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The effects of preoperative ingestive events on feeding and drinking behavior following brain damage

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Preoperative ingestive events can protect animals against lesion-induced deficits in ingestive behavior. The phenomenon is clearly present following lesions in hypothalamic regions of the brain and other brain regions implicated in ingestive behavior. If a brain region is necessary for the ingestive behavior, the preoperative treatments will not be protective. In this review, it is suggested that the amygdala may be critically involved in these protective effects on ingestive behavior.

A general observation in behavioral neuroscience is that brain damage does not always result in an expected debilitation. Some animals appear to be protected against the behavioral effects of the lesion. The question is, why? One answer is that specific preoperative events minimize the debilitating effects of brain damage. The term "sparing" has been used for such effects, and it has usually been associated with preoperative overtraining (e.g., Lukeszewska & Thompson, 1967; Marcotte & Ward, 1980; Orbach & Fantz, 1958; Thatcher & Kimble, 1966; but also see Braun, in press). As Dean and Weiskrantz (1974) put it, "simple repetition of an event increases its resistance to amnesia."

It has become increasingly clear that protective effects on behavior emerge from specific preoperative treatments. Such effects are not exclusively due to overtraining. For example, septal lesion-induced hyperactivity in mice or rats is averted by preoperatively housing the animals in a social environment that is richer than that provided by the usual cages (Donovick, Burright, & Bengelloun, 1979). Exposure to an enriched environment and preoperative practice on a motor task protects against locomotor coordination deficits following damage to the sensorimotor cortex. Only specific sensorimotor tasks that were learned preoperatively, however, are protected (Held, Gordon, & Gentile, 1985). Impairments to the ability to find sources of reinforcement in solving spatial problems following partial dorsal hippocampal damage in rats are reduced through the animals' preoperative exposure to problem-solving situations or through enriched experience (see, e.g., Handelmann & Olton, 1980; Hughes, 1965; Jarrard, 1983). However, more complete lesions of the hippocampus abolish this protection (Olton & Markowska, in press).

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Other examples of protection have been observed (Finger & Stein, 1982; Schulkin, in press). How protection occurs is largely an open question, but the phenomenon has been anecdotally noted for some time (Geschwind, 1965/1975; Hebb, 1949; Morgan, 1951).

My purpose here is to review the protective effects of preoperative manipulations. Most of the work cited focuses on the lateral and ventromedial hypothalamus and the central gustatory system. There is some evidence that other areas in the brain also may be involved in providing such protection, and I suggest that it is the amygdala that is the anatomical region that may be essential for these protective effects. Examples of protection on body sodium behavioral regulation are depicted in the work of the author and his colleagues. Alternative explanations are presented.

This review is organized around anatomical regions, or systems. These are, first, the two classic hypothalamic regions, followed by the central gustatory system, septum, area postrema, amygdala, and midline structures surrounding the third ventrical.

LATERAL HYPOTHALAMUS

Lesions in the lateral hypothalamus (LH) of the rat result in a classic syndrome of postoperative aphagia and adipsia (Teitelbaum & Epstein, 1962). Animals with such lesions actively avoid the ingestion of food and water and suffer gastrointestinal disturbances (Epstein, 1971). These effects are long lasting, and if special postoperative care (e.g., intragastric feeding and palatable liquid diets) is not administered, the animal will die. With proper care, the animal passes through stages of recovery. Following recovery, LH animals are still somewhat impaired in short-term ingestion tests of acute glucoprivic and thirst challenges (Epstein, 1971). However, many of these challenges are severe enough to mask regulatory competence by promoting sensorimotor debilitation. For example, if the treatment is less severe, or the test time is ex-

tended, LH rats do show glucoprivic feeding (Stricker, Friedman, & Zigmond, 1975).

These facts are well known. Perhaps less well known is that many, if not all, of the abnormalities that result from LH damage can be avoided by specific preoperative manipulations. Powley and Keesey (1970) provided an outstanding early example. They showed that the aphagia that results from an LH lesion was nearly abolished in rats whose body weights were reduced by about 20% over an 8-day period prior to the lesioning. A larger lesion produced greater aphagia and reduced protective effects. Powley and Keesey argued that an alteration of body-weight set point was the main protective factor; but this thesis is disputable (cf. Grijalva, Lindholm, Schallert, & Bicknell, 1976; Kolb, Whishaw, & Schallert, 1977). When rats are preoperatively dieted, with their body weights abruptly reduced by the elimination of all access to food for 6 days, there is no protective effect (Grijalva et al., 1976). But body-weight set point should be altered, and yet there is no recovery. Such treatments are extreme. No doubt such rats are debilitated by the abrupt loss of body weight resulting from total food deprivation. This is aggravated further by the effects of the LH lesion. Therefore, it is not surprising to find no recovery from such preoperative treatments. Moreover, as DiCara (1970) reported, when the LH-damaged rat is preoperatively familiarized with a milk diet, the aphagia is diminished. Body weights were not changed preoperatively. The familiar, and presumably palatable, milk diet facilitated recovery when the rat was ingesting it postoperatively. Thus, alteration of body weight set point is clearly not essential for the protective effects.

The syndrome of regulatory impairments is not unique to LH damage. For example, damage to the globus pallidus is known to produce regulatory impairments in feeding and drinking, as does the LH syndrome. In these cases, too, preoperative dieting (body weight loss of 20%) over a 2-week period also reduces the aphagia (Grijalva, 1980x).

