Disruption of the taste aversions acquired subsequent to LiCl poisoning: an investigation of some factors which interfere with an organismic defense mechanism.

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DISRUPTION OF THE TASTE AVERSIONS ACQUIRED SUBSEQUENT TO LlCl POISONING: AN INVESTIGATION OF SOME FACTORS WHICH INTERFERE WITH AN ORGANISMIC DEFENSE MECHANISM.

A Dissertation Presented

by

Timothy L. Ralph

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DISRUPTION OF THE TASTE AVERSIONS ACQUIRED SUBSEQUENT TO LACI POISONING: AN INVESTIGATION OF SOME FACTORS WHICH INTERFERE WITH AN ORGANISMIC DEFENSE MECHANISM.

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ABSTRACT

After ingesting a distinctively tasting substance and experiencing certain noxious consequences an organism will, upon subsequent encounters, refuse to ingest substances with similar tastes. In the case of toxic LiCl the learned aversion is generalized to similarly tasting solutions of NaCl.

Once-poisoned animals, however, will overcome their generalized aversion if, among several manipulations, they are subjected to a substantial need for either water or sodium. Repeated intoxications intensify the aversion and render these inducements ineffective.

Similarly, amnesia-producing electroconvulsive shock (ECS) and cortical spreading depression by KCl disrupt acquisition of taste aversions. Intracranial electrical stimulation (ICS) also interferes with the acquisition of certain tasks in addition to producing rewarding and analgesic effects, but at intensities which, unlike ECS and spreading depression, leave the organism in other respects intact. Considering these ICS effects this investigation was conducted to determine whether continuous, low intensity ICS, delivered during the severest malaise would disrupt acquisition of the LiCl aversion and its generalization to NaCl.

The first experiment found that the LiCl intake of ICS animals was similar to that of non-stimulated controls indicating that the primary learned aversion was left intact. Subsequent testing for
the generalized NaCl aversion showed, however, that stimulated animals drank NaCl more than controls indicating that the generalization of aversion had been disrupted or that the animals' abilities to make chemosensory discrimination had been facilitated.

Since variation of more than one stimulus dimension increases generalization decrements it was essential to determine whether stimuli other than ICS would disrupt the generalized aversion. In the second experiment rats were subjected to the same procedure except that, instead of ICS, they received low intensity footshock.

Like ICS, footshock had no effect on the primary LiCl aversion. Unlike ICS, however, footshock also left the generalized NaCl aversion intact indicating that the taste aversion generalization decrement is at least somewhat specific to ICS.

To assess the disruptive efficacy of ICS, rats underwent a repetition of the intoxication-stimulation situation. After two poisonings ICS animals ingested more NaCl than controls. After two more exposures, however, the generalized aversion in stimulated animals was similar to that of the non-stimulated controls. In the third test, following two additional exposures, the ICS animals' NaCl consumption rebounded, but in the fourth (and last) test NaCl intake was zero regardless of ICS.

Originally, intracranial reward and/or electrically induced analgesia were suspected, along with a direct impairment of association, as possible bases for the ICS effect. However, since the pri-
mary learned aversion in the first experiment remained intact, the possibility of any direct interference with the taste-consequence association was eliminated. An experiment was therefore conducted to determine if the disruptive effect depended upon either intracranial reward or analgesia and to find if stimulation of a variety of brain loci produced the effect.

Before poisoning, rats with mesencephalic, diencephalic or telencephalic electrodes were screened for intracranial reward and for peripheral analgesia. The animals then underwent the intoxication-ICS procedure to discover if the disruption of the taste aversion was related to any rewarding or analgesic effects.

ICS induced some analgesia in all mesencephalic rats, in 4 of 5 self-stimulating MFB animals, in 2 of 5 non-self-stimulating MFB rats, but in none of the telencephalic animals (which also showed no self-stimulation). In testing for the generalized NaCl taste aversion, except for animals with electrodes in the corpus callosum, all ICS animals drank more NaCl than did non-stimulated controls indicating that neither analgesia nor intracranial reward are necessary for the effect of ICS on acquired taste aversion.
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GENERAL INTRODUCTION

Fundamental to the survival of more complex animals are the physiological defense mechanisms which enable an organism in jeopardy to escape a dangerous situation, and the behavioral capacity to profit from the experience. Any individual, after an escape from danger, which, upon subsequent encounters, would be capable of dealing more effectively with the threatening situation would have a substantial selective advantage. An instance of this dual capability is the rat's defense against poisoning. Following ingestion of a toxic substance such as lithium chloride (LiCl), a rat, along with other responses, tends to increase its fluid intake as if the fluid were an antidote. This antidotal thirst permits, in turn, accelerated renal elimination of the poisonous substance, in this case the toxic lithium ions (Smith, Balagura and Lubran, 1970a; 1970b). Then, if the animal survives the intoxication, it will, upon any future encounters, tend to avoid or refuse to ingest substances with that particular flavor (Garcia, Kimeldorf, and Koelling, 1955; Fregly, 1958; Nachman, 1963; Revusky, 1968; Smith and Balagura, 1969). Such learned taste aversions are typically acquired following a single pairing of a distinctive taste with certain noxious aftereffects, and can be learned with interstimulus or taste-consequence intervals of up to even several hours (Garcia, Kimeldorf, and Koelling, 1955; Revusky, 1968; Nachman, 1970a).
In the earliest report of a learned aversion to a substance with a distinctive taste after a long taste-consequence interval, Garcia, Kimeldorf, and Koelling (1955) found that, by being made sick, rats would learn to avoid an initially preferred substance. While drinking a solution of non-toxic saccharin, animals were gamma-irradiated to produce radiation-sickness, a malaise characterized by inactivity, anorexia, and diarrhea. Following this taste-nausea pairing the rats at first completely avoided the sweet tasting solution, but then, over a two-month period, gradually increased their consumption to pre-irradiation levels.

Learned taste aversions to a salty taste were first reported by Fregly (1958) who found that rats, after consuming toxic solutions of LiCl decreased their subsequent intake. Nachman (1963) confirmed the occurrence of this learned avoidance and found further that rats would generalize their aversion to equimolar solutions of NaCl. This generalization of aversion is a result of the similarity in taste of the two substances. In comparing a variety of substances in several species Beidler, Fishman, and Hardiman (1955) discovered that, in certain equal concentrations, NaCl and LiCl solutions applied to the tongue produced similar neural discharge patterns from the glossopharyngeal nerve. Erickson (1963) also reported that rats could not discriminate the tastes of the substances from each other. So similar are the tastes, in fact, that LiCl was used as a substitute for table salt (NaCl) in hypertensive human patients (Hanlon, Romaine,
Gilroy, and Deitrick, 1949). This use was, of course, discontinued when the toxic qualities of LiCl came to light (Corcoran, Taylor, and Page, 1949). LiCl in carefully regulated doses nowadays is used for its sedative effect in the treatment of manic-depressive disorders (Gatozzi, 1970).

Humans usually develop muscular weakness, hypoactivity and tremor, and complain of fatigue and sleepiness after ingestion of toxic, but non-lethal quantities of lithium. They also may experience nausea, abdominal pain, diarrhea, and vomiting (Schou, Amdisen, and Trap-Jensen, 1967). Ingestion of greater quantities of lithium (more than 2 mEq/L) leads to hypertonicity, impaired consciousness, coma and death. Rats, after administration of LiCl are observed to become hypoactive, lie extended on the floor, have abnormal wetness of the snout, and usually become diarrheic. In short, following ingestion of a non-lethal but toxic dose of LiCl (about 15 to 20 ml of a 0.12 M solution), a rat "looks sick". Higher doses exaggerate and prolong these signs, and may result in death.

