 cm distant in either direction. Moreover, the absence of an initial effect upon the forelimbs suggests that the more rostral spinal segments were not initially affected by the lumbar injection. With regard to the second alternative, the intravenous injection of 15 μg of morphine did not alter the response of the animal on any of the three measures employed (*8*). The assumption that the spinally administered morphine did not move into more rostral brain regions was further substantiated on the basis of studies in which ^{14}C-labeled morphine sulfate was administered through the spinal catheter and animals were sacrificed at intervals of up to 60 minutes after the injection. At even the longest intervals, neither forebrain nor brainstem radioactivity ever exceeded 0.15 percent of that recovered from the spinal cord. It thus seems certain that the behavioral effects observed resulted from a local pharmacological action of these narcotics on the lower spinal segments. Injections of the potent local anesthetic dibucaine (1 to 10 μg) not only blocked responding on the experimental tasks, but unlike equipotent doses of morphine, it resulted in pronounced motor incoordination. Moreover, such effects produced by dibucaine were not antagonized by naloxone.

Morphine can antagonize reflexes (*9*) and alter evoked spinal activity in animals with sectioned spinal cords (*10*), as well as depress the discharge (by local iontophoresis) of spinal units responding characteristically to strong peripheral stimuli (*11*). Moreover, narcotics given by arterial injections directed toward the spinal cord are more potent in blocking the monosynaptic reflex than when they are injected intravenously (*12*). Such findings, while showing a pharmacological action of narcotics at the cord level, do not indicate that the physiological effect observed after analgetics have been systemically administered plays any role in the animal's perception of or response to environmental stimuli. Our principal finding, therefore, is that narcotics exert a direct, pharmacologically specific effect on spinal function, which diminishes the response of the intact, behaving animal to otherwise aversive peripheral stimulation. Although the mode of action of spinally administered narcotics is not clear, the fact that they were effective in antagonizing responses to the hot-plate and pinch and elevated the operantly defined shock titration threshold indicates that the narcotic effect was not due simply to a local attenuation of reflex activity. Substantial stereospecific binding of a narcotic occurs within the spinal cord in the vicinity of the substantia gelatinosa (*13*). In light of this binding and of the proposed importance of the substantia gelatinosa to the transmission of noxious stimuli (*14*), it is reasonable, if speculative, to suggest that narcotics directly modulate the activity of the substantia gelatinosa. Two things remain to be determined: (i) the relative importance of this narcotic-sensitive spinal system compared to supraspinal systems, and (ii) the specific role played by the spinal cord in the mediation of the analgesia observed following the systemic administration of narcotics.

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2. A length of polyethylene (PE-10) tubing was inserted through the hub of a disposable 20-gauge needle from which the needle segment had been removed. The tubing was then fastened with an epoxy cement so that 8.5 cm of tubing extended from the hub. During insertion, the catheter was slightly stiffened by inserting a length of 0.005-inch wire, which extended to within 1 cm of the catheter tip. By flexing the head downward and continually rotating the catheter during insertion, the incidence of damage to spinal tissue was limited to one or two rats in ten (T. L. Yaksh and T. A. Rudy, in preparation).
3. The solution consisted of an osmotically and ionically balanced mixture consisting of NaCl (7.46 g), KCl (0.19 g), $MgCl_2 \cdot 6\,H_2O$ (0.19 g), and $CaCl_2$ (0.14 g) made up in 1 liter of distilled water and filtered with 0.22-μm Millipore filter into pyrogen-free containers.
4. The tail flick, a spinally mediated reflex, was assessed by laying the tail across a slit through which light from a focused bulb projected. The time between the light's being switched on to the tail's being abruptly moved was the measured response. In the absence of a response, the light was turned off after 10 seconds to prevent tail damage.
5. The hot-plate response was defined as the interval between the time the animal was placed on a heated surface (55° ± 1°C) to the time it licked its hindpaw. The trial was terminated after 30 seconds if no response was observed.
6. The forelimbs and face were pinched lightly and systematically with a pair of forceps having a pressure area of 3 mm^2. In normal animals, this pinch resulted in squeaking, signs of agitation, and a vigorous effort to dislodge the forceps.
7. The animal was restrained in a plastic box with a lever at one end; its tail protruded from the other. Shock was applied to the tail in an ascending stepwise fashion from 0 to 4 ma by operant programming equipment. If the animal pressed the lever, the shock was reduced one step; if the lever was not pressed, the shock level was raised one step, and so on. In this manner, the animal was able to control or titrate the level of shock that it received [J. Yeung, T. L. Yaksh, T. A. Rudy, *Clin. Exp. Pharmacol. Physiol.* **2**, 261 (1975)]. With this paradigm, the shock titration threshold is the shock that will support an 80 to 90 percent level of escape behavior (T. L. Yaksh and T. A. Rudy, unpublished observation).
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15. This conversion was used to permit comparison between animals having slightly differing baselines, where the percent maximum effect is the difference between the postdrug and predrug latencies divided by the difference between the cutoff time and the predrug latency, times 100.
16. We thank M. Caine, P. Huang, M. Kuzmicki, R. Plant, and J. Yeung for their assistance in carrying out the experiments and in preparing the manuscript.

2 February 1976; revised 30 March 1976

Evolution on the Level of Communities

Abstract. *According to traditional models, natural selection is largely insensitive to an organism's effect on its community. Effects on the community at large cannot feed back differentially to the organisms that cause them, and, hence, cannot lead to the differential fitness of the organisms. However, if a spatial variation exists in community composition, organisms do differentially feel their own effects on the community, and this leads to a form of evolution on the community level. Without violating the principle of individual selection, the concept of an organism that exists for the "function" it performs in its community may be valid in some cases.*

The idea that biological communities are "super-organisms" has arisen many times in the history of science (*1*). In this analogy a species is likened to an organ whose function can only be understood in terms of its role in the maintenance of a larger whole.

At present there is little theoretical support for the super-organism concept. Current evolutionary theory explains the traits of species in terms of their advantage to individuals; community functions, if they exist, are viewed as coincidental.

Elsewhere I and others have presented a model of structured demes that leads to