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4. The shallow waters of the West Indies are covered with "fish pots" which attract all varieties of reef-dwelling fish. The adult size classes of many species are virtually absent.
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6. *Diadema* do not move as much on stormy nights. This may be because they could be tumbled about by surge on the unconsolidated substrate of the halo.
7. The surface of PR-3 appears completely barren at first glance, but actually has abundant growth in mats which are actively fed upon by *Diadema*. See Ogden *et al.* (*3*) for a detailed discussion of the feeding habits of *Diadema*. It is not known whether all urchins eventually end up feeding in the halo. J. Konigsberg and I. Braverman (personal communication) found that the percentage of *Thalassia* in the guts of *Diadema* on the reef decreases with distance from the halo, but many urchins on the reef have *Thalassia* in their gut contents. The major exploiters of the halo region, however, are the urchins at the perimeter of the reef. J. B. Lewis [*Can. J. Zool.* **42**, 549 (1964)] found that *Diadema* feed largely on algae. In nature, feeding was concentrated in the late afternoon and early evening, while in the laboratory feeding occurred at night.
8. The coral *Acropora palmata* on PR-3 provided much daytime hiding space for *Diadema*. Another coral, *Porites porites*, was rarely crossed by moving *Diadema*. These corals may well influence movement into the halo. The urchins are not distributed uniformly on the reef surface. The largest populations are found in the northeast portion. Another possibility is that the urchins concentrate grazing on certain portions of the halo at a time, shifting slowly so that eventually the entire halo is grazed.
9. The area of PR-2 is approximately 1000 m^2 and over 7000 urchins were removed. The reef is repopulated at a rate of up to 500 urchins per month, which move in from the shoreline or other reefs. Almost all of the urchins on the patch reefs are of adult size (mean test diameter between 50 and 60 mm). Following the clearing of PR-2 a lush growth of benthic algae rapidly developed on the formerly bare substrate. The dominant species was the brown alga, *Padina sanctae-crucis*.
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11. We thank I. Braverman and J. Konigsberg for the use of some of their unpublished data. P. Sammarco, R. Steneck, D. P. Abbott, I. Abbott, and T. Keller inspired this study. J. B. Adams, W. Adey, J. Burk, P. R. Ehrlich, and L. C. Gerhard read the manuscript. Many students, especially those in course W.I. 405 on problems in marine biology (January 1973), assisted in the field work. This is Contribution No. 12 of the West Indies Laboratory of Fairleigh Dickinson University.

5 June 1973; revised 16 July 1973

Recovery of Feeding and Drinking by Rats after Intraventricular 6-Hydroxydopamine or Lateral Hypothalamic Lesions

Abstract. *Rats given intraventricular injections of 6-hydroxydopamine after pretreatment with pargyline become aphagic and adipsic, and show severe loss of brain catecholamines. Like rats with lateral hypothalamic lesions, these animals gradually recover ingestive behaviors, although catecholamine depletions are permanent. Both groups decrease food and water intakes markedly after the administration of α-methyltyrosine, at doses that do not affect the ingestive behaviors of control rats. Thus, both the loss and recovery of feeding and drinking behaviors may involve central catecholamine-containing neurons.*

6-Hydroxydopamine (6-HDA) administered intracerebrally along the nigrostriatal bundle (*1, 2*), within the lateral hypothalamus (*1, 3*), or by way of the lateral ventricles (*4*), can produce aphagia, adipsia, and prolonged anorexia in rats. The same effects occur after bilateral electrolytic lesions of the far lateral aspects of the ventrolateral hypothalamus (*1, 4–9*) or of other areas along the nigrostriatal pathway (*10*). Ungerstedt (*1*) and others (*4, 9*) have suggested that the disruptions of ingestive behaviors are due to the almost complete disappearance of striatal dopamine that is observed in each of these preparations. In the present studies, we sought to determine whether details of the progressive recovery from aphagia and adipsia after intraventricular administration of 6-HDA were similar to the well-known syndrome that is observed following electrolytic damage to the lateral hypothalamus (*7, 8*). We now report that they are. We also report that residual brain catecholamines appear to make a significant contribution to the recovery of ingestive behaviors in rats with either 6-HDA or electrolytic lesions.

