room temperature. Samples were stored at 5°C in a desiccator until they were used. Residues were applied with cotton swabs directly to the backs of males.

19. Soluble proteins were extracted overnight at 5°C with 100-ml portions of 0.05*M* phosphate-buffered saline and 1*M* NaCl in 0.05*M* phosphate from 5-g portions of body skin that had been homogenized with a Polytron. After centrifugation for 15 minutes at 2000 rev/min, the supernatants were dialyzed (Spectrapor, MW cutoff 3500) against five changes of distilled water at 5°C and lyophilized. Lyophilized samples were stored at −20°C until they were used; a sample was dissolved in 1 ml of distilled water immediately before it was used in behavioral testing. The entire extracts were applied to the backs of males.
20. Total serum lipid was measured by the sulfuric acid–vanillin reaction, and calculation of concentration was based on an olive oil standard [N. Tietz, *Fundamentals of Clinical Chemistry* (Saunders, Philadelphia, 1970)].
21. Snakes were anesthetized with Brevital at a dosage of 1.5 mg/kg [R. Wang, J. Kubie, M. Halpern, *Copeia* **1977**, 738 (1977)]. The dorsal aorta anterior to the liver was cannulated; 20 ml of heparinized saline (10 U/ml) and then 20 ml of saline without heparin were infused to wash the liver. Homogenates (1:10 in saline) were prepared with a Polytron, stored at −20°C, and the equivalent of 0.5 g of liver was applied to the backs of males. Fat bodies were used in direct application to males.
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26. Female *T. s. parietalis* were treated with estradiol benzoate (40 μg per gram of body weight). Liver weight increased from 2.9 ± 0.2 percent of the body weight in the control group to 4.1 ± 0.2 percent by 3 days and 5.9 ± 0.6 percent after 7 days of treatment and 3 days without (*17*). Fat body weight was 4.8 ± 0.7 percent of the body weight in the control group.
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Increased Intracranial Self-Stimulation in Rats After Long-Term Administration of Desipramine

Abstract. *The effects of long- and short-term administration of the tricyclic antidepressant desipramine on intracranial self-stimulation in rats were studied with electrodes in the A10 region of the dopamine-containing cell bodies of the ventromedial tegmentum. Long-term desipramine administration resulted in a significant shift to the left in the ascending portion of the rate–current intensity function, indicating that the activity of the mesolimbic dopamine system was enhanced. These findings point to a possible dopaminergic mechanism of action of antidepressants and support speculations concerning the role of dopamine-containing neurons in the pathophysiology of depression.*

The catecholamine hypothesis of affective illness posits that mania and depression are related to abnormal increases and decreases, respectively, in the function of central noradrenergic systems (*1*). More specifically, it has been proposed that depression may result from a pathological hypoactivity of a reward system in the brain which uses a catecholamine as its neurotransmitter (*2*). The observation that clinically effective antidepressants, such as desipramine and related tricyclic compounds, block neuronal uptake and increase synaptic concentrations of norepinephrine is consistent with this hypothesis (*3*). However, not all clinically effective antidepressants share this property (*4*), and many recent studies have failed to provide evidence that central norepinephrinergic systems are involved in the mediation of reward (*5*). Instead, both basic and clinical studies have indicated that central dopamine (DA)-containing neurons—specifically, the mesolimbic system—may be important neuronal substrates for some forms of reward. For example, intracranial self-stimulation (ICS) obtained from electrodes in the origin or the pathway of the mesolimbic DA system has been shown to be dependent on the integrity of the ascending projections of this system (*6*). Furthermore, the reinforcing properties of cocaine and amphetamine are blocked by DA receptor antagonists and by selective lesions of DA terminals in the nucleus accumbens, a major area of projection of the mesolimbic DA system (*5, 7*).

These considerations prompted us to examine the effect of desipramine on a DA-mediated behavior, namely, ICS obtained from electrodes in the ventromedial tegmentum (*6*). Because the clinical effects of tricyclic antidepressants typically require several weeks to become manifest, we administered desipramine on long- and short-term bases. Twenty-four male Wistar rats weighing 300 to 330 g were anesthetized and implanted with electrodes in the A10 DA region (*8*). For 5 days following surgery all the animals were given a 30-minute test once each day to screen them for ICS (*9*). On days 6 and 7 ICS rate–current intensity functions were obtained by using an ascending and descending method of limits (*10*). Beginning on day 8, half the animals received daily injections of desipramine HCl (10 mg/kg) for 14 days and half received an equal volume of vehicle (*11*). On days 8 and 9 the effect of short-term desipramine administration on the rate-intensity functions was determined 30 minutes after the injection. The effect of long-term desipramine treatment on the rate-intensity functions was determined on days 15 and 16, 24 and 48 hours after the last injection. The data were analyzed by repeated-measures analysis of variance and appropriate post hoc tests (*12*). After completion of the behavioral experiments the electrode placements were confirmed histologically (*13*).