In order for a taste aversion to be acquired it is necessary that the organism be able to associate distinctive gustatory or, after a number of poisonings, olfactory cues of a substance with certain noxious post-ingestional consequences. The necessity of the taste cues was established by Smith and Balagura (1969) who found that after direct intragastric loading of LiCl, bypassing the gustatory receptors, rats developed no taste aversions. In another study,
after repeated LiCl poisonings, rats began to identify the drinking fluid as something to be avoided on the basis of olfaction alone (Palagura, Brophy, and Devenport, 1972).

That only certain external stimuli would come to be avoided following sickness was established by Garcia and Koelling (1966) who exposed rats to a compound taste-audiovisual stimulus which was paired with radiation-produced nausea. The rats acquired an aversion to the taste but not to the audiovisual stimulus. In the complimentary experiment, in which the taste-audiovisual compound stimulus was paired with footshock rather than with nausea, an aversion was acquired to the audiovisual cues but not to the taste.

Taste aversion learning, in comparison with much of the information gathered in traditional laboratory learning situations, has some "unusual" features. In traditional learning theory it has been accepted that interstimulus intervals or response-reinforcement contiguities must be on the order of about 0.5 seconds to be effective (Spence, 1947; Kimble, 1961, p. 156; Perkins, 1968). Revusky (1968) found, however, that a taste aversion was readily learned with a taste-consequence interval of up to 6 hours. A delay of 8 hours produced no aversion. In a similar situation Nachman (1970a) permitted rats to drink a novel saccharin solution for 10 minutes. Then, after intervals ranging from 1 to 720 minutes, the rats were intraperitoneally loaded with LiCl. Nachman found that strong aversions were produced after delays of 60 minutes and in some animals after even
the longest interval tested.

Another feature of learned taste aversions which distinguishes it in the field of learning and conditioning is that, whereas in more traditional paradigms the number of trials required for learning has been in considerable question (e.g., Kimble, 1961, p. 109), in acquired taste aversions one trial is sufficient for the taste-consequence association to be essentially complete (e.g., Seligman and Hager, 1972). Recent experiments have shown, however, that the aversion can be strengthened by repeated pairings of the taste and its noxious consequences (Balagura, Brophy, and Devenport, 1972; Garcia, Ervin, and Koelling, 1966).

After a single LiCl intoxication it is not unusual for rats to still drink substantial quantities of NaCl and to sample even LiCl. In other words, a single pairing may produce an incomplete or partial aversion. By repeatedly subjecting rats to LiCl, Balagura, Brophy, and Devenport (1972) found a complete refusal to ingest both LiCl and NaCl. In a similar situation Garcia, Ervin, and Koelling (1966) discovered that repeated pairings of saccharin and nausea-producing apomorphine led to stronger saccharin aversions than did a single taste-effect association.

The strength of the aversion is also positively correlated with the dose intensity of the irradiation and the concomitant degree of sickness (Revusky, 1968). The amount of toxic LiCl which is ingested is, in this same manner, crucial for the occurrence and magnitude of
the generalized aversion to NaCl (unpublished observations by the present investigator; Nachman and Ashe, 1973). Animals which consume 5 ml of a 0.12 M solution of LiCl do not appear to be as sick, nor do they show an aversion as strong as animals which ingest 10 ml. These animals, in turn, are apparently not as sick and are less likely to avoid a solution of NaCl than are animals which drink 10 ml of a 0.12 M LiCl solution followed by an intragastric supplement of 5 ml of a 0.24 M LiCl solution.

It is possible, after a single LiCl experience, to induce rats to overcome their generalized aversion to NaCl by making them sufficiently thirsty (by deprivation or by subcutaneous injections of polyethylene glycol), or sodium deficient (by adrenalectomy), or by testing them under conditions of illumination which differ from those prevailing during the poisoning experience (Balagura and Smith, 1970). The acquired NaCl aversion was overcome most rapidly, however, when deficits of both water and sodium were established by a subcutaneous injection of formalin. Interestingly, a reversal of illumination conditions from light to dark increased the consumption of NaCl in previously poisoned rats while the opposite was found when the conditions were reversed from dark to light.

In their study of the effects of multiple LiCl exposures, Balagura, Brophy, and Devenport, (1972) administered formalin to the rats which had been repeatedly poisoned to determine if they too would overcome their aversion to the needed NaCl. Unlike the situation obtained
following a single intoxication, in which the rats were able to promptly overcome their aversion, the distaste of these rats was of sufficient strength to impair their salt seeking behavior when offered the NaCl solution.

In a different assessment of the strength of acquired taste aversions, Nachman (1970b) found that administration of usually temporally more effective amnesia-producing electro-convulsive shock (ECS) disrupted the acquisition of the learned aversion only if delivered within a quite limited interval. The rats were permitted to make their initial taste contact with a novel substance and then, after a variety of intervals, were administered ECS. Nachman found that the learned aversion was substantially reduced as long as the taste-ECS interval was less than 30 seconds indicating a very restricted period of effectiveness. ECS delivered after longer delays did not disrupt the formation of taste aversions.

Since taste-aversions appear to be such a strong, readily acquired form of learning - to use Seligman's terminology (1970), organisms are "prepared" to associate taste cues with nausea and thereafter to avoid the distinctive taste - it is of special interest to gain as much understanding of the physiological basis of this biologically crucial form of learning as possible, and to discover some of the operations which influence it.

In addition to the factors already mentioned there is evidence that lateral hypothalamic lesions interfere with the generalized
aversion to NaCl which normally follows LiCl intoxication (Balagura, personal communication; Teitelbaum, personal communication). The involvement of hypothalamic structures suggests that intracranial electrical stimulation (ICS) might also have some effect.

It has been known for some time that delivery of electrical stimulation to certain areas of the brain interferes with at least some learning processes. Electrical stimulation of the ventral thalamus has been shown to disrupt maze learning in rats (Walut, 1962) while stimulation of the anterior thalamus and lateral hypothalamus interferes with a discrimination reversal task (Olds and Olds, 1961). This latter effect was found only with stimulation of areas known to support intracranial reward but not with stimulation of areas which produce aversive effects (dorsomedial tegmentum), nor of "neutral" areas such as the neocortex.

Another effect of ICS, which in the last few years has come under experimental scrutiny, is electrically induced analgesia. Focal electrical stimulation, delivered to discrete neural structures via permanently implanted electrodes, has been applied to a variety of structures including the septum (Breglio, Anderson, and Merrill, 1970), the lateral hypothalamus (Cox and Valenstein, 1965; Balagura and Ralph, 1973), and the mesencephalic reticular formation-central grey interface (Mayer, Wolfle, Akil, Carder, and Liebeskind, 1971; Balagura and Ralph, 1973) in more or less successful attempts to reduce an animal's reactivity to painful stimuli. In a striking de-
monstration, Reynolds (1969) found that electrical stimulation of the mesencephalon without any supplementary chemically induced analgesia induced a level of analgesia sufficient to permit performance of a laparotomy in 3 of 8 stimulated rats.

Since brain stimulation can disrupt certain learning associations, and since it has been shown to be capable of reducing an animal's reactivity to aversive stimulation, it is possible that ICS might also serve as an experimental tool to disrupt the acquisition of taste aversions - a behavioral defense mechanism crucial to the organism's survival. Intracranial stimulation, delivered to coincide with the most severe effects of intoxication, could interrupt some basic learning mechanism or perhaps, by some analgesic effect, reduce the noxiousness of the animal's post-poisoning experience, or, by a rewarding effect, improve the post-ingestional condition - providing as it were a hedonistic balance of pleasure and pain. In other words, ICS might permit experimental interference with the acquisition of either the usual learned LiCl or generalized NaCl taste aversions which follow LiCl intoxication by disrupting the association of taste and post-ingestional cues or by reducing, eliminating, or offsetting the noxious effects of the poisonous LiCl.
EXPERIMENT 1

The Effect of ICS during LiCl Intoxication on the Subsequent Learned Aversion to LiCl and Generalized Aversion to NaCl.