Twenty-two rats of the Sprague-Dawley strain (Zivic-Miller Laboratories, Pittsburgh), weighing 250 to 300 g, were given pargyline (50 mg/kg, intraperitoneally) followed 30 minutes later by an intraventricular injection of 6-HDA (200 μg) (*11*), as in previous studies (*4*). The animals were aphagic and adipsic for 24 hours, but ingestive behaviors resumed within the next day or two. Control animals given either pargyline or 6-HDA alone showed no aphagia or adipsia. Four days after the first treatment, animals were given the same injections of pargyline and 6-HDA for a second time. Sixteen of them became aphagic and adipsic and were given access to highly palatable foods, such as Pablum, Metrecal, and sucrose solution; nevertheless, eight rats remained aphagic or anorexic, lost more than 35 to 40 percent of their body weights, and died within 1 to 2 weeks. We attempted to keep the other eight rats alive by intragastric feeding. Of these, one rat continued to lose body weight and died, but the other seven rats ultimately recovered feeding and drinking behaviors. Five were eating dry Purina laboratory chow pellets and drinking water within 2 to 3 weeks, while two rats recovered much more slowly. These seven rats displayed the same general pattern of recovery, which differed only in its time course.

Consideration of a rat which recovered slowly will highlight features of the recovery sequence (Fig. 1). At first, this animal ate nothing and had to be maintained by daily intragastric intubations of liquid diet. After 4 days, the animal passed into a second stage in which it would ingest the palatable foods. Gradually, larger amounts of these special foods were consumed, and eventually tube feeding was no longer required for body weight maintenance. After 58 days, the animal entered a third stage in which it would eat dry chow, but only if hydrated. Although it still would not drink water, the rat would accept 5 to 10 percent sucrose solutions and thereby maintain body fluid hydration. Finally, 92 days after the second 6-HDA treatment, the animal entered a fourth stage in which it maintained body weight on dry chow and tap water, although at a level that was considerably below that of control rats.

In contrast to these 16 animals, the other six rats recovered from the second 6-HDA treatment within a few days. These animals were given the same injections of pargyline and 6-HDA for a third time. Aphagia and adipsia were observed in each rat. In four of them, this was followed by an extended recovery period that was similar to (and, in two instances, even longer than) that just described. However, two animals never did progress

beyond the second stage of recovery and were killed 12 months after the third treatment.

In addition to these deficits in ingestive behaviors, rats given intraventricular 6-HDA treatments, unlike pair-fed controls, showed other pronounced impairments. For example, they frequently failed to groom, were irritable when held, showed piloerection, and had an arched back. They rarely tried to descend and explore while being weighed on a platform scale even after months of daily weighing experiences. Furthermore, they did not move immediately from the front upper edge of a suspended cage down the wire-mesh grid toward the cage floor but often remained perched where they had been placed for several minutes (*12*). Finally, they showed disturbed sensorimotor integration by their impaired responses to olfactory stimuli, pinpricks, and orientation to moving objects or to sudden noises. Recovery of feeding and drinking behaviors was not paralleled by complete recovery from these impairments.

At the conclusion of these tests, the 13 rats that had shown aphagia and adipsia after two or three injections of 6-HDA were killed and their brains were removed for assay by methods described previously (*4*). For purposes of comparison, the brains from six vehicle-treated rats also were removed and assayed, as were the brains from six additional rats given two treatments with pargyline and 6-HDA (as above) that did not show aphagia or prolonged anorexia. Greater than 90 percent loss of striatal dopamine was observed in each of the rats that had been aphagic. Surprisingly, comparable losses also were observed in the six rats that had not been aphagic, although it should be noted that the residual dopamine which we were measuring approached the sensitivity limits of our assay, and thus it is possible that small but significant differences did exist between these groups of rats.