Difference scores were obtained for statistical analyses by subtracting the individual baseline rates from those obtained after treatment. Scores were obtained for the control group and both desipramine-treated groups under current presentation modes in which intensity was increased or decreased at regular intervals. Analysis of variance yielded a significant three-way interaction ($P < .05$) which indicates that, at suprathreshold current intensities, the ICS rates for rats receiving long-term desipramine treatment were significantly higher than those for the vehicle control and short-term desipramine groups (Fig. 1). This interaction was found only for data obtained during current presentation in the ascending mode. No significant differences were observed between the baseline ICS rates and those following short-term desipramine treatment, and the associated data are omitted from Fig. 1.

The effect of desipramine was also analyzed by determining the amount of current necessary to increase ICS to half the maximal rate before and after drug treatment (*14*). Vehicle treatment did not affect this value (Table 1). In contrast, long-term but not short-term desipramine treatment significantly reduced the current necessary to produce half-maximal ICS rates during presentation of ascending intensities. Before drug treatment the ICS rates obtained at the middle current intensities were higher during presentation in the ascending order than in the descending condition. These higher rates can be attributed to positive contrast effects. In previous work with the ICS paradigm, positive contrast was found under similar circumstances (*15*).

These results suggest that the function of the mesolimbic DA system is facilitated by long-term but not short-term desi-

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pramine administration. Previous research demonstrated that ICS obtained from the A10 region is mediated by ascending DA projections (*6*). A shift in the rate-intensity function to the left has been caused by other pharmacological treatments known to enhance central DA function (*16*). On the other hand, compounds that selectively block DA receptors shift the rate-intensity function to the right (*17*). This, therefore, is a sensitive behavioral procedure with which to study central DA systems. Neither the maximum rate of ICS nor the threshold current intensities were influenced by long-term desipramine administration (Fig. 1), and no effect would have been observed had these been the only measures.

The mechanism by which this drug enhances ICS from the A10 region is not known. However, there is increasing evidence that many clinically effective antidepressant compounds influence central DA mechanisms. For example, both tricyclic and newer "atypical" antidepressants are weak blockers of synaptosomal uptake of DA at what may be clinically relevant concentrations (*4, 18*). Tricyclic antidepressants also produce dose- and time-dependent changes in the levels of striatal DA and its metabolites (*19*). Recent neurophysiological and behavioral findings suggest that repeated administration of various antidepressants induces progressive subsensitivity in DA autoreceptors and supersensitivity in some postsynaptic DA receptors (*20*). Such changes induced by desipramine would be consistent with the present observations. Subsensitivity of presynaptic receptors would enhance synaptic release of DA per electrical impulse and shift the rate-intensity function to the left. Supersensitivity of postsynaptic DA receptors would enhance the postsynaptic effects of transmitter released from DA terminals, with similar behavioral consequences. It is not known whether such effects of antidepressants are due to direct effects on DA neurons or whether they are secondary to actions on norepinephrine- and serotonin-containing neurons (*21*). Electroconvulsive shock enhances behavioral responses to dopamine receptor agonists through a mechanism that appears to be secondary to effects on norepinephrine neurons (*22*).

Table 1. Effect of short- and long-term desipramine administration on the current required to elicit ICS at half-maximal rates with ascending or descending increments in intensity. Values are means ± standard errors.

Treatment	Current intensity (μA)	
	Ascending mode	Descending mode
Desipramine		
Baseline	14.8 ± 4.0	18.7 ± 2.8
Short-term	14.8 ± 3.4	19.4 ± 2.3
Long-term	10.9 ± 2.9*	17.2 ± 2.4
Vehicle		
Baseline	14.5 ± 4.3	18.7 ± 2.6
Short-term	15.6 ± 4.5	19.1 ± 3.1
Long-term	13.8 ± 4.9	17.2 ± 2.8

*Significantly different from baseline ($P < .01$).

These results have implications not only for the mechanism of action of antidepressants but also for the etiology of depression. The observation that long- but not short-term desipramine treatment potentiates a DA-mediated behavior is consistent with the slow onset of action of antidepressants. The facilitation of a reward-related DA pathway by desipramine suggests that this pathway may be functionally hypoactive in clinical depression. Although there is not complete agreement (*23*), a number of research groups have reported decreased probenecid-induced accumulation of the DA metabolite homovanillic acid in the cerebrospinal fluid of depressed patients (*24*). Post *et al.* (*25*) reported that the DA agonist piribedil has mild to moderate antidepressant effects. Taken together, these observations are consistent with an impaired function of DA systems in at least some types of depression and support the dopamine hypothesis of affective illness (*26*).