Two types of aphagia are known to result from LH damage and have been described in terms of the location of the lesion (Schallert & Whishaw, 1978): (1) a passive form of aphagia, with which LH rats will not eat unless the food is delivered directly into the oral cavity; and (2) a more active form of aphagia, with which rats will reject food even if it is delivered to the oral cavity—in fact, rats turn away from it. Both kinds of aphagia are ameliorated by preoperative dietary restriction, again replicating this basic phenomenon (Schallert & Whishaw, 1978).

Glick, Greenstein, and Zimmerberg (1972) suggested that preoperative manipulations of the central catecholamine system, which is critically involved in the LH syndrome (Stricker & Zigmond, 1976; Ungerstedt, 1970), also contributes to reduction of the behavioral effects of the lesion. More specifically, they suggested that recovery from LH damage requires the remaining catecholamine system to become supersensitive. Therefore, if one were to provoke supersensitivity preoperatively (e.g., Glick et al., 1972, used the drug a-methyl-p-tyrosine), the LH syndrome should be reduced or abolished. Glick et al. found just that: LH-damaged animals, preoperatively treated for 3 days with this drug, ingested food and water as normally following surgery. This work was verified by other investigators, who found that rats were protected from the debilitating effects of the LH damage when pretreated with methyltyrosine, haloperidol, or morphine (which is said to decrease dopamine receptor activity, and therefore to promote supersensitivity as a compensatory response) for 3 days before incurring LH damage (Hynes, Anderson, Gianutsos, & Lal, 1975). Although one can dispute the essential role of catecholamine supersensitivity in this recovery process (e.g., Kolb et al., 1977; Kolb, Nonneman, & Whishaw, 1978), it has nonetheless been shown to play a very important role in recovery. The fact remains that, with these preoperative treatments, animals eat and drink following LH damage.

Cortical lesions prior to LH damage are also known to diminish the LH syndrome. Glick and Greenstein (1972a) reported that frontal cortical damage 30 days before LH lesioning reduced the duration of the aphagia and adipsia to only several days. They suggested that supersensitivity occurred as a result of the frontal cortex ablation. Others (Balagura & Harrell, 1974; Kolb, Nonneman, & Whishaw, 1978) later reported that orbital, medial, as well as frontal cortical damage prior to LH damage reduced the postoperative aphagia and adipsia. This protective effect occurs when the cortical damage is administered between 30 and 60 days before the LH lesion. If the cortex is removed 10 days before the LH lesion, there appears to be no protective effect (Glick & Greenstein, 1972a). In this regard, note again that abruptly reducing the body weight of rats over a period of a few days before LH lesioning does not produce the protective effect (Grijalva et al., 1976).

Sensorimotor impairments are known to result from LH damage. Animals with such damage, as well as with catecholamine depletion, display regulatory incompetence (e.g., Marshall, Blair, & Teitelbaum, 1971; Marshall, Richardson, & Teitelbaum, 1974; Stricker & Zigmond, 1976). The preoperative treatments that promote recovery of feeding are, to some extent, independent of the sensorimotor deficits. In other words, although preoperatively treated rats show recovery of function (Grijalva, 1980b; Schallert & Whishaw, 1978), LH motor impairments remain postoperatively.

Preoperative insulin treatment also reduces the postoperative LH syndrome (Balagura, Harrell, & Ralph, 1973; Grijalva, 1980b). Insulin pretreatment has also been thought to promote noradrenergic supersensitivity (Balagura et al., 1973). In one experiment in which insulin was given once daily (4 units per injection) for 5 to 7 days before the lesion, the postoperative aphagia again was diminished. It is interesting that the hormonal treatments that influence food intake can be given 5 to 7 days before the lesion and result in protective effects, whereas abrupt weight loss does not produce such effects. Moreover, the insulin pretreatments do not alter the sensorimotor impairments (Grijalva, 1980b).

Recovered LH animals with minimal signs of sensorimotor impairments showed enhanced responsiveness to glucoprivation in a 6-h feeding test (Kanarek & Konecky, 1985; Kanarek, Schoenfeld, & Matthews, 1986). One group of animals had been food deprived preoperatively. This resulted in a reduction of body weight by 20% over a 2-week period. Another group was treated with 5 units of insulin per week. Kanarek et al. (unpublished observations) and Kanarek and Konecky (1985) replicated the basic phenomenon of averting the postoperative aphagia. Three weeks following LH surgery, rats were given various doses of 2-deoxy-D-glucose (100, 250, and 500 mg/kg) or insulin (5 and 7.5 units). Although the lesion animals did not ingest the same amount postoperatively as did intact animals, the preoperatively treated groups ingested more food than did those not given the preoperative experience.

Gastric pathology is known to result from the LH lesion (Grijalva, Deregnaucourt, Code, & Novin, 1980). Animals with preoperative dietary restriction have reversed the postoperative gastric pathology and the LH syndrome (Grijalva et al., 1976). Preoperative dieting to a 20% body weight loss has reduced the aphagia from the LH lesion and retarded the gastric pathology by preventing the development of an ulcerated stomach (Grijalva et al., 1976). Gastric pathology is not a necessary precondition for the aphagia that results from LH damage (Schallert, Whishaw, & Flannigan, 1977). This reduction in gastric pathology may hold for the preoperative food restriction phenomenon, but it does not do so nearly as well with the preoperative insulin treatment (Grijalva, 1980b); nevertheless, in both cases, aphagia is reduced.