To summarize, adult rats rapidly recover from a single intraventricular injection of 200 μg of 6-HDA after pargyline pretreatment, but after two or three such treatments aphagia and adipsia are observed. During the gradual recovery from these deficits, animals invariably eat palatable foods and fluids first, then accept dry chow, and finally drink water. These observations, together with sensory and motor

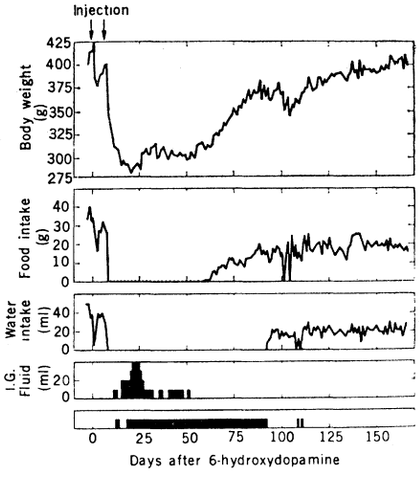

Fig. 1. Food and water intake and body weight in a rat given two intraventricular injections of 6-HDA (200 μg), each 30 minutes after pargyline (50 mg/kg, intraperitoneally). Intragastric (*I.G.*) feedings are shown. The bottom line indicates access to special, highly palatable foods.

impairments that also are evident, closely resemble the well-known syndrome that is reported in rats with bilateral electrolytic or 6-HDA–induced lesions in the lateral hypothalamus or other portions of the nigrostriatal bundle (*2, 8, 13*), and therefore suggest that the common neurochemical basis for the aphagia and adipsia that is initially observed in each of these preparations is the destruction of central catecholamine-containing neurons.

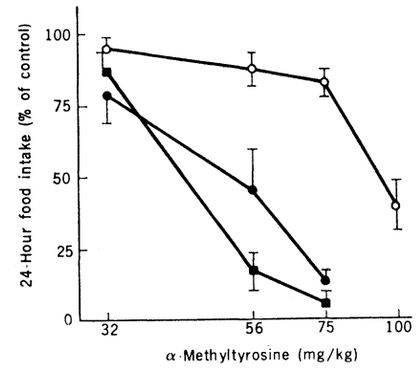

Fig. 2. The effect of α-methyl-*p*-tyrosine on 24-hour food intake in control rats (○) and rats with either two pargyline (50 mg/kg, intraperitoneally) + 6-HDA 200 μg, intraventricularly) treatments (■) or bilateral electrolytic lesions of the far-lateral hypothalamus (●). α-Methyl-*p*-tyrosine was given (intraperitoneally) at 8 a.m., 4 p.m., and midnight, and food intake was measured during the 24 hours following the first injection. Each point represents the mean ± the standard error of the mean for 4 to 8 rats (32, 56, and 100 mg/kg doses) or 8 to 12 rats (75 mg/kg).

It is more difficult to account for the observed recovery of ingestive behaviors, since catecholamine depletions appear to be permanent (*14*). Several explanations may be suggested for this apparent paradox: (i) the initial aphagia may be due to catecholamine depletions, while resumption of feeding may result from functional recovery of this same system that is not detectable by conventional measurements of amine concentration; (ii) the initial aphagia may be due to catecholamine depletions, but resumption of feeding may result from transfer of the function formerly served by these monoamines to another neurochemical system that is not affected by the lesions; (iii) the initial aphagia may not be causally related to observed catecholamine depletions but to another, as yet unknown, effect of the lesions that is more temporary.

The third hypothesis cannot yet be ruled out, although it should be noted that the concentration of other putative transmitter substances, such as serotonin, acetylcholine, γ-aminobutyric acid, glutamic acid, or glycine, do not appear to be altered by intraventricular 6-HDA treatments (*15*). In order to differentiate between the first two hypotheses, we examined the effects of α-methyl-*p*-tyrosine (AMT), an inhibitor of catecholamine synthesis, on the food and water intakes of lesioned rats that had recovered from an initial aphagia and adipsia (*16, 17*). Separate groups of animals received bilateral electrolytic lesions of the lateral hypothalamus (*18*), or two intraventricular injections of 6-HDA after pargyline pretreatment (as above). Both groups of rats ($N = 8$ and 12, respectively) became aphagic and adipsic and required intragastric feeding for body weight maintenance until, after 2 to 28 weeks, ingestive behaviors recovered (although four rats with lateral hypothalamic lesions remained adipsic and were tested in the third stage of recovery). After intake of Purina chow pellets and water had stabilized, intraperitoneal injections of AMT were given at 8 a.m., 4 p.m., and midnight, and food intake was measured during the 24 hours following the first injection.

