Lithium chloride produces illness-induced analgesia

RAZ YIRMIYA, ISRAEL LIEBLICH, JOHN C. LIEBESKIND, and JOHN GARCIA
University of California, Los Angeles, California

The analgesic effects of lithium chloride (LiCl) and their interaction with the analgesic effects of morphine were studied in rats. After recording rats' baseline pain sensitivity in the hot-plate test, we injected half the rats with LiCl (127 mg/kg i.p.) and half with saline. A second hot-plate latency measurement was taken 100 min later. Following this measurement, half the LiCl- and half the saline-injected rats were injected with morphine (10 mg/kg s.c.), and the others with saline. A third hot-plate latency measurement was taken 20 min later. LiCl produced strong analgesic effects that were comparable to those produced by morphine. The analgesic effects in the group that received both LiCl and morphine was approximately equal to the sum of the analgesic effects measured in the groups that received each of these drugs with saline. The results support our hypothesis that drugs that produce gastrointestinal illness and nausea also produce analgesia.

A general theory of aversion learning, proposed by Garcia, Lasiter, Bermudez-Rattoni, and Deems (1985), suggests that in the vertebrate brain, two separate defense systems have evolved in response to selection pressures inherent in the food chain. The *skin-defense system* is used by the animal to protect itself from predatory attack and involves a selective association of exteroceptive stimuli with peripheral insult and pain. The *gut-defense system* is used to protect the animal from ingested toxins and involves an association between taste and delayed illness and nausea.

Garcia et al. (1985) further suggested that an inhibitory mechanism separates the two systems. This hypothesis was based on the common observation that excitation of external coping mechanisms is accompanied by inhibition of the internal digestive processes. For example, fear or apprehension attenuates feeding, appetite, and gastric motility. Reciprocally, activation of the gut system has an inhibitory effect on the external coping mechanism. For example, a heavy meal often is followed by drowsiness and muscular relaxation. According to Garcia et al.'s theory, an illness-inducing agent that activates the gut-defense system should inhibit the skin-defense system and, therefore, produce analgesia. The present experiment was designed to test this hypothesis by studying the effect of lithium chloride, which is known to induce gastrointestinal illness and nausea, on pain responsiveness. Additionally, these effects were compared with the analgesic ef-

fects of morphine, and a possible interaction between the two drugs was explored.

METHOD

Subjects

The subjects were 33 male Sprague-Dawley rats (Simonson, Gilroy, CA) that weighed 233-288 g. The rats were housed individually in standard stainless steel cages in an animal colony. Testing was done in a different room during the first third of the dark portion of a 12:12-h light:dark cycle.

Procedure

Pain sensitivity was measured with the hot-plate test. The apparatus consisted of a circular plate platform at the bottom of a clear Plexiglas cylinder 22 cm in diameter and 30 cm high. The plate's temperature was maintained at 51.5° C by a thermostatically controlled water bath. The rat was placed onto the plate, and the latency to lick the hind paw was recorded. In the absence of this behavior, the rat was taken out after 60 sec. A baseline hot-plate latency measurement was taken for each rat, followed immediately by an injection of lithium chloride (LiCl) (127 mg/kg) in 17 rats and saline in the others. The injections were in a volume of 20 ml/kg i.p. A second hot-plate measurement was taken 100 min later. Following this test, about half of the LiCl-injected rats (Group LiCl-Mor, $n=8$) and half of the saline-injected rats (Group Sal-Mor, $n=8$) were subcutaneously injected with morphine (10 mg/kg, dissolved in saline in a volume of 1 ml/kg). The other rats received an injection of saline (Group LiCl-Sal, $n=9$; and Group Sal-Sal, $n=8$). A final hot-plate measurement was taken 20 min later.

RESULTS

The latencies ($\pm$ standard errors of the mean) to lick the hind paw in the hot-plate test are presented in Figure 1. No significant baseline differences were observed among the groups. LiCl significantly elevated hot-plate latency 100 min after its administration [$t(31) = 3.46$, $p < .05$]. A two-way analysis of variance showed that both LiCl and morphine significantly elevated hot-plate latency 120 min after LiCl administration [$F(1,29) = 6.18$, $p < .02$, and $F(1,29) = 15.5$, $p < .001$, respectively].

We note with sorrow the death of our colleague and friend, Professor Israel Lieblich, September 25, 1986.

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Figure 1. Analgesic effects of lithium chloride (LiCl) and morphine (Mor) in the hot-plate test. Mean hot-plate latencies were recorded immediately before and 100 and 120 min after an injection of either LiCl or saline (Sal). A second injection of either morphine or saline was administered to each rat immediately after the second hot-plate latency measurement. Error bars represent standard errors of the mean.

Post-hoc comparisons using the Newman-Keuls test showed no significant difference between the hot-plate latency of Group LiCl-Sal and that of Group Sal-Mor. The hot-plate latency of group LiCl-Mor was significantly higher than that of Group LiCl-Sal ($p < .05$) and was about equal to the sum of the analgesic effects observed in Groups LiCl-Sal and Sal-Mor.

DISCUSSION

The results indicate that an injection of a high dose of lithium can produce strong analgesic effects that are comparable to the analgesic effect of a 10-mg/kg dose of morphine. Additionally, the lithium-induced analgesia can summate with the analgesia produced by morphine. These results support the hypothesis that an illness-inducing agent also produces analgesia. Other illness-inducing agents, such as apomorphine (Paalzow & Paalzow, 1975; Vedernikov, 1969) and centrifugal rotation (Hayes, Bennett, Newlon, & Mayer, 1978), have also been found to produce analgesia, giving further support to this hypothesis. Morphine has been shown to produce gastrointestinal illness and can support taste-aversion learning (LeBlanc & Cappell, 1975). Thus, it is possible that some of morphine's analgesic action and its enhanced effect when given with lithium result from its illness-inducing properties.

Studies of the interaction of lithium with morphine have yielded inconsistent and contradictory results. Several studies found that lithium administration increases the analgesic properties of morphine (Jensen, 1974; Tulunay, Kiran, & Kaymakalan, 1971), whereas others found no such interaction (Saarnivaara & Mannisto, 1976). The results of the present experiment confirm previous demonstrations of the enhancement of morphine analgesia by lithium. It may be suggested that the use of different species (e.g., mice vs. rats), drug administration parameters (e.g., acute vs. chronic), or analgesia tests (e.g., hot-plate vs. tail-flick tests) accounts for these conflicting findings.

Previous studies of the effects of lithium on responsiveness to painful stimulation have also yielded inconsistent and sometimes contradictory results. In some studies, for example, both acute (Tulunay et al., 1971) and chronic (Amir & Simantov, 1981) administration of lithium produced analgesia in animals, whereas in others, either no analgesia (Jensen, 1974; Mannisto & Saarnivaara, 1976) or heightened sensitivity to painful stimulation (Harrison-Read & Steinberg, 1971) has been reported. The results of the present study are in agreement with previous studies showing lithium-induced analgesia in animals. The failure of other studies to find this effect may also have resulted from use of different species, lower doses of lithium, or the different analgesic test used. For example, several studies that did not find lithium-induced analgesia used lower doses than the one used in the present experiment, and thus might have induced less or no illness. Further research is needed to assess the relations between the magnitude of the illness and the analgesia it produces.

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