

## Failure of the Opiate Antagonist Naloxone to Modify Hypnotic Analgesia

(endogenous opioid/ischemic pain and distress/overt and covert analgesia)

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Contributed by Ernest R. Hilgard, March 7, 1975

**ABSTRACT** Hypnotic analgesia in some respects resembles opiate analgesia. We tested the hypothesis that some features of hypnotic analgesia are mediated through neuronal pathways activating specific opiate receptors in brain. The opiate antagonist naloxone had no effect on hypnotic analgesia in three subjects. Thus, the hypothesis was not confirmed.

The discovery and localization of highly specific opiate receptors in the central nervous system (1-4) has suggested that there might be a natural ligand (i.e., an endogenous substance with conformational similarity to the opiates), which would interact with the opiate receptors in the manner of a neurotransmitter. One of us proposed that such an endogenous opioid might have a modulatory function in pain pathways, serving, perhaps, to obtund chronic pain (5). Recent experimental evidence points in the same direction. Naloxone, a specific opiate antagonist, lowers the pain threshold in mice tested by the hot plate procedure (6). Analgesia is produced by electrical stimulation in periaqueductal gray and other mesencephalic and diencephalic sites (7, 8). These are precisely the areas in brain where high densities of opiate receptors are found (9, 10), and where microinjection of morphine produces analgesia (11). The analgesia resulting from electrical stimulation, just as that resulting from microinjection of morphine, is blocked by naloxone (12). Acupuncture analgesia is also reported to be blocked by naloxone (D. J. Mayer, D. D. Price, and A. Raffi, manuscript in preparation).

In the ordinary procedures of hypnosis with suggested analgesia both sensory pain and suffering (distress) are reduced. Pain and distress reported under these usual circumstances we shall refer to as *overt* pain and distress. The failure to perceive pain and distress appears to be in part a function of some amnesic process so that pain and distress, felt at some level, may not be available to the consciousness of the hypnotically analgesic patient. Special techniques are required to relieve the amnesia for the hidden experience; the reports obtained in this way we shall indicate as *covert* pain and distress. Under some conditions it can be demonstrated that covert experience of sensory pain has been felt close to its normal value, while the distress component is reduced or absent (13). The failure to find a clear evidence for the reduction of covert distress in one experiment of the series from the same laboratory (14) we now interpret as having resulted from the rapid alternation of inquiry by the direct and indirect methods, although some uncertainties remain. The differences between the effect of hypnotic analgesia on covert pain and on distress has been found in experiments currently under way for both cold pressor pain and for ischemic pain by the tourniquet-exercise method.

The property of hypnotic suggestion in producing a differential effect as between sensory pain and distress, especially in covert pain and distress, appears in some respects to be similar to the analgesia produced by opiates. This, together with the findings on opiates and electrical stimulation cited above, suggested to us the possibility that analgesia produced by hypnotic suggestion might be mediated by a neuronal pathway containing the postulated opioid neurotransmitter. This hypothesis requires, at the least, that naloxone be able to block covert hypnotic analgesia, especially the distress component. The phenomenon of indifference to pain under hypnotic suggestion is so dramatic and clearcut that even a few experiments with naloxone suffice to test the hypothesis. Here we report a number of trials with three subjects, in which no effect of naloxone could be discerned.

### Experimental procedures for studying the reduction of pain and distress through hypnotic analgesia

Each of the subjects used in the study was highly susceptible to hypnosis and had demonstrated his ability to eliminate both pain and suffering under usual analgesic procedures.