Food and water intakes in each group were inhibited by AMT, for a period of 24 to 48 hours. This suggested to us that brain catecholamines were still functioning to maintain in-

gestive behaviors in the lesioned animals. Not only did AMT reduce food and water intakes in rats with either 6-HDA or electrolytic lesions, but the animals were 70 to 110 percent more sensitive than controls to these effects of the drug (Fig. 2) (*19, 20*). This increased sensitivity can be seen most clearly when mean responses to a dose of 75 mg/kg are considered. This dose had little or no effect on the food and water intakes of control rats but reduced the intakes of lesioned rats by 80 to 100 percent (*21*).

In contrast to their increased sensitivity to AMT, lateral hypothalamic lesions (*22*) and intraventricular 6-HDA treatments (*23*) both decrease the sensitivity of rats to the anorexic actions of amphetamine. Thus, their sensitivity to AMT does not represent a general heightened responsiveness to anorexic agents, but may instead reflect a lesion-induced increase in the rate of turnover in central catecholamine terminals or a reduction in the number of such terminals. On the other hand, it is also possible that some more general effect of AMT, such as hypotension (*24*) or sedation (*17*), causes a nonspecific disruption of behavior, and that lesioned animals simply are either more sensitive to this or suffer bigger changes than controls.

Several weeks after the tests with AMT, the animals were killed and their brains were removed and assayed for brain catecholamine levels (*4*). Animals treated with pargyline and 6-HDA showed an almost complete loss of both telencephalic norepinephrine and striatal dopamine. However, electrolytic lesions of the lateral hypothalamus caused a more variable decrease in brain catecholamines. In several rats which had exhibited marked aphagia and adipsia, only 50 to 60 percent loss of striatal dopamine was observed (*25*). Histological examination of stained sections through the lesioned areas in the diencephalon revealed that damage was often to the medial aspects of the lateral hypothalamus and seemed to spare most of the medial portion of the internal capsule, at least unilaterally. These animals tended to recover feeding and drinking behaviors more rapidly (usually within 14 days) than did animals with larger dopamine depletions. This observation is similar to that of Morgane (*6*), who reported that far-lateral damage (which included the medial edge of the internal capsule) caused a more intractable aphagia than medial damage to the ventrolateral hypothalamus.

We have now observed that 6-HDA treatments do not necessarily produce prolonged anorexia even after 90 percent depletion of striatal dopamine, whereas electrolytic lesions can cause deficits in ingestive behaviors requiring tube-feeding maintenance with much less damage to the dopamine-containing fiber system (*26*). These observations may suggest that the destruction of only a portion of the nigrostriatal bundle is necessary to produce these behavioral deficits, or that electrolytic lesions of the lateral hypothalamus produce a more severe effect on the dopamine projections of the nigrostriatal bundle than does intraventricular dopamine (perhaps because the former has a greater effect on dopamine axons), or that damage to fibers that do not contain dopamine can be significant in the production of deficits in ingestive behaviors. While we cannot yet differentiate among these possibilities, several lines of evidence suggest that neural systems other than the nigrostriatal bundle (but possibly involving catecholamine-containing neurons) are important to feeding behavior (*3, 10, 27*).

In conclusion, we have observed that many features of the lateral hypothalamic syndrome can be obtained by intraventricular administration of 6-HDA. We have also observed that animals which have recovered from aphagia and adipsia induced either by the 6-HDA treatment or by electrolytic lateral hypothalamic lesions will decrease food and water intakes markedly after the administration of AMT, and at a dose that has little or no effect on control animals. This suggests the possibility that recovery from either lesion is dependent on compensatory processes occurring within the damaged systems. Several mechanisms have been proposed which might account for this compensation, such as an increase in catecholamine turnover in terminals of remaining fibers (*28*), an increase in sensitivity of postsynaptic receptors (*29*), and sprouting of new terminals from transected axons (*30*). Which, if any, of these processes might account for the observed recovery requires further investigation.