Preoperative water-deprivation facilitates the ingestion of water following LH damage, and it has been suggested that "attentional" factors are called into play by the preoperative water or food restriction (Roland, Grijalva, & Dess, 1986; Schallert, 1982). The rats become conditioned to expect the food and water, and its arrival and consumption. In the case of preoperative water restriction, rats were water-deprived 23 h a day for 15–17 days prior to LH lesions. The LH water-restricted group showed greater ingestion of water than the nonrestricted group after surgery. As with food intake, the larger the lesion, the more reduced the protection (Schallert, 1982). Food intake was also affected postoperatively by water restriction, but less so than was water intake. Limited preoperative water intake also restricted the food intake of dry pellet rat chow during the period of water access. In other words, the rat was probably hungry preoperatively. Moreover, severe acute water deprivation (48–72 h), like food deprivation, does not facilitate a protective effect (Schallert, 1982). Glick and Greenstein (1972b), however, reported that total deprivation of food and water 2 days prior to LH damage facilitated recovery.

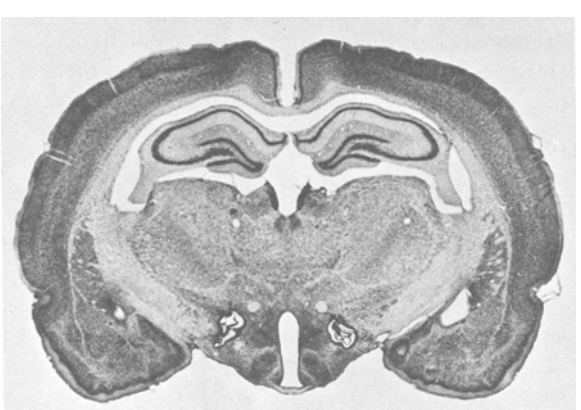

Figure 1. Photomicrograph of a representative lateral hypothalamic lesion. The lesion is centered at the level of the ventromedial hypothalamus and is ventrolateral to the fornix.

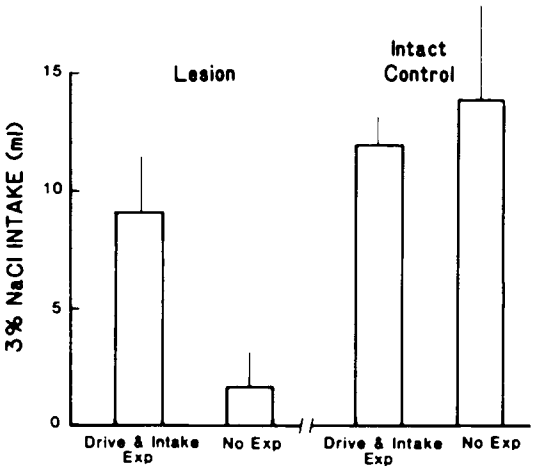

Figure 2. Mean increases of salt over baseline intakes, with the standard error indicated. Unlike the experienced group, the nonexperienced group showed a significant decrease in salt intake when compared with intact controls ($p < .001$).

In other investigations, LH lesions, as depicted in Figure 1, have also been found to impair or abolish salt appetite (Ruger & Schulkin, 1980; Wolf, 1967). However, recovered LH rats that have been preoperatively treated once weekly with the combination of furosemide (which depletes the body of sodium) and mineralocorticoid are protected against the LH-lesion effects on salt appetite. With this treatment, however, the rats still tended to ingest less salt than did nonlesioned groups (see Figure 2) (Ruger & Schulkin, 1980; Wolf, Schulkin, & Fluharty, 1983). In a further study (Schulkin & Fluharty, 1985), it was shown that the arousal of salt hunger, even without access to salt, protected the brain-damaged animal. Preoperative exposure to salt alone, water deprivation (1 h access to water twice weekly during the preoperative salt-hunger treatments), or insulin preoperative treatments (for 6 days prior to the lesion; see Grijalva, 1980b) were not protective (see Figure 3). On the other hand, the protective effect was greatly reduced if the pre- and postoperative treatments in generating a salt appetite were different (Figure 4) (Schulkin & Fluharty, 1985). In this case, rats were depleted of body sodium preoperatively, and then given a mineralocorticoid to generate the salt appetite postoperatively.

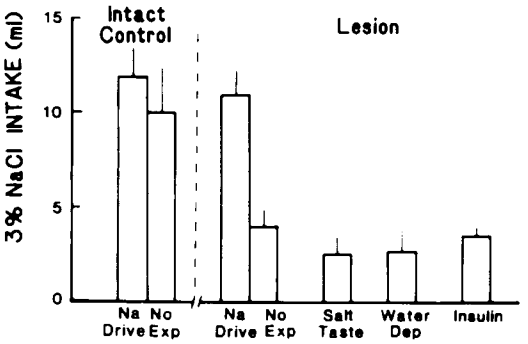

Figure 3. Mean increases of salt over baseline intakes, with the standard error indicated. Unlike the experienced group, the non-sodium-deprived treated groups ingested significantly less salt than the intact groups ($p < .01$).

Finally, LH rats have difficulty in learning a taste aversion (Schwartz & Teitelbaum, 1974). Two appetitive measures were used: (1) the rate at which the rats approached a food source, and (2) the amount of food they ingested. The food, which was poisoned with 5 cc of .64% LiCl, was intubated into the rats 30 min before the ingestion test. LH rats retained the preoperatively learned aversion, but they had difficulty in, or were incapable of, learning a new aversion.