The first trial provided a baseline for experienced pain under normal waking conditions. Pain was induced by the tourniquet-exercise method, as developed in the Harvard laboratory (15). As a precaution, subjects were first tested with a petechiometer to be sure that capillary resistance was high enough to avoid damage by the tourniquet procedure (16). The arm was held high to promote venous drainage, and the blood was further removed by wrapping the forearm with an elastic bandage prior to inflating the tourniquet, a sphygmomanometer cuff above the elbow, inflated to 250 mm Hg ( $3.3 \times 10^4$  pascals). The bandage was removed and the arm lowered; the subject then exercised by pressing a hand dynamometer loaded to 10 kg, 20 times for a 2-sec hold and a 2-sec release. Then he waited as the pain mounted, and reported the felt pain and the distress engendered by it on numerical scales upon request, with reports every 30 sec. Two numerical scales were used, one for sensory pain and one for distress, modified slightly from those previously used in this laboratory. Both scales were explained to the subject as beginning at 0 for no pain (or no distress), 1 for just noticeable pain or distress, and then up through moderate and severe to 10 as intense. This was interpreted as a critical value, although the scale was explained as open at the top so that both pain and distress might be assigned numbers higher than 10. When asked to indicate what they would think of as the most extreme pains or distress they had experienced outside the laboratory, the subjects assigned values in the neighborhood of 20, indi-

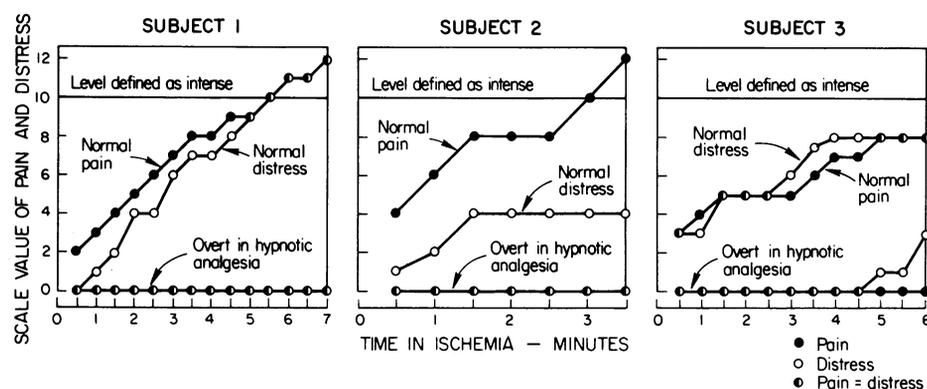


FIG. 1. Pain and distress as a function of time in ischemia after exercise: normal condition and hypnotic analgesia (overt reports only).

cating that they understood what was desired. The distinction between pain and distress was explained by example, with pain referring to the sensory consequence of stimulation, and distress a motivational-emotional reaction more widespread than the localized sensory pain. The time required to reach a pain near to or slightly beyond the critical value was determined in the pretest under normal conditions, and then used in the subsequent analgesia tests. When the tourniquet was removed and the arm returned to its normal appearance, the subject was questioned about his experience of pain and distress. Distress, as we shall see, in the normal nonanalgesic condition, varied in relation to the sensory pain from subject to subject; prior experiments had usually shown it to lag somewhat behind the reported sensory pain.

The next trial provided a baseline for hypnotic analgesia and for using the special techniques for uncovering the concealed aspects of the experience. The subject was hypnotized, with the suggestion that neither pain nor distress would be felt, and the procedure described above was repeated. All three subjects consistently reported pain as at 0, that is, entirely absent. For two of them distress was also reported as 0 throughout, although the third subject reported some distress (without pain) toward the end of the ischemia, reaching a level of 3 on the scale.

The results for hypnotic procedures, independent of the testing of the special hypothesis, can best be presented graphically, and are shown for the subjects in Fig. 1. For all subjects pain and distress mounted with time of ischemia in the normal condition, with the relationship between pain and distress varying somewhat from subject to subject. The main point, however, is that both overt pain and distress were reduced to essentially zero as manifested by the reports given within hypnotic analgesia. The subjects were entirely at ease and showed no signs of discomfort, although while not reporting any pain, Subject 3 reported some mild distress toward the end of the analgesia period.