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18. Electrolytic lesions were made with a monopolar stainless steel electrode by passing 2-ma anodal current for 15 seconds. Each rat was placed in a stereotaxic instrument with its skull positioned flat, and the electrode was placed 6.0 mm anterior to the interaural line, 2.0 mm lateral to the sagittal sinus, and 8.0 mm ventral to the dura of the cortex.
19. This estimate is based on the amount of AMT necessary to inhibit food intake by 50 percent, as calculated graphically from Fig. 2.
20. Sensitivity to AMT appeared to be proportional to length of recovery period. For example, in one animal treated with pargyline and 6-HDA and requiring 7 months for recovery, 32 mg/kg produced an almost complete suppression of food intake. This animal was not included in Fig. 2.
21. Apparently, other behaviors also are more sensitive to a drug-induced disruption of catecholamine function following biochemical or electrolytic lesions of catecholamine-containing fiber systems. See J. A. Harvey, *J. Pharmacol.* **147**, 244 (1965); F. Grabarits and J. A. Harvey, *ibid.* **153**, 401 (1966); R. I. Schoenfeld and M. J. Zigmond, *Pharmacologist* **12**, 227 (1970); B. R. Cooper, G. R. Breese, J. L. Howard, L. D. Grant, *Psychopharmacologia* **27**, 99 (1972); R. I. Schoenfeld and N. J. Uretsky, *Eur. J. Pharmacol.* **20**, 387 (1972).
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25. Pargyline and 6-HDA treatment produced a 96 ± 2 percent depletion of telencephalic norepinephrine and a 94 ± 2 percent depletion of striatal dopamine. Similar depletions are observed in whole brain. After electrolytic lateral hypothalamic lesion, telencephalic norepinephrine concentration ranged from 52 to 103 percent of control, while striatal dopamine ranged from 29 to 49 percent of control. Brainstem catecholamines were unaffected. The endogenous concentration of norepinephrine in the telencephalon was 0.21 ± 0.01 μg/g; striatal dopamine concentration was 8.68 ± 0.37 μg/g.
26. In addition, Oltmans and Harvey (*9*) have observed aphagia and adipsia in rats following bilateral electrolytic lesions of the ventrolateral hypothalamus that produced a mean depletion of 68 percent of striatal dopamine, although 19 of 24 rats resumed spontaneous feeding and drinking without being given special palatable foods, and none required intragastric feeding for body weight maintenance.
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Pentobarbital: Selective Depression of Excitatory Postsynaptic Potentials

Abstract. *The effects of pentobarbital (Nembutal) on synaptic transmission and postsynaptic potentials were studied by the use of several invertebrate preparations. Pentobarbital selectively and reversibly depressed both excitatory postsynaptic potentials and sodium-dependent postsynaptic responses to putative excitatory transmitters without affecting either inhibitory postsynaptic potentials or chloride- and potassium-dependent postsynaptic responses to putative transmitters. A selective depression of postsynaptic excitatory events was also observed with other central nervous system depressants (ethanol, chloroform, chloralose, diphenylhydantoin, and urethane). The results suggest that central and peripheral depression observed during general anesthesia is due to a selective depression of excitatory synaptic events.*