Summary

The results presented in this section indicate that preoperative body-weight reduction over an extended period of time or treatment with hormones that increase food intake reduce or abolish postoperative aphagia. These preoperative events also facilitate postoperative ingestive responses to glucoprivic challenges in recovered LH rats. The experience of thirst by water deprivation or the arousal of salt hunger reduces the postoperative adipsia or the lack of responsiveness to salt hunger treatments, respectively. Finally, although LH rats can recall an old taste aversion, they cannot learn a new one. How can these diverse phenomena be explained?

It seems clear that catecholamine supersensitivity contributes significantly to promoting recovery of function

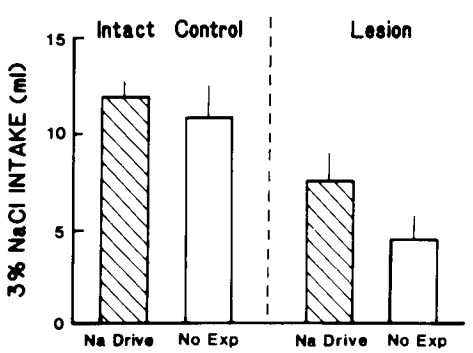

Figure 4. Mean increases of salt over baseline intakes, with the standard error indicated. Both lesion groups ingested less salt than the intact groups ($p < .005$).

from LH damage (e.g., Stricker & Zigmond, 1976), and that various preoperative manipulations may facilitate this phenomenon and thereby reduce the postoperative syndrome. This, combined with the stomach ulceration that is averted by preoperative regulatory challenges, suggests that both central and peripheral mechanisms are involved in the reduction of the LH syndrome. However, one can see protective effects with sensorimotor impairments, and one can see the LH syndrome without gastric pathology.

Recovered LH rats that were given preoperative glucoprivic challenges or were deprived of food demonstrated glucoprivic regulatory competence postoperatively. This may have nothing to do with supersensitivity, gastric pathology, or set point alteration. The same holds true for the protective effects on salt appetite. Catecholamine depletion, for example, has no effect on salt appetite (Stricker & Zigmond, 1974). However, the preoperative effects of water deprivation, food deprivation, and glucoprivic and salt-hunger challenges may have produced alterations in such critical brain regions as the amygdala, which may also be the region for remembering preoperatively learned taste aversions and the conditioning factors that contribute to the protection of the animal postoperatively.

VENTRAL MEDIAL HYPOTHALAMUS

Lesions in the ventral medial hypothalamus (VMH) lead to hyperphagia and a number of metabolic disturbances (see, e.g., Powley, 1977). Rats with such lesions are typically "finicky" about their food or water source (see, e.g., Corbit & Stellar, 1964). If food or water is adulterated with quinine, they ingest less than do normal rats (Teitelbaum, 1955). If they have to work for a food source, they show less motivation for it (Miller, Bailey, & Stevenson, 1950). Although VMH rats overeat palatable and normal food, they are less willing to ingest or work for food that tastes bad. There are, nevertheless, preoperative effects.

First, preoperative insulin treatments, which elevate body weight, reduce the hyperphagia that results from the lesion (Hoebel & Teitelbaum, 1966). The effect is analogous to that obtained by reducing body weight before the LH lesion, which reverses the aphagia. Whether this is due to an altered physiological state is unknown. More is known about the behavioral effects.

Second, the finickiness can be averted. VMH rats can be made to look relatively normal, relative to intact rats, when they are given preoperative quinine (.12%) mixed in water and then tested for its ingestion postoperatively (Singh, 1974). Quinine was given as the sole drinking solution to a preoperative group (for 30 days), and to all groups postoperatively. While intact nonexposed rats initially avoided the quinine-water, by Day 3 they looked like the preexposed group. By contrast, the intake of the nonexposed VMH animals remained low, unlike that of the preexposed lesion group.

Third, during the dynamic phase of the syndrome, the VMH rat will not work for its food on a difficult rein-

forcement schedule (Teitelbaum, 1957) unless it has been trained preoperatively. VMH rats that are trained preoperatively on successively increased fixed-ratio schedules for food reinforcement, after 20 h of food deprivation, look relatively normal on a FR 256 schedule postoperatively; VMH rats, however, still barpress less than nonlesion animals (Singh, 1973). Preoperative weight reduction, without the operant training, does not produce this phenomenon (King & Gaston, 1976). This operant effect on rats has been found by others (Beatty, 1973; Beatty, Vilberg, Shirk, & Siders, 1975; King & Gaston, 1973, 1976; Peters, Sensenig, & Reich, 1973; Porter & Allen, 1977), and, in an earlier study, was also found with monkeys (Hamilton & Brobeck, 1964).

In addition, VMH rats preoperatively trained to barpress for water are protected against such deficits postoperatively (King & Gaston, 1976), and the typical impairment of bait shyness can be averted with preoperative experience (Gold & Proulx, 1972).

Summary

The hyperphagia and the impairments in ingestive behavior that occur when the VMH rat has to work for its food, or when the food tastes bad, can be averted. The preoperative experience of working for food or water, or simple exposure, render the VMH animal more like a normal animal. Although there are no data to support the specific role of the amygdala in these phenomena, it would be an ideal structure to mediate these effects. The amygdala is involved in motivated behavior (e.g., Fonberg, 1974). Moreover, the major taste visceral projection passes from the brainstem to the central nucleus of the amygdala (Norgren, 1984) and is involved in taste-related motivated behavior (Norgren, Flynn, Grill, & Schwartz, 1985; Schulkin, Flynn, Grill, & Norgren, 1985).