While the subject was still hypnotized, the tourniquet was removed and the feeling restored in the arm. Inquiry led to confirmation of the experiences reported on the numerical scale during the course of the ischemia. At this point the method of inquiry previously described was used to reveal the covert experience of felt pain and distress (13). The subject was told that some part of himself, not previously available to his consciousness, would now be in communication with us; as a legitimizing gesture, a hand was placed on the subject's shoulder to permit talking with this "hidden part." The report from two of the subjects was that there had been a felt sensory pain which, at its maximum, had been essentially like

the waking pain, but of distress that on a numerical scale would be reported as 0—no suffering at all. The third subject differed in reporting both pain and distress in this condition beyond what they were in the overt reports. This separation of pain and suffering, complete in two of the subjects, provided an appropriate background for testing the effect of blocking the postulated endogenous opioid with naloxone. The rest of the experiment was initially designed as a double-blind procedure to test this effect.

#### Testing the effect of naloxone

Informed consent was obtained for participation in the experiment. Sterile vials, identical in appearance, contained either physiologic saline solution or naloxone hydrochloride (0.4 mg/ml). These were identified by code numbers drawn from a table of random numbers. An assistant who had no other contact with the experiment assigned the medications in such a way that on each day there was equal probability of a subject receiving saline or naloxone. The experiment was repeated in the same form until the experimenters were informed by the assistant that a subject had received both treatments. In this way anticipatory biases based upon previous results were avoided.

The subject received a deep subcutaneous injection (3 ml) in the upper arm. After allowing 30 min for the drug to be fully absorbed, the hypnotic analgesia procedures were repeated exactly as before. Both the overt and covert reports of pain and distress within hypnotic analgesia were unchanged throughout.

Because the injections were subcutaneous, we were concerned lest the data might not be entirely convincing as negating the hypothesis, if, for example, the 30 min allowed for the absorption of 1.2 mg of naloxone hydrochloride might have been either not long enough, or perhaps too long for the effects we were studying. Hence, it was decided to repeat the experiment with the same subjects, using intravenous injection of 1 mg, and carrying out the testing under hypnosis starting 5 min later. This intravenous dose is well established as producing an immediate blockade of the effects of heroin or morphine administered at high dosage (17, 18). It is also a typically effective dose and route of administration for the rapid and complete arousal of comatose victims of narcotic overdosage (19).

The number of trials required for the double-blind procedure appeared unnecessary in view of the consistent absence of any effects to be attributed to the influence of the investigators, the subjects' expectations, or the active agent, so that the rest of the experiment was done with only the subject blind

TABLE 1. Effect of naloxone\* on maximum overt and covert pain and distress in hypnotic analgesia

Condition		Maximum pain and distress in hypnotic analgesia			
		Overt		Covert	
		Pain	Dis-tress	Pain	Dis-tress
Subject 1 (male)	Control	0	0	13	0
	Naloxone	0	0	15†	0
Subject 2 (male)	Control	0	0	15	0
	Naloxone	0	0	15	0
Subject 3 (female)	Control	0	3	7	8
	Naloxone	0	1	6	7

\* 1 mg intravenously; testing began 5 min after injection, completed 3-7 min later.

† Ischemia continued 10 min compared with 8 min in no-injection condition.

as to whether or not he was receiving the drug or the placebo. In fact, only one additional session was required with each, and each received the active agent.

The results are summarized in Table 1, separately for each subject. The negative findings are convincing for the first two subjects. The third subject, because of the high level of reported distress in the covert hypnotic analgesia condition without the drug, does not provide as clearcut a test of the hypothesis. All the data agree in supporting the interpretation that naloxone is having no noticeable effect, one way or the other.

The disconfirmation of the hypothesis appears conclusive enough to require that the explanation of hypnotic analgesia must be found elsewhere.

This work was supported by Research Grants MH-03859 from the National Institute of Mental Health and DA-249 from the National Institute on Drug Abuse.

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