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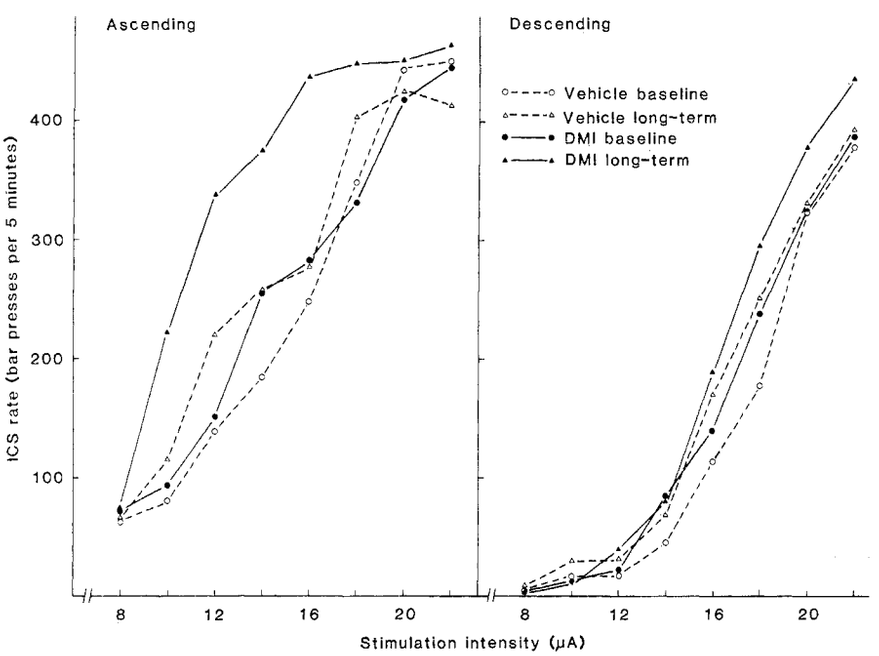

Fig. 1. Effect of long-term administration of desipramine (DMI) on ICS obtained from the A10 region of the ventromedial tegmentum. In the ascending mode current was increased 2 μA every 5 minutes; in the descending mode it was decreased 2 μA every 5 minutes. DMI shifted the ICS rate–current intensity function significantly to the left in the ascending mode ($P < .05$). The data are means for 12 animals in each condition.

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8. The animals were anesthetized with pentobarbital (50 mg/kg), and bipolar, 0.005-inch-diameter Nichrome electrodes (MS-303, Plastic Products Co.) were implanted unilaterally with a stereotaxic apparatus (Kopf). The coordinates, from stereotaxic zero, were anterior +2.4 mm, lateral 0.6 mm, and dorsal +2.2 mm. The electrodes were implanted perpendicular to the horizontal plane, with the stereotaxic incisor bar set 4.2 mm ventral to stereotaxic zero.
9. The dimensions of the operant chamber were 46 by 30 by 24 cm. Depression of a 2.5-cm-wide bar activated a variable intensity, constant current stimulator which generated a 60-Hz sine wave 0.2 second in duration. Intracranial self-stimulation was initially established by varying the current for each animal until a stable rate was obtained. For each animal this current was used in each of the 30-minute test sessions on the subsequent 4 days.
10. The current intensity was varied in 2-μA steps

from 0 to 28 μA. Ascending and descending series of intensities were counterbalanced over 2 days, providing separate ascending and descending rate-intensity functions for each animal. In both series the experimenter delivered three primes at each current intensity; the subsequent rate of ICS was determined over 5 minutes.
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Central Noradrenergic Pathways for the Integration of Hypothalamic Neuroendocrine and Autonomic Responses

Abstract. *Immunohistochemical and axonal transport methods were used to describe the organization of a series of central noradrenergic pathways that interrelate the nucleus of the solitary tract, which receives primary visceral sensory information, and the paraventricular and supraoptic nuclei of the hypothalamus, which participate in autonomic and neuroendocrine modes of homeostatic control. The results indicate that pathways arising from noradrenergic cells in the dorsal vagal complex, the ventrolateral medulla, and the locus coeruleus end in specific subdivisions of the paraventricular and supraoptic nuclei which are involved in the regulation of responses from the pituitary gland and from both divisions of the autonomic nervous system. This circuitry may play an important role in the integration of hypothalamic responses to visceral stimuli.*

The maintenance of a stable internal milieu requires precise coordination of autonomic and endocrine responses to particular visceral stimuli. One approach to understanding the central mechanisms that mediate this coordination involves the elucidation of neural pathways that interrelate the nucleus of the solitary tract (NST), which is the principal recipient of primary visceral afferent information carried by the vagus (X) and glossopharyngeal (IX) nerves, with the hypothalamus, which plays an important role in the expression of neuroendocrine and autonomic responses. Since the paraventricular nucleus (PVN) of the hypothalamus appears to be involved in both modes of hypothalamic control (*1*), it may be useful for the study of neural mechanisms that underlie integrated visceral responses.

The magnocellular division of the PVN and the supraoptic nucleus (SON) play a role in synthesizing vasopressin and oxytocin and in controlling their release from the posterior lobe of the pituitary gland (*2*). Essentially separate and topographically distinct populations of cells in the parvicellular division of the PVN project to preganglionic cell groups of both divisions of the autonomic nervous system and to the median eminence, affording the nucleus a measure of control over anterior pituitary function as well (*3*). Because the PVN contains both functionally and anatomically distinct cell groups, neuroendocrine and autonomic responses may be integrated by way of afferent pathways that differentially innervate various subpopulations of neurons in the nucleus (*1*).

The experiments reported here clarify the organization of pathways that interrelate the NST and the PVN and SON in the rat. The NST projects directly to the PVN (*4*) through a pathway that is at least partially noradrenergic (*5*). However, this projection appears to innervate primarily the parvicellular division of the