Theories of general anesthesia have been divided into those which account for depression of synaptic transmission in terms of a blockade of axonal conduction (*1*) and those which account for the phenomenon in terms of a disturbance in the mechanism of synaptic transmission (*2–10*). Since general anesthetics depress synaptic transmission at concentrations which do not block axonal conduction (*3, 6, 9*), it is more likely that the depression is occurring at the synaptic site. Many investigations have demonstrated that general anesthetics depress excitatory postsynaptic potentials (*3–7, 10*), while others have shown that inhibitory postsynaptic potentials are preserved under the same conditions (*4, 8*). The synaptic mechanisms which have been proposed to account for general anesthesia include (i) a decrease in the presynaptic release of excitatory transmitter (*2, 3*), (ii) an increase in the presynaptic release of inhibitory transmitter (*4*), (iii) a decrease in the postsynaptic chemosensitivity to excitatory transmitter (*6, 10, 11*), and (iv) a stabilization of the postsynaptic membrane to inhibit action potential generation (*7*). In this report we present evidence to support the hypothesis that the action of general anesthetics (and central nervous system depressants) is primarily postsynaptic in nature and involves a *selective* depression of excitatory postsynaptic events without change in inhibitory postsynaptic events.

To test the effects of anesthetics on synaptic transmission and postsynaptic sensitivity we used several molluscan and crustacean preparations with readily obtainable excitatory and inhibitory postsynaptic potentials. The preparations studied included identified nerve cells in *Aplysia californica* (sea hare) and *Otala lactea* (a land snail) and walking leg neuromuscular junctions in crayfish (*Orconectes virulis*) and lobster (*Homarus americanus*). They were placed in appropriate chambers and perfused with artificial salines (*12*), and one or two KCl-filled glass micropipettes were inserted into the neurons or muscle fibers for the purpose of recording membrane potentials and passing current across the membrane. Potentials were measured with conventional techniques and were displayed on an oscilloscope and recorded on a pen-recorder. Drugs were dissolved in the salines just prior to perfusion (*13*).

Pentobarbital, in concentrations present under conditions of surgical anesthesia ($2 \times 10^{-4}M$), reversibly antagonized the excitatory postsynaptic potentials in lobster muscle fibers, but did not affect the inhibitory postsynaptic potentials (Fig. 1A). Under control conditions the excitatory postsynaptic potentials were approximately 5 to 7.5 mv, while in the presence of $2 \times 10^{-4}M$ pentobarbital these had decreased to 2

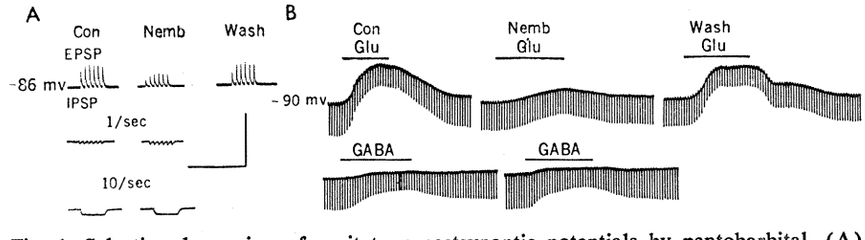

Fig. 1. Selective depression of excitatory postsynaptic potentials by pentobarbital. (A) Membrane potential traces showing excitatory and inhibitory postsynaptic potentials (*EPSP* and *IPSP*) recorded in a lobster muscle. The IPSP's have been evoked at frequencies of one and ten stimuli per second. Pentobarbital (*Nemb*) ($2 \times 10^{-4}M$) reduces the amplitude of the EPSP's without altering the size of the IPSP's. Washing (*Wash*) with drug-free saline restores the EPSP's to their original size. (B) Membrane responses of lobster muscle [from a different preparation than that used in (A)] to the perfusion of putative transmitters glutamate (*Glu*) ($10^{-4}M$) and GABA ($10^{-5}M$) (during the period indicated by the horizontal bars). The downward deflections in the records are voltage responses to constant current pulses. The excitatory transmitter glutamate causes a depolarization and decrease in membrane resistance. The glutamate response is depressed by $10^{-4}M$ pentobarbital. The inhibitory transmitter GABA also produces a depolarization in these experiments, since the muscle fibers were hyperpolarized in K^+-free salines [see (*12*)], and hence the equilibrium potential of the IPSP (or E_{Cl}) was shifted in a depolarizing direction relative to the resting potential. The depolarization and decrease in membrane resistance in response to GABA remain unchanged. Washing with drug-free saline restores the glutamate depolarization. Calibration: 15 mv, 12 seconds in (A), 2 minutes in (B). *Con*, control.