Since the appearance of the first experiments on long-delay taste aversion learning understanding of the principles of learning has been undergoing considerable change. Until (and to some extent even after) the initial reports of Garcia and his collaborators (Garcia, Kimeldorf, and Koelling, 1955; Garcia and Koelling, 1966; Garcia, Ervin, and Koelling, 1966) conventional learning theory held as axiomatic that the optimal stimulus-consequence interval for learning was in the neighborhood of 0.5 seconds (Kimble, 1961, p. 156). It was further thought that without the mediation of secondary or conditioned reinforcers it was "unlikely that learning (could) take place at all with delays of more than a few seconds" (Kimble, 1961, p. 165).

These conventions are, however, obviously inadequate to account for the common occurrence of acquired aversions or bait shyness. This one-trial learning takes place over intervals even hours in length (Garcia, Ervin, and Koelling, 1966; Revusky, 1968; Nachman, 1970a), during which a multitude of stimulus events can transpire. These intervening or alternative stimuli, however, are not associated with
the malaise (Garcia and Koelling, 1966). The strong tendency for an organism to associate the cues of taste and ingestion with internal discomfort (Garcia and Koelling, 1966; Seligman, 1970) provides an excellent system for the pursuit of greater understanding of adaptability. The study of this indispensable behavioral defense mechanism should illuminate not only homeostatic behaviors which enable the organism to regulate its bodily functions in a variable environment but also the complex and as yet dimly understood principles of learning.

Since it has been reported that intracranial electrical stimulation (ICS) interferes with at least some learning processes (Mahut, 1962; Mogenson, 1959; 1963; Olds and Olds, 1961), and since focal ICS has been reported to be effective in the reduction of an animal's reactivity to pain or discomfort (Balagura and Ralph, 1973; Cox and Valenstein, 1965; Mayer, Wolfe, Akil, Carder, and Liebeskind, 1971; Reynolds, 1969), it is possible that ICS might disrupt the acquisition of taste aversions. Delivered immediately following a poisoning experience, ICS could disrupt the association of taste or ingestional cues with the eventual internal malaise. It is also possible that, because of its analgesic properties, ICS delivered for the duration of the internal discomfort might reduce or even eliminate the noxious post-ingestional effects. Or, because of its rewarding effect, ICS might offset the aversiveness of the intoxication.

In order to determine the effectiveness of ICS in the disrup-
tation of taste aversions and to give indirect information important to the establishment or elimination of certain of these potential explanations this first experiment was conducted. The outcome, by producing further questions as well as answers, should also contribute to the understanding of the mechanisms of association between ingestive behavior and its consequences and the manner in which electrical stimulation of the brain affects them.

Methods

Subjects

Twenty-five naive male Holtzman albino rats weighing between 400 and 450 grams were housed in individual cages in a colony room on a 12 hr. dark - 12 hr. light cycle (lights ON at 6 a.m.) at a temperature of 72±2°F. All of the rats, under Nembutal anesthesia, were fixed by means of blunt, non-perforating earbars to a stereotaxic apparatus. This precaution was taken to prevent penetration of the tympanic membrane which might disrupt the taste fibers which pass through the chorda tympani. Fifteen rats were implanted with bipolar electrodes made of twisted 250μ diameter stainless-steel wires insulated except at the cross-section of the tips. Electrodes were aimed at the medial forebrain bundle (MFB) at the level of the ventromedial hypothalamus. The remaining 10 rats underwent the same surgical procedure whereupon electrode-holding caps were affixed to
their skulls. Only the absence of an implanted stimulating electrode distinguished these sham operated control animals (SOC) from the MFB rats.

**Apparatus and Procedure**

After a post-surgery recovery period of at least 10 days, the rats were placed on an 18-hour water deprivation schedule with fluids available beginning at 9 a.m. Food was always present. After 5 days on this schedule the 15 MFB animals and 5 of the SOC rats (MFB-Li and SOC-Li, respectively) were poisoned by offering them, for 10 minutes at the beginning of their usual drinking period, 10 ml of a 0.12 M LiCl solution. At the end of the 10-minute period each rat was intragastrically loaded with an amount of LiCl necessary to complete an intake of 10 ml. In addition, 5 ml of a 0.24 M LiCl solution was administered to increase the toxic effects experienced by each animal. The remaining 5 SOC animals (SOC-W) underwent the same procedure except that they were offered and subsequently loaded with tap water instead of LiCl.

Immediately following the intubation procedure wire leads from a brain stimulator were attached to each animal's skull cap at which time the animal was placed for 6 hours, with water available, into a 25x25x45 cm high Plexiglas chamber. This chamber was, in turn, situated in a sound-attenuated compartment illuminated by a 7.5 watt white bulb and equipped with an exhaust fan which also served as a masking
noise generator. Brain stimulation for the MFB animals consisted of 60 Hz AC, delivered constantly, at current intensities adjusted individually to produce activation without motor impairment or apparent aversive effects.

At the end of the 6-hour post-ingestional stimulation period the animals were returned to their home cages where they continued their drinking schedule for the next 3 days. On the 4th drinking session following intoxication, the animals were offered, in their home cages, a 0.12 M solution of LiCl rather than water. Fluid intake was recorded at 5-minute intervals for the first 30 minutes, then at each hour for the duration of the 6-hour period.

Following completion of the tests for the LiCl aversion the animals continued to receive water for 6 hours per day for three more days. Then, on the following drinking session, they all were offered a 0.12 M solution of NaCl instead of water. Fluid consumption was measured as before. This entire procedure, i.e., three daily 6-hour drinking sessions followed by a 6-hour drinking test of 0.12 M NaCl, was repeated two additional times.

Following completion of all testing the MFB animals were sacrificed and perfused with isotonic saline followed by 10% formalin. Coronal sections, 50 μ thick were stained with cresylecht-violet for histological verification of electrode placements.
Results

Testing

The first time the rats were offered the toxic LiCl solution they quickly ingested it in amounts sufficient to cause moderate noxious effects, and then subsequently refused to consume any more (see SOC-W, Figure 1).

It had been anticipated that, if delivery of the post-ingestional brain stimulation disrupted the learned aversion to LiCl, the LiCl intake of the MFB-Li rats would approximate that of the SOC-W controls which had had no previous opportunity to associate noxious effects with the salty taste of lithium. Instead, as is apparent in Figure 1, these MFB-Li animals demonstrated an intact aversion, ingesting no more of the lithium chloride solution than the poisoned SOC-Li animals that had not received brain stimulation. Statistical analysis of the LiCl intake revealed a significant treatment effect \( (F = 35.3; df = 2,22; p < .001) \) accounted for by the difference between the non-poisoned SOC-W group and the two poisoned groups (MFB-Li and SOC-Li). Clearly, therefore, long-term diencephalic electrical stimulation in this test had no effect on the primary learned aversion to LiCl which follows LiCl poisoning.

With respect to the generalized aversion to NaCl, Figure 2 (top) shows that, whereas rats of both of the non-brain stimulated groups generalized the aversion to NaCl, the brain stimulated MFB animals
Figure 1. Cumulative LiCl intake. Test for the primary learned aversion following LiCl intoxication.
Figure 2. Tests for the generalized aversion to NaCl following LiCl intoxication. Top, Middle, and Bottom graphs refer to test sessions which occurred every fourth day.
did not. The SOC-Li animals, which had had 2 LiCl experiences, compared with the SOC-W group which had been poisoned but once, showed an increased tendency to avoid the NaCl solution (ANOVA, p < .001). The MFB-Li rats, on the other hand, also exposed twice to LiCl, ingested substantially greater quantities of the NaCl solution. An analysis of variance revealed a significant treatment effect (ANOVA, p < .001). These findings indicate that diencephalic stimulation did interfere with the generalized aversion to NaCl that ordinarily follows poisoning with LiCl, but left the primary learned aversion to LiCl intact.

The two subsequent NaCl acceptance tests (Figure 2, middle and bottom), examined the extinction of the generalized avoidance to NaCl in both SOC groups. As can be seen, by the third NaCl drinking session, the generalized aversion as indicated by the cumulative intake curves had almost disappeared (ANOVA, p > .20).

**Histology**

Examination of the brain sections of the 15 MFB animals revealed that the electrode tips were situated in the medial forebrain bundle at the level of the caudal half of the ventromedial hypothalamus in an area extending from the innermost edge of the internal capsule to 400 μ from the lateral aspect of the fornix. Figure 3 depicts the cross-sectional area in which electrode tips were found.
Figure 3. Diagrammatic representation of electrode loci. All electrode tips were found to be situated in the medial forebrain bundle.
Discussion

Diencephalic stimulation failed to disrupt the primary learned aversion to LiCl following LiCl intoxication. Such stimulation did, however, disrupt the generalization of the aversion to a similarly tasting equimolar NaCl solution. Therefore, the stimulus-consequence association was probably not disrupted since the animals did learn the primary LiCl aversion. The integrity of the primary aversion also rules out the possibility that the rats had associated the aversive post-ingestional factors with the delivery of brain stimulation rather than with the salty taste of LiCl. Since the MFB stimulated animals refused to drink the LiCl solution, it was clear that they must have experienced aversive effects sufficient to produce the proper learned avoidance.

The disruption of the generalization of aversion to NaCl, however, indicates that there was some important effect. The possibility that this phenomenon resulted from any structural or functional iatrogenic disruption of the taste fibers coursing via the chorda tympani was minimized by the use of the non-perforating earbars and may be eliminated from consideration on the basis of the finding that the sham operated control animals (SOC) acquired both the learned and generalized aversions.

The interference with the NaCl aversion also cannot be explained by any shock-induced amnesia. For amnesia-producing ECS to be effec-
tive it must be delivered within less than 30 seconds of the initial
taste (Nachman, 1970b). In the present study ICS was not adminis-
tered until at least 600 seconds after the initial taste. And further,
since the rats showed an intact LiCl aversion it is obvious that they
were able to make the necessary associations and retrieve them from
memory when the situation demanded.

It appears then that continuous, low intensity ICS delivered
during the post-ingestional period of most intense internal malaise
may produce its effect either by interfering with the operation of
some "generalization mechanism," or by enhancing the rats' ability
to make fine chemosensory discriminations. Whether this disruption
might be produced by any low-level, long-term, unescapable, non-
contingent activating stimulation, or if it is at least somewhat
specific to ICS will be considered in Experiment 2.
EXPERIMENT 2

The Effect of Low Intensity, Non-contingent, Inescapable Footshock during LiCl Intoxication on the Subsequent Learned Aversion to LiCl and Generalized Aversion to NaCl.

Part of the paradigmatic experiment in long-delay, taste aversion learning done by Garcia and Koelling (1966) involved the pairing of a distinctive taste with subsequent footshock. The taste in this situation, did not acquire aversive properties. Whereas rats had readily associated nausea with gustatory and ingestional cues and had nearly as quickly come to associate footshock with an audio-visual stimulus, they did not associate external discomfort with gustatory or taste cues.

Since prolonged, continuous, intracranial electrical stimulation (ICS) following LiCl poisoning has been found to be capable of disrupting the generalized NaCl aversion, it seemed necessary to determine whether this disruption might be produced by some other long-term, non-contingent, inevitable stimulation. If the effect could be produced by stimulation other than ICS it would indicate that the disruption of the generalization was due simply to an enhanced discriminability produced by the presence of an additional stimulus element (Kalish, 1969) rather than by some unique, specific property of ICS. To test this possibility a low, but noticeable intensity of
inescapable footshock was administered to LiCl poisoned rats during the period of the most intense internal malaise.

**Methods**

Except where noted the methods used in this experiment were similar to those in Experiment 1. Fifteen individually housed, naive male Holtzman albino rats weighing between 400 and 450 grams were separated into three groups of five rats each. After five days, during which the animals became accustomed to the 18-hour water deprivation schedule, the Li-Foot Shock (LiFS) and Li-Control (LiC) rats were offered, for 10 minutes at the beginning of their usual drinking period, in their home cages, 10 ml of a 0.12 M LiCl solution. The Na-Foot Shock (NaFS) rats were offered 10 ml of an equimolar solution of NaCl. At the end of the 10-minute period each rat was intragastrically loaded with an amount of the appropriate solution necessary to complete an intake of 10 ml. For the rats of the poisoned LiC and LiFS groups an additional 5 ml of a 0.24 M LiCl solution was administered to increase the ill effects. Rats of the NaFS group received a similar load of a 0.24 M NaCl solution.

Immediately following these loads each animal was placed individually into a 20x35 cm Plexiglas chamber which was equipped with a grid floor. For the rats of the two groups which received footshock (LiFS and NaFS) an 80μA grid-scrambled DC stimulus was delivered to
the floor of the cage for 5 seconds on a VI-30-second schedule for the 6-hour post-ingestional period for a total of 720 5-second foot-shocks. For rats of the LiCl poisoned, but unshocked control group (LiC) the shock source was not turned ON. At the end of the 6-hour stimulation period the rats were returned to their home cages where they continued on their drinking schedule for the next three days. On the 4th drinking session following intoxication or, in the case of the NaClS animals, ingestion of NaCl, and the period spent in the grid box, the animals were offered, in their home cages, an appropriate 0.12 M solution of either NaCl or LiCl rather than water. Fluid intake was recorded at 5-minute intervals for the first 30 minutes, then at each hour for the duration of the 6-hour drinking period.

Following completion of the testing for LiCl ingestion and any learned aversion which might have been produced by the footshock the animals were maintained on the 18-hour water deprivation schedule for three more days. Then, on the following drinking session they were all offered a 0.12 M solution of NaCl instead of water. Fluid intake was measured as before. This entire cycle, i.e., three interim water days followed on the next day by a 6-hour NaCl intake test was repeated one additional time.

Results

When the salt solution was first presented to the animals all
rats readily consumed the 10 ml within the allotted 10 minute period. In the subsequent footshock situation, informal observation of the animals' reactions indicated that the non-poisoned NaFS animals were very much more activated, even at the lowest intensity, than were the intoxicated LiFS rats.

When the animals' ingestion of the appropriate salt solution was measured it became apparent that rats of the NaFS group had acquired no aversion to NaCl. The animals began drinking as soon as the solution was presented, as may be seen in Figure 4, and continued their consumption for the duration of the test session. This outcome confirms the previous report (Garcia and Koelling, 1966) that rats do not easily associate a noxious external stimulus with a taste cue.

Animals of the LiCl-poisoned LiFS group, which had received footshock during their intoxication, showed an intact learned taste aversion which was indistinguishable from that of the poisoned but unshocked LiC control group, or from the learned LiCl aversion observed in the preceding experiment. This finding indicates clearly that footshock delivered during LiCl intoxication does not disrupt the primary LiCl taste aversion.

Of somewhat greater interest are the cumulative NaCl ingestion curves shown at the top of Figure 5. In this test for a generalized aversion to NaCl the footshocked LiFS rats displayed an intact avoidance of NaCl of the same magnitude as that of control animals. If footshock had disrupted the generalized NaCl aversion it would be
Figure 4. Test for a primary learned aversion to a salty taste which had preceded a post-ingestional footshock session.
Figure 5. (Top) First test for generalized aversion following a post-ingestional footshock session. (Bottom) Second test for the generalization of aversion following footshock showing extinction of the aversion.
expected that the NaCl intake of the LiFS group would have been similar to that of the non-poisoned NaFS group. This obviously was not the case ($F = 15.44; \text{df} = 2,12; p < .001$). Considering only the two LiCl poisoned groups, there was no significant difference in the effects of the treatments ($F = 0.12; \text{df} = 1,8; p > .20$).

The small amount of NaCl sampled late in this second intake test by the rats of the two previously poisoned groups (Figure 5, top) was apparently sufficient for them to overcome their aversion to the salty taste or to discover that the NaCl solution was harmless since, on their next opportunity, shown at the bottom of Figure 5, they drank no less NaCl than did the NaFS group ($F = 1.85; \text{df} = 2,12; p > .20$).

**Discussion**

Like diencephalic stimulation, footshock, delivered during LiCl intoxication, had no effect on the primary learned aversion to LiCl. But, whereas low intensity, long-term non-contingent brain stimulation in Experiment 1 did interfere with the usual generalization of aversion to the similar taste of NaCl, footshock delivered under similar circumstances did not. This suggests that the disruptive effect on the generalization is perhaps unique to ICS. In other words, the ICS-produced decrement of generalization (or facilitated taste discrimination) is probably not due simply to the addition of a stimulus dimension to the general compound stimulus situation of LiCl.
poisoning. At least, if that were to be the case, footshock does not contribute an effect similar to that of brain stimulation.

It is well known that discrimination is facilitated when the amount of similarity between stimuli is decreased (Kalish, 1969, p. 249), and that there is a greater decrement in generalization when stimuli are varied in two dimensions rather than in one alone (Fink and Patton, 1953; White, 1958; Butter, 1963). In the present paradigm a number of stimulus dimensions vary with the switch from the poisoning situation to the test for generalized NaCl aversion, and, before the present study, it would have been possible to explain the disruptive effect of ICS as merely the variation of an additional stimulus dimension. Since the ICS-type effect was not observed following footshock, however, we can assume either that ICS is at least somewhat specific in the disruption, or that footshock is unusual in its failure to produce the effect.

Of interest in passing is the observation of reduced reactivity on the part of the poisoned animals to the footshock situation. This depression may be due to the sedative effect of LiCl in large doses (Kety, 1967, p. 450). Superficially, it could also be attributed to the general malaise of LiCl intoxication in which case the rat could be thought of as being "too sick" to react to just one more aspect of an uncomfortable situation. Another possible interpretation, however, involves an analgesic reduction of reactivity to pain. Since administration of LiCl is thought to affect the synthesis of
serotonin (Knapp and Mandell, 1973), and since serotonergic systems have been implicated in recent work done on electrically induced analgesia (Mayer, Wolfle, Akil, Carder, and Liebeskind, 1971; Akil and Mayer, 1972) it is interesting to speculate that administration of LiCl in large doses might produce some analgesic effect.

In any event the outcome of this experiment has shown that mere delivery of just any extraneous stimulation is insufficient to produce the change in the LiCl taste aversion generalization gradient that is produced by ICS. How, where, and how effectively such electrical stimulation of the brain produces the disruption of the generalized aversion to NaCl are subjects of the remaining experiments.
EXPERIMENT 3

The Effect of Repeated LiCl Poisoning - ICS Sessions on the Generalized NaCl Taste Aversion.

The aversion acquired to a taste which has been associated with an internal malaise is strengthened by repeated exposures to the poison (Garcia, Ervin, and Koelling, 1966; Balagura, Brophy, and Devenport, 1972; Cullen, 1970; Frunkin, 1971; Stricker and Wilson, 1970). Although avoidance of or refusal to ingest the poison can be learned after a single pairing of the taste and its consequences, the animal still may be observed to sample the substance (Balagura, Brophy, and Devenport, 1972). Further, by inducing an elevated water need, a sodium deficiency, or both, a rat may be readily induced to overcome the taste aversion acquired in a single taste-consequence experience (Balagura and Smith, 1970). After 10 experiences with toxic LiCl, however, even the drastic sodium and water deficiency created by a subcutaneous injection of formalin could not force the rats to overcome their aversion to the salty taste (Balagura, Brophy, and Devenport, 1972).

In their repetitive procedure Balagura, Brophy, and Devenport (1972) found in a 10-minute latency test that, whereas actual intake of either LiCl or NaCl was essentially zero after two exposures to LiCl, the rats would at least sample solutions of both LiCl and NaCl.
even after five poisoning experiences. Apparently, after the initial learning experience, the subsequent exposures tend to confirm and strengthen the association between the gustatory and post-ingestional cues leading to an eventually absolute refusal of commerce with the distinctively flavored, dangerous substance.

Since intracranial electrical stimulation (ICS) has been found to produce at least some generalization decrement in the aversion to NaCl following LiCl intoxication, its use in a repetitive paradigm should permit assessment of the degree of this effect. That is, repetition of the basic poisoning - ICS procedure should determine whether the ICS produces a complete or total disruption of the generalized aversion or if it is but a partial effect. In the former case repeated taste-poisoning experiences would not strengthen the intensity of the aversion to NaCl so long as each intoxication was accompanied by ICS. If the brain stimulation produces only a partial disruption then repetition of the poisoning-stimulation procedure would probably be marked by a gradual increment in the intensity of the generalized aversion. The present experiment was intended to determine which of these situations held.

**Methods**

The methods used in this experiment were similar in many respects to those detailed for Experiment 1. Twenty-four individually
housed, naive male Holtzman albino rats weighing between 400 and 450 grams were stereotaxically implanted with bipolar electrodes aimed at the medial forebrain bundle at the level of the ventromedial hypothalamus.

After a post-surgery recovery period of at least 10 days, the rats were introduced to an 18-hour water deprivation schedule. Food was available ad libitum. After 5 days, in which they became accustomed to the drinking schedule, the rats were separated into four groups of 6 animals each to begin the repeated poisoning experiment. Basically, the procedure was to administer the training solution and deliver ICS on one day followed by three water days (LiCl-W-W-W). This subcycle was then repeated once. Then, on the following day, the rat was offered NaCl to test for the generalized aversion. This entire procedure (LiCl-W-W-W-LiCl-W-W-W-NaCl) was repeated four times (a total of four complete cycles).

The ingestion and administration of the toxic LiCl solution was identical to that described in Experiment 1. The animals of one group received LiCl in the usual 10-minute, 10 ml session which was immediately thereafter followed by 6 hours of brain stimulation in the ICS chamber (LiCl plus immediate brain stimulation - LiS). The animals of the non-stimulated LiCl control group (LiC) were treated identically except that the brain stimulator was not turned ON. The other two groups were treated similarly except that for the group which was administered NaCl plus immediate brain stimulation (NaS),
the toxic LiCl solution was replaced by innocuous NaCl, while the fourth group received ICS only on the second water day following intoxication (LiCl plus delayed brain stimulation - LiDS). The NaS group was included to provide a non-poisoned baseline for purposes of comparison and to show any cumulative obnoxious effects of repeated, prolonged ICS. The LiDS group was included to study any disruptive effect such ICS might have on previously formed associations. To clarify the procedure for this last group, LiCl was administered just as it was to animals of the LiS group, but the LiDS rats remained in their home cages during the intoxication. Then, two days later, presumably long after the acute effects of the poisoning had subsided, they were administered brain stimulation.

At the end of the stimulation session the rats were returned to their home cages to continue their usual drinking schedule. On the days when the rats were tested for the generalized aversion to NaCl, a 0.12 M solution was offered to the rats for one hour at the beginning of the usual drinking session in their home cages. NaCl intake was recorded at 5-minute intervals for the first 30 minutes, then again at the end of the 60-minute test period. At that time the NaCl solution was removed and the rats were offered tap water for the remainder of their normal intake session. The rationale for this shorter test period was to prevent the rats from obtaining too much experience with the test solution in the absence of the poisoning cues.
After the cycle had been completed four times the animals were sacrificed and intracardially perfused with isotonic saline followed by 10% formalin. Coronal sections, 50μ thick were stained with cresylecht-violet for histological verification of the electrode locations.

Results

Testing

The first time that they were offered the salt solution the rats ingested the allotted 10 ml with the alacrity characteristic of animals on a restrictive schedule. This continued to be the case throughout the entire experiment for the non-poisoned rats of the NaS group. Animals of the LiCl-poisoned groups, on the other hand, soon acquired the learned aversion to LiCl and came to refuse to ingest the toxic solution. This avoidance was clearly established in the non-stimulated LiC group after two poisoning experiences and in the LiS and LiDS groups after three exposures. To determine whether this indicates some effect of the ICS on the primary learned aversion to LiCl or not will require further testing.

As the number of experiences increased, the oft-intoxicated rats were observed to refuse even to approach the tube which dispensed the offensive fluid. This observation corroborates the Balagura, Brophy, and Davenport (1972) finding that, after five poisoning experiences, the rats in their study were able to identify and avoid the drinking
fluid on the basis of olfaction alone.

It was further noted that the animals' general appearance did not deteriorate as a result of the repeated, intensive intoxications. They looked, of course, quite bedraggled during each intoxication period, but were able to recover and to groom themselves well before the next session. Also, although not specifically measured, the animals appeared to maintain their body weight throughout the course of the experiment.

The ICS current intensities required to elicit the expected activation differed substantially among the three stimulated groups. As might be expected, the immediately stimulated LiS group required generally the greatest intensities (6 - 50μA), while the non-poisoned animals were sufficiently activated by 5 to 30μA. But, most curious was that the LiDS animals, poisoned two days earlier, were greatly agitated by current intensities of only 1 - 3μA.

The effects of the post-LiCl ICS over repeated intoxication may be seen in Figure 6. In the first NaCl intake session the non-poisoned NaS group consumed more of the test solution than did the LiCl poisoned groups (F=18.26; df=3,20; p<.001). This relationship was maintained and became even more striking over the subsequent three test sessions.

During the first test for the generalized NaCl aversion, both of the stimulated groups consumed more of the 0.12 M solution than did the non-stimulated control group (F=4.18; df=2,15; p<.05).
Figure 6. (Top-left) First test for generalized NaCl aversion after repeated exposures to LiCl.
(Top-right) Second test for the generalized aversion to NaCl following four exposures to LiCl.
(Bottom-left) Third test for generalized aversion. By this test the animals had experienced six LiCl poisonings.
(Bottom-right) Fourth test for generalized aversion to NaCl after, at this point, eight LiCl exposures.
By the second test this difference had disappeared ($F = .86; df = 2, 15; p > .20$). On the third test, however, the animals of the immediately stimulated LiS group rebounded and drank more of the NaCl solution than did either the delayed ICS group (LiDS) or the animals of the non-stimulated control group (LiC) ($F = 14.02; df = 2, 15; p < .001$). This rebound proved to be short-lived and on the fourth and final test those rats (LiS) like those of the other two groups (LiDS and LiC) refused to ingest any NaCl at all ($F = 0.00; df = 2, 15; p > .20$).

**Histology**

Histological examination of brain sections from the rats used in this experiment revealed that the electrode tips were situated in and near the medial forebrain bundle as depicted in Figure 7. In general, the tips were located in the lateral portion of the MFB along the medial border of the internal capsule. A few electrode tracks ended just dorsal to the internal capsule and some terminated directly in it. In general, the placements in the rats of the LiS group were more ventral and closer to the tip of the internal capsule than those of the other groups. Otherwise, there were no consistent differences between groups.

**Discussion**

It is quite apparent from these findings that ICS delivered to
Figure 7. Diagrammatic representation of rats' electrode loci in the repeated LiCl poisoning experiment. The drawings represent coronal diencephalic sections at the level of the posterior half of the ventromedial hypothalamus. (Top-left) NaCl-ICS (NaS) group. (Top-right) LiCl-ICS (LiS) group. (Bottom-left) LiCl-Delayed ICS (LiDS) group. (Bottom-right) LiCl-No ICS (LiC) control group.
coincide with LiCl intoxication does not produce any absolute disruption of the usual generalized NaCl aversion. By the fourth NaCl test session the poisoned animals, regardless of ICS, demonstrated a complete and full-blown avoidance of the NaCl solution. In fact, it seems possible that the generalized aversion was essentially complete by the second test, and that the rebound observed on the part of the LiS group on the third test was some sort of aberration which cannot be explained at this time.

Of considerable interest is the behavior of the LiDS rats during the first generalized aversion test. It was not expected, to make an understatement, that these animals would display anything but the normal aversion to NaCl. By this test they had been poisoned twice and each time left in their home cages to quietly suffer the consequences. Two days subsequent to each instance of intoxication they were removed to the ICS chamber to undergo the 6 hours of stimulation. That brain stimulation, delivered 48 hours after the association of a taste and its consequences, could have any effect upon that association seems highly unlikely, but none the less, the animals in this group behaved very much like those of the LiS group in their ingestion of the NaCl solution. What the basis for this effect might be will require further research.

Also of some interest are the differences in ICS current intensities required to elicit moderate activation. These differences may be due, at least in part, to the direct effects of the LiCl. Whether
electrode location played any role, given the size of the electrode tracks, is difficult to determine. Also, whether there might be some rebound effect from the sedative effect of lithium remains for further empirical investigation. Such a possibility, however, would certainly have substantial implications for the use of lithium in the treatment of manic-depressive states.
EXPERIMENT 4

The Effect of Mesencephalic, Diencephalic, and Telencephalic Stimulation on the Generalized Aversion to NaCl which usually follows LiCl Intoxication: The Role of Intracranial Reward and Analgesia.

The foregoing experiments dealing with the effect of ICS on the LiCl taste aversion generalization gradient have been primarily concerned with the establishment of the phenomenon and with the determination of its magnitude. The question at this point seems to require some direct evidence about the effect's underlying basis. This experiment actually represents a series of manipulations designed to more directly determine whether intracranial reward or electrically induced analgesia have any correlative or perhaps even causal relationship with the disruptive effect, and to learn which brain structures might or might not produce the effect.

Focal intracranial electrical stimulation delivered to specific areas of the brain has been shown to interfere with the learning of certain responses. Ventral-thalamic stimulation disrupts maze learning in rats (Mahut, 1962), while stimulation of some sites known to support intracranial reward (anterior thalamus and lateral hypothalamus) has been found to interfere with a discrimination reversal task (Olds and Olds, 1961). This interference was not found with stimula-
tion of aversive (dorsomedial tegmental) or "neutral" (neocortical) loci. Another effect, perhaps related to intracranial reward is an electrically induced reduction in reactivity to noxious stimulation (Cox and Valenstein, 1965; Mayer, Wolfe, Akil, Carder, and Liebeskind, 1971; Falagura and Ralph, 1973).

Since it is known that such ICS produces a decrement in the generalization of the acquired LiCl taste aversion, and since ICS, delivered to these aforementioned structures, is known to produce effects which could contribute to such a reduction of aversion, it was decided to specifically investigate the relationship of intracranial reward, analgesia, and the disruptive effect, and the efficacy of stimulation of some of these neural structures.

Methods

Subjects

Forty naive male Holtzman albino rats weighing about 400 to 450 grams were housed in individual cages in a colony room maintained on a 10-hour dark—14-hour light cycle (lights ON at 7 a.m.) at a temperature of 74±2°F. Thirty of the animals were stereotaxically implanted, while under Nembutal anesthesia, with bipolar electrodes made of twisted stainless-steel wires 250μ in diameter, insulated except at the cross-section of the tips. Fifteen rats had electrodes aimed at the medial forebrain bundle (MFB) at the level of the ventro-
medial hypothalamus. Five had electrodes aimed at the interface of the mesencephalic reticular formation and central gray area (MRF). Five rats had electrodes aimed at an area 1 mm below the surface of the dorsal somato-sensory neocortex (NC). And five rats had electrodes aimed superficially at this same area but projecting somewhat deeper into and through corpus callosum (CC).

Of the remaining 10 rats, 5 served as unoperated controls (UOC) and 5 were used as sham implanted controls (SIC). Each animal, except those of the UOC group, was fixed to the stereotaxic apparatus and had at least an electrode holding plastic cap fastened to its skull.

**Apparatus and Procedure**

The animals were permitted a recovery period of at least 10 days following surgery. At that time each implanted rat was screened to find if its electrode would support intracranial reward and/or any peripheral analgesic effects.

An electrode was considered to be at a rewarding locus if the rat could be shaped to consistently self-administer single 0.5-second pulse trains of 60 Hz AC via the implanted electrode. Self-stimulation was accomplished by pressing a 2.5 cm wide rat lever which protruded 2 cm into the 25x25x45 cm Plexiglas self-stimulation chamber. Current intensities were adjusted in 5 μA increments for each individual until the animal could be trained to self-stimulate or until
the stimulation came to produce apparent motor or aversive effects. Response rates were recorded in cumulative counters.

After an interval of at least 24 hours following screening for intracranial reward, the rats were tested for an analgesic reduction in reactivity to sharp, localized pain. This screening was done in a small 12x22x45 cm Plexiglas chamber which was built to permit ready access to the animal by way of a 2 cm gap between the floor and each of the walls.

At the beginning of the screening procedure the brain stimulator leads were connected to the rat's electrode assembly and the animal was placed into the chamber. Before the onset of the stimulating current the animal's base response was determined to painful pricks produced by a long sharp-tipped metal probe or by a No. 23S Miltex curved stainless-steel explorer. Peripheral sensitivity was mapped for the paws, limbs, the dorsal, lateral, and ventral body surfaces, and for the tail. The head region was not stimulated in order to avoid any inadvertent damage to the eyes, and because of the presence of the electrode holding skull cap. After these preliminaries the current was turned ON and was elevated in 2μA increments until reactivity to the painful stimulation was reduced by the ICS or until the ICS itself produced motor or aversive reactions.

Based on the outcome of the self-stimulation screening the 15 MFB subjects were assigned to one of three groups. Of the seven self-stimulators (75±12 responses/minute), five were assigned to
the MFB⁺ group. The other two, plus three non-self-stimulators were placed into a non-poisoned control group which received only innocuous NaCl followed by stimulation of the MFB (MFB-Na). The remaining five non-self stimulating animals formed the MFB⁻ group.

The other groups (NC, CC, SIC, and UCC), as the MRF group, had been established on the basis of surgical procedures rather than on the outcome of any screening.

Upon completion of screening procedures and group assignments the animals were introduced to the 18-hour water deprivation schedule described in the previous experiments with fluids made available beginning at 9 a.m. Food was available ad libitum. As before, after five days, during which the animals became accustomed to the drinking schedule, all rats except those of the MFB-Na group were poisoned in their home cages by offering them for 10 minutes at the beginning of their usual drinking period, 10 ml of a 0.12 M LiCl solution. At the end of this 10-minute period each rat was given intragastrically whatever amount of the solution was necessary to complete the 10 ml intake. Then, an additional 5 ml of a 0.24 M solution was intragastrically loaded to increase the effects. Animals of the MFB-Na group were treated identically except that instead of LiCl they were offered and loaded with the appropriate solutions of NaCl.

Immediately following the supplementation injections the rats were connected to the brain stimulator leads and were placed into the stimulation chamber for a period of 6 hours with water available.
During this period of intoxication the ICS was ON continuously at an intensity which produced moderate activation without apparent motor or aversive effects. These parameters corresponded closely to those found to induce analgesia.

The SIC animals were connected to the stimulator like the implanted rats except that they received no brain stimulation. The UOC rats spent 6 hours in the stimulation chamber during intoxication but, of course, had no leads connected to their heads. In every other respect their treatment was identical to that of the experimental groups.

At the end of this stimulation session the animals were returned to their home cages to continue the 18-hour deprivation schedule for three more days. Then, on the fourth drinking session following intoxication, the rats, again at their home cages, were offered a 0.12 M solution of NaCl. Fluid intake was measured hourly for the duration of the 6-hour NaCl intake session.

Upon completion of the test for generalization of the LiCl taste aversion, the implanted rats were given a lethal dose of sodium pentobarbital and intracardially perfused with isotonic saline followed by 10% formalin. Their brains were cut into coronal sections 50 µ thick which were stained with cresylecht-violet to permit histological verification of the electrode placements.
Results

Histology

Examination of the MRF electrode placements revealed that in all five cases the electrode tips were situated toward the medial portion of the reticular formation near the border of the mesencephalic central gray at the level of the anterior third of the bed nucleus of the posterior commissure, and the anterior half of the red nucleus. Electrode placements in the five rats of the MFB⁺ group were found to be uniformly situated in the dorsal portion of the medial forebrain bundle, between the internal capsule and the fornix, at the level of the posterior ventromedial hypothalamus and the anterior pole of the prefrontal cortex. The electrode placements for the MFB⁰ group were situated in the most ventral aspect of the medial forebrain bundle, at the level of the anterior half of the ventromedial hypothalamus. Two were above the optic tract, the other three medial to it. The electrode tips of the MFB-Na rats were situated between the placements of the MFB⁺ and the MFB⁰ groups with respect to both the antero-posterior and the dorso-ventral dimensions. The electrode tips of the NC animals were located in an area that corresponds to somato-sensory association cortex (Brodman's area 7; Krieg, 1954). The deeper electrodes of the CC rats fell about 0.5mm more posterior than the NC placements and were in contact with the corpus callosum. Three of the electrodes actually
pierced it, and were in contact with the hippocampus. These findings are summarized in Figures 8 and 9.

Testing

Of the animals implanted in the medial forebrain bundle, only those that had dorsal placements proved to be self-stimulators showing a mean response frequency of 73 bar presses per minute. The rats with the ventral medial forebrain bundle placements were not self-stimulators. Of the animals with electrodes in the mesencephalic reticular formation, one self-stimulated at 30 responses per minute and a second at 10 responses per minute. None of the rats in either the NO or the CC group self-stimulated, nor did any of them display any apparent analgesia during screening.

Continuous electrical stimulation of the brain induced at least some analgesia in all of the MRF rats, in four of the MFB+ animals, in two of the MFB0 subjects, and in two of the MFB-Na rats. The extent of the analgesia ranged from glove or sock analgesia to analgesia comprehending about 80 percent of the body surface. Table 1 summarizes the results obtained with respect to self-stimulation and analgesia.

As expected, both the UOC group and the SIC group showed a typical generalized aversion to NaCl following LiCl poisoning. Their cumulative 0.12 M NaCl intake was almost identical to that of comparably treated animals reported by Balagura and Smith (1970) and
Figure 8. Diagrammatic representations of the electrode loci and their effectiveness. (Top) Coronal diencephalic sections at the anterior (left), medial (middle), and posterior (right) ventromedial hypothalamus. Abbreviations for structures: F = fornix, HpC = hippocampus, IP = interpeduncular nucleus, LM = medial lemniscus, MFB = medial forebrain bundle, MTT = mammillothalamic tract, OT = optic tract, P3 = posterior commissure, PVG = periventricular gray, RF = reticular formation, RN = red nucleus, VMH = ventromedial hypothalamus. O = no self-stimulation nor analgesia; • = analgesia; □ = self-stimulation; ● = self-stimulation and analgesia.
Figure 9. Diagrammatic representation of the electrode loci for the Neocortex (NC) and Corpus Callosum (CC) groups. □ = NC, Δ = CC. Section of the brain through a sagittal plane 2.5 mm from the midline. Abbreviations for the Structures: CC = corpus callosum, HpC = hippocampus, IC = internal capsule, RF = reticular formation, Str = striatum, T = thalamus.
TABLE 1

Self-stimulation response rates and surface analgesia, (listed from most to least analgesic) induced by brain stimulation.

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S's, Groups and subjects; S-S, Self-stimulation; Ag., Analgesia.

FL, forelimb; HL, hindlimb; D, dorsal surface; L, lateral surface; VL, ventrolateral surface; T, tail.

The subscripts r and l indicate right or left.

xxx, strong; xx, moderate, and x, weak analgesia.
In the preceding experiments of this dissertation. The animals restricted their drinking during the first three hours of their intake period, and began to overcome their aversion thereafter (see Figure 10).

With the exception of the CC animals, irrespective of electrode placement, all the animals that received brain stimulation following lithium poisoning, drank more sodium than animals of the UOC group (MRF vs UOC, p < .025; MFB° vs UOC, p < .001; MFB+ vs UOC, p < .025), and consumed amounts similar to and actually slightly in excess of those consumed by animals of the MFB-Na group (p > .05).

The only stimulated animals which showed the generalized aversion that usually follows ingestion of toxic LiCl, when offered the 0.12 M NaCl solution, were members of the CC group (see Figure 9). The NC group, however, not only drank significantly more than the CC group (p < 0.005), but their intake of NaCl was as great as that of any other brain stimulated groups. Clearly, stimulation of the deeper telencephalic structures did not disrupt the generalization of aversion to NaCl while involvement of the neocortex at least at these coordinates did.

Discussion

The behavior of the NC and CC groups was somewhat of a surprise in that both groups were intended as "neutral" controls with the an-
Figure 10. The test for a generalized aversion to NaCl following LiCl intoxication. Except for the Corpus Callosum group (CC), electrical stimulation of each brain structure during the 6-hour post-ingestional period led to a disrupted NaCl aversion, regardless of any concomitant analgesic or intracranial rewarding effects.
ticipation that, if anything the CC animals would be more likely to display a disruption of the NaCl aversion. Stimulation of the corpus callosum would supposedly affect more tissue than the more discrete direct stimulation of cortex. The most plausible explanation for what actually occurred seems to be that the NC animals were being stimulated in a cortical somato-sensory association area, possibly interfering with interoceptive sensory feedback, while the CC animals were not. A reported central response facilitation produced by electrical stimulation of the corpus callosum (Burns and Mogenson, 1961) might possibly have contributed to an enhanced avoidance, but further research would be necessary before such a conclusion could be taken too seriously.

The results of the screening procedures indicate that animals which displayed self-stimulation behavior were not necessarily analgesic when stimulated through the same electrodes. Furthermore, the animals in which stimulation induced analgesia could not in all cases be induced to self-stimulate. On the other hand, three of the eight rats with diencephalic implants that did not sustain self-stimulation showed analgesia, while five of the seven animals with diencephalic implants that self-stimulated were analgesic. Thus, although the analgesic effects of continuous brain stimulation are not necessarily carried by the same neural systems that mediate intracranial reward, at least in the diencephalic rats there seemed to be a substantial relationship.
It is evident that, as before, electrical stimulation of certain brain areas diminishes the generalization of aversion to NaCl that usually follows non-lethal poisoning by LiCl. The possibility that this phenomenon resulted from iatrogenic disruption of taste fibers coursing via the chorda tympani was eliminated since the sham implanted animals (SIC) learned the generalized aversion. It is also unlikely that this effect was due to an analgesic state induced by the brain stimulation since seven diencephalic and all five neo-cortically implanted animals showed diminution of the generalized taste aversion even though no peripheral analgesia was found. It is possible, however, that electrical stimulation induced some visceral hypoalgesia, which might have reduced the sensations of sickness that would ordinarily occur during the period of intoxication. Any involvement of intracranial reward also has been found to be unnecessary since both the NC and the MFB\(^0\) groups ingested the NaCl solution. Therefore, it seems that none of the suspected bases are required for the generalization decrement produced by ICS. By whatever means ICS disrupts the generalization of aversion to NaCl which ordinarily follows LiCl intoxication, it appears to be independent of any rewarding effect or of ICS-induced analgesia.
GENERAL DISCUSSION

In the acquisition of a learned taste aversion the organism makes an association between distinctive ingestional cues (primarily taste and ingestion itself with a substantial olfactory contribution) and non-lethal noxious internal consequences. Then, upon subsequent encounters, the individual refuses to ingest the substance.

Initially it was thought that ICS might disrupt the usual generalized aversion to NaCl following LiCl intoxication, most likely by influencing either the association itself or the noxiousness of the post-ingestional cues. Based on the known effects of electrical stimulation of the brain it was presumed that ICS might interfere with the association of the taste and post-ingestional cues because rewarding ICS delivered during intoxication might offset the aversive consequences of the poison, or because an analgesic effect of ICS could reduce or even eliminate the noxious aspects of the internal malaise. In short, it was expected that the decrement in the aversion to NaCl was due to an interference with some primary association produced by a change in either the value of the cue or its consequences or by a direct disruption of some associative mechanism.

These hypotheses have not been supported by the results of this dissertation. Brain stimulation, administered during the intoxica-
tion period of most intense internal discomfort seems to have had no substantial effect upon the acquisition of the primary aversion itself, but it readily disrupted the generalization of the LiCl aversion to the similar taste of NaCl. This indicates that, contrary to earlier suggestions, ICS did not interfere with the association of a cue with its consequences, at least in the case of this crucial, readily learned organismic defense behavior. Rather, ICS appears either to have interfered with the utilization of the learned association, or it may have influenced the organism's ability to distinguish the two substances from each other.

In regard to an interpretation of these findings, considering the current views on stimulus generalization and how certain manipulations may affect generalization gradients, it would be most parsimonious to attribute the disruptive effect of ICS to the simple variation of an additional, albeit unusual stimulus dimension. This explanation, however, was not supported by the finding that stimulation of the corpus callosum and footshock, delivered under circumstances similar to those pertaining for the delivery of ICS, did not lead to a generalization decrement.

A consideration addressed in recent thinking on the issue of generalization is the intimately related concept of discrimination. There are, in fact, some who regard stimulus generalization to be nothing more than an organism's failure to make an appropriate discrimination (Kalish, 1969). In the case of the taste aversion to
poisonous LiCl, the avoidance usually generalizes to the innocuous NaCl because the tastes are so similar that the poisoned animal fails to discriminate between the harmful and the harmless substances. Therefore, the effect of the ICS could just as accurately be considered as a facilitation of a taste discrimination which somehow enables the stimulated animal to more effectively distinguish the taste of NaCl from that of LiCl.
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