CENTRAL GUSTATORY SYSTEM

Lesions in the central gustatory system are known to affect ingestive behavior, presumably by altering taste perception (e.g., Braun, Lasiter, & Kiefer, 1982; Norgren, 1984). There are, however, preoperative protective effects similar to those described above.

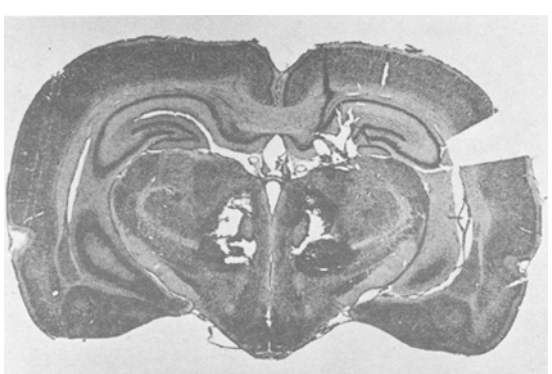

Figure 5. Photomicrograph of a representative lesion at the level of the caudal thalamic gustatory region. In addition to damage to the thalamic gustatory region, there is damage to the posterior intralaminar nuclei and the dorsomedial subthalamus. Most important, the lesion interferes with gustatory pathways from the brainstem en route to the ventral forebrain.

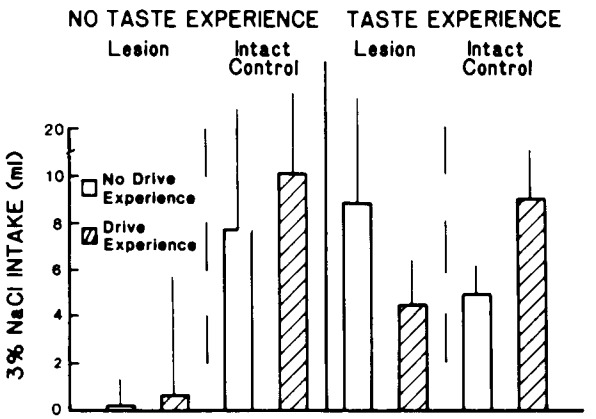

Figure 6. Median increases of salt over baseline intake, with the interquartile range indicated. Unlike the two groups that tasted salt, the two lesion groups ingested significantly less salt than did the intact groups ($p < .01$).

Large lesions of the central gustatory system, at the level of the thalamic taste relay (VPMpc), that disconnect both the dorsal and ventral gustatory projections from the parabrachial taste region impair salt appetite (Paulus, Eng, & Schulkin, 1984; Wolf, 1968). Figure 5 depicts a typical lesion. It was discovered serendipitously that if the rats were simply exposed to the salt before the administration of the lesion, they would manifest protective effects on salt appetite postoperatively (Wolf, unpublished observations). In a 2×2×2 factorial design, rats were given salt taste experience, salt drive (a combination of deoxycorticosterone with furosemide treatment) with access to salt, salt drive without access to salt (once weekly for 4 weeks), or nothing at all. After a 1-month recovery period, the rats were tested for salt appetite. Only rats that had tasted the salt preoperatively or had had both the salt drive and salt access together were protected (Figure 6). Moreover, the salt drive alone did not protect them (Ahern, Landin, & Wolf, 1978; Wolf & Schulkin, 1980). Taste, then, was the critical factor. The critical factor for the LH animal was, by contrast, salt drive, and not salt taste (Schulkin & Fluharty, 1985).

In the Ahern et al. (1978) study, the salt solution was placed in the same location both pre- and postoperatively. Rats are known to recognize the significance of salt; they are aware of where it is located and will go there when they are salt hungry (Krieckhaus, 1970). Thus, the animals might have been protected in the Ahern et al. study because they remembered tasting the salt in a particular place. This hypothesis has been tested simply by changing the location of the salt pre- and postoperatively (Paulus et al., 1984). Rats were exposed to the salt in different locations (Figure 7) for 2 weeks before receiving central gustatory damage. Following their recovery, they were tested for evidence of salt appetite. Only those rats that found the salt in the same location were protected (Figure 8).

Finally, it has been shown that a 30-sec preoperative exposure to the salt was enough to produce the protective effect (Hartzell, Paulus, & Schulkin, 1985). Rats require only a short exposure (2 to 5 min) to a salty taste to learn something about how to acquire it (Bregar, Strombakis, Allan, & Schulkin, 1983; Wirsig & Grill, 1982). In the Hartzell et al. experiment, after having been trained with water for several days, thirsty rats were preoperatively given access to either salt or sucrose for 30 sec. Following recovery from central gustatory ablation, the rats were tested for salt appetite. Only the preoperative salt group was protected (Figure 9). This demonstrates that the protective effect can be implemented with a brief exposure to salt. Comparison of these results and those of the other preoperative studies reveals that the degree of protection is essentially the same whether the preoperative exposure to salt is for 4 weeks (Ahern et al., 1978), 2 weeks (Paulus et al., 1984), or 30 sec (Hartzell et al., 1985). Thus, in addition to taste, other mechanisms (e.g., mnemonic spatial ones) are employed by the brain in organizing the appetite for salt. These facts explain the earlier observation of Wolf and his colleagues (Ahern, Landin, & Wolf; 1978). There are other protective effects elsewhere in the central gustatory system.

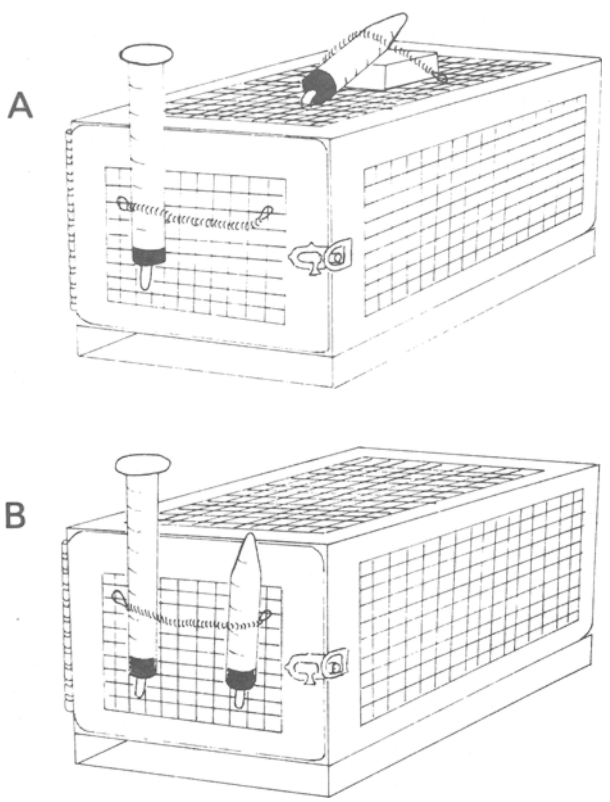

Figure 7. (A) Position of salt and water tubes during preoperative experience for the same place group. This is also the position of two water tubes during preoperative experience for the water control group, and the position of salt and water tubes during the postoperative salt appetite test for all groups. (B) Position of salt and water tubes during preoperative experience for the different-place group.

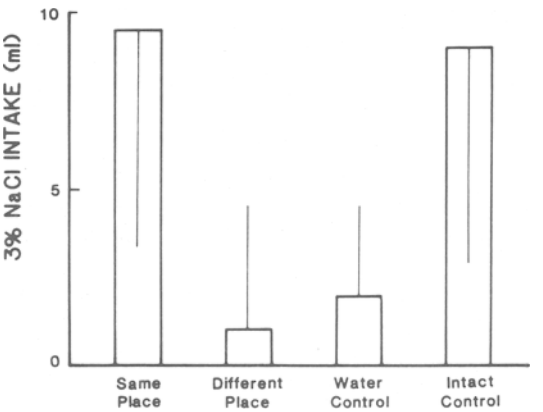

Figure 8. Median increases of salt over baseline intake, with the interquartile range indicated. Only the group that tasted salt in the same place was protected; the other two lesion groups manifested deficits in their salt intake when compared with the intact group ($p < .01$).

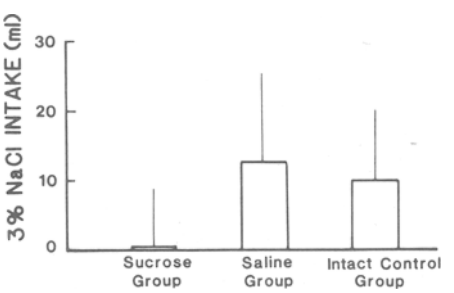

Figure 9. Median increases of salt over baseline intake, with the interquartile indicated. The group preoperatively exposed to the salt was protected. The other group manifested deficits in salt intake when compared with the intact group ($p < .01$).

Lesions that damage the cortical taste nucleus may influence taste perception (Benjamin, 1959). The ingestion of quinine is altered by the lesion, but an animal that is preoperatively exposed to the quinine reacts more normally to it (but see Braun, in press). Additional work with cortical gustatory lesions has shown that, while not disrupting the acquisition of a taste aversion, cortical gustatory damage disrupts its retention in rats treated with 20 mg/kg of apomorphine hydrochloride (Braun, Kiefer, & Quellet, 1981). This is in contrast to the LH animals that could not acquire a new taste aversion but remembered the old one (Schwartz & Teitelbaum, 1974).

It is interesting to note that, after removal of the gustatory cortex, rats retain the ability to acquire salt in an operant situation. In a study by Krieckhaus and Wolf (1968), rats were preoperatively taught to barpress for salt when thirsty, and then were rendered salt hungry. Water was then returned to them, and the reinforcement for salt was extinguished. This paradigm is well known to apply to intact rats; only rats that, when thirsty, have tasted the salt (and not something else) barpress under extinction. When rendered salt hungry, Krieckhaus and Wolf's rats continued to barpress after the salt was no longer avail-

able. Neodecorticated rats show similar behavior and also retain information that is obtained preoperatively (Wirsig & Grill, 1982). This contrasts with their loss of a taste aversion. One notable difference is that salt appetite is an innate appetite (Denton, 1982; Richter, 1956; Wolf, 1969); taste aversions are learned (Garcia & Ervin, 1968; Rozin, 1976).

Summary

Following damage to the central gustatory system, in which afferents and efferents are disconnected from the second-order gustatory region to the ventral forebrain (e.g., the central nucleus of the amygdala), rats use memory of salt location to maintain behavioral competence. Despite the usual deficit in expressing salt appetite, rats are protected because they remember, from preoperative experience, where the salt is located. In fact, they require just a brief experience of preoperative access to salt for such an effect. As a result of preoperative exposure to quinine, rats with cortical gustatory lesions react more normally to the taste of it. On the other hand, they lose preoperatively learned taste aversions. Unlike the LH rat that retains the old aversion but fails to learn a new one, the cortically lesioned rat quickly relearns a taste aversion. While the gustatory cortex may be essential to remembering a preoperatively learned taste avesion, it is not essential for such innate behaviors as salt hunger. Rats taught how to acquire salt preoperatively retain the knowledge postoperatively. Since the major taste-visceral pathway en route to the forebrain is through the central nucleus of the amygdala, this region may be critical for these protective effects.

SEPTUM

Septal lesions also are known to influence ingestive behavior, and fluid ingestion in particular (e.g., Burright, Donovick, & Zuromski, 1974). The usual restricted environment of laboratory rats produces aberrations in behavior of septal-lesioned rats; this does not occur when they are preoperatively housed in more enriched environments (Donovick, Burright, & Swidler, 1973). Preoperative housing in an enriched environment also eliminates the evelated ingestion of fluids in septal-lesioned rats (Donovick et al., 1973). Little work has been done in this area, so little else is known.

AREA POSTREMA

Lesions of the area postrema, in the caudal brainstem, produce a hypophagic animal (e.g., Hyde & Miselis, 1983). As with the LH animal, preoperative dietary restrictions that reduce body weight by 20% increase the amount of food intake postoperatively; the amount of postoperative water intake is also increased. Contreras, Fox, and Drugovich (1982) found that despite this, the body weights of both preoperative- and nonpreoperative-lesion groups remained lower than those of the intact rats. Moreover, neither lesion group responded to a variety of doses of 2 deoxy-d-glucose (100, 200, 400, and 800 mg/kg) in a 6-h test. In this context, the reversal of hypophagia by the preoperative dieting is evident, but the body-weight reduction and the responsiveness to the 2 deoxy-d-glucose are not (unlike the findings with LH animals).

AMYGDALA

Lesions in the amygdala disrupt food and water ingestion (Fonberg, 1974). Preoperative operant manipulations of food and water ingestion in hungry and thirsty dogs and rats have little or no protective effect on their postoperative behavior (Fonberg, 1974; Fonberg, Brutkowski, & Mempel, 1962; Korczynski & Fonberg, 1976). Water intake tends to be more disrupted (Korczynski & Fonberg, 1976). In this regard, water intake, like salt intake (and unlike food intake), is dependent upon forebrain mechanisms (see review by Norgren & Grill, 1984).

In addition, preoperative environmental enrichment has no effect on the known heightened reactivity to novel foods and quinine consumption in rats with amygdala lesions (Kemble & Davies, 1981). Taken together with the above findings, this suggests that there is no protection from preoperative experience. However, the data is minimal, and more behavioral evidence needs to be gathered.

MIDLINE THIRD VENTRICULAR STRUCTURES

Animals given preoperative angiotensin are not protected against the deficits in angiotensin-induced thirst that result from subfornical organ or anterior third ventricular damage (e.g., Buggy & Johnson, 1977; Simpson & Routtenberg, 1974). Rats with subfornical lesions are preoperatively treated with systemic angiotensin followed by a lesion and are then tested for the dipsogenic effects of systemic angiotensin. These operated animals are not protected; they simply do not respond to the treatment. They do, however, respond to centrally administered angiotensin and intracellular-induced thirst, for which this brain lesion is not critical (for a review, see Simpson, 1981). Although they show normal food intake, rats with lesions in the anterior third ventricular region do not respond to a variety of dipsogenic challenges, despite the preoperative manipulations (Buggy & Johnson, 1977). In the above examples, these brain regions appear to be essential for water ingestion. No preoperative thirst experience is protective.

CONCLUSIONS

Clearly, preoperative manipulations can have profound effects on something as fundamental as the expression of ingestive behavior following brain damage. This is most obvious following damage to hypothalamic and central gustatory regions of the brain.

The purpose of this review was to briefly present the range of protective effects that preoperative ingestive experiences can have on ingestive behavior. The phenomena are real, substantive, and diverse. In analyzing the effects of a lesion on postoperative ingestive behavior, investigators should note that the preoperative experience may be a relevant factor to consider. The evidence presented, however, does not specifically support any one explanation for the diverse protective phenomena. The protective phenomena require different levels of explanation, and may arise from many separate mechanisms even within the same level. Finally, several generalizations that may be helpful in diagnosing preoperative phenomena are considered.

An animal's need for a particular brain region for ingestive behavior can be assessed by the effects of specific preoperative ingestive events. If the brain region is not essential, the preoperative ingestive events should facilitate a protective effect on behavior. This does not imply that the brain region is not necessary in the naive animal.

There are examples in which certain brain structures retain critical roles in organizing behavior; that is, some brain regions are essential for ingestive behavior (such as the subfornical organ and systematic angiotensin-induced drinking). Regardless of the amount of preoperative experience subjects have had, they will not be protected from postlesion deficits. Similarly, no matter how much experience a human has in language use, damage to critical brain regions impairs its expression (Geschwind, 1965/1975; see also Hebb, 1949). Interestingly, unlike in the LH rat (Kanarek et al., unpublished observations), preoperative dieting does not help the area postrema damaged rat against deficits to glucoprivic challenges (Contreras et al., 1982). The necessary mechanisms for this feeding behavior lie in the caudal brainstem (Flynn & Grill, 1985; Ritter, Slusser, & Stone, 1981), which may explain why the caudal-brainstem-damaged rat was not protected.

Lesion size also is a relevant factor with regard to whether protective effects are found. For example, the greater the LH damage, the less likely the chances of observable protective effects (Powley & Keesey, 1970; Schallert, 1982). Similarly, more complete hippocampal damage results in reduced protection of spatial discrimination tasks as a result of preoperative spatial learning (Olton & Markowska, in press).

Impoverishment of preoperative ingestive experiences probably contributes significantly to many of these ingestive deficits. The relative specificity of protective effects supports this claim. That is, the greater the ingestive experiences, and the more varied those experiences are, the more likely it is that the animal will be protected. This may occur because of greater redundancy of function in the brain (Geschwind, 1965/1975). Thus, an example of this is the learning that takes place preoperatively when the LH-damaged rat is given a drive for water, satisfied by the ingestion of isotonic saline, and then protected postoperatively against deficits in salt appetite (e.g., Wolf et al., 1983). In this case, the rats might have learned that the weak saline satisfied the thirst; the two drives were linked, and so the LH-damaged animal was protected.

In beginning to explain the protective phenomenon, one possibility is that alternative anatomical brain regions play a larger role in ingestive behavior. For example, the enhanced avidity for salt in pretreated sodium-depleted rats (Berridge, Flynn, Schulkin, & Grill, 1984; Falk, 1966; Sakai, Fine, Epstein, & Frankmann, 1987), could be a result of aldosterone-induced organizational changes within the medial nucleus of the amygdala (see, e.g., Goy & McEwen, 1980). As a result of the hormone's action on this brain region, the amygdala plays a larger role in generating the behavior on subsequent occasions. The protective effect on feeding and drinking behavior, in recovered LH-damaged animals, may also result from a greater role of amygdala function in orchestrating the behavior. For example, the amygdala has been hypothesized to play a role in the anticipation of rewards (Mishkin & Appenzeller, 1987), and is known to be involved in feeding and drinking behavior in general (Fonberg, 1974). In addition, the VMH-damaged rat preoperatively exposed to a bad taste or to a situation in which the animal must work for its food may be protected, because these events trigger amygdala function through the taste-visceral projection to this region (Norgren, 1984) and through known amygdala projections to the striatum and the motor system (Nauta, 1982).

Thus, one critical brain region that may be involved in all of these appetitive protective effects is the amygdala. Most of the examples cited concern a drive that is elicited or the learning of some behavioral function, both of which potentially serve a regulatory role. The amygdala is an important anatomical site in this regard (see, e.g., Herrick, 1948). Moreover, damage to this region is known to impair or abolish preoperatively learned events (e.g., Dean & Weiskrantz, 1974; Mishkin, 1954). There is little evidence of a protective effect on feeding and drinking behavior following amygdala damage (Fonberg, 1974; Kemble & Davies, 1981). Similarly, the protective effects on salt appetite following LH or central gustatory damage would probably be abolished following amygdala damage, and some unpublished observations of my own suggest that this is true.

Other taste- and drive-related preoperative protective effects also may involve the amygdala. Anatomically, the amygdala is richly interconnected with the hypothalamus, cortex, and brainstem regulatory regions (e.g., Krettek & Price, 1978; Schwaber, Kapp, Higgens, & Rapp, 1982). Again the major taste-visceral projection to the forebrain lies along the pathway to the central nucleus of the amygdala (Norgren, 1984); it is therefore in an ideal position to organize the taste-motivational changes that result from preoperative treatments.

In the salt-hunger regulatory system, changes in the amygdala may include structural changes in morphology,

synaptic organization, and neural connectivity. The medial nucleus of the amygdala is a primary target of the mineralocorticoid hormones (e.g., McEwen, Lambin, Rainbow, & DeNicola, 1986). Structural changes are known to occur in this nucleus during development (Nishizuki & Arai, 1981), and additional changes that result from steroid action in the nervous system may occur during adulthood in brain nuclei (Arnold & Breedlove, 1985). The behavioral result of the hormone's action on the medial nucleus during sodium depletion and following the restoration of body sodium is to enhance the value of salty commodities to the animal. The animal therefore ingests the salt in greater amounts. This occurs because a steroid-senstive circuit has been activated by the hormone. One node in the circuit is the medial nucleus of the amygdala. Other node members include the medial preoptic and the bed nucleus of the stria terminalis (Schulkin, Marini, & Epstein, in press). All three bind aldosterone and are richly interconnected (Simerly & Swanson, 1986). When the hormone acts on this circuit, the synthesis of new proteins in the form of neurotransmitters may occur. The mineralocorticoids may, in effect, upregulate the binding properties of these brain regions for the steroid and induce greater production of putative neurotransmitters involved in the behavior—angiotensin.

Although the above scenario may have some promise for explaining some aspects of the protection of salt hunger, we are far from understanding the other protective effects cited in this review. My intention was to invite others to think about the protective effects, and to suggest that we may be in a better position to understand these protective effects when we know more about the changes that may occur in amygdala function and structure (as in Greenough, 1975) as a result of feeding and drinking experiences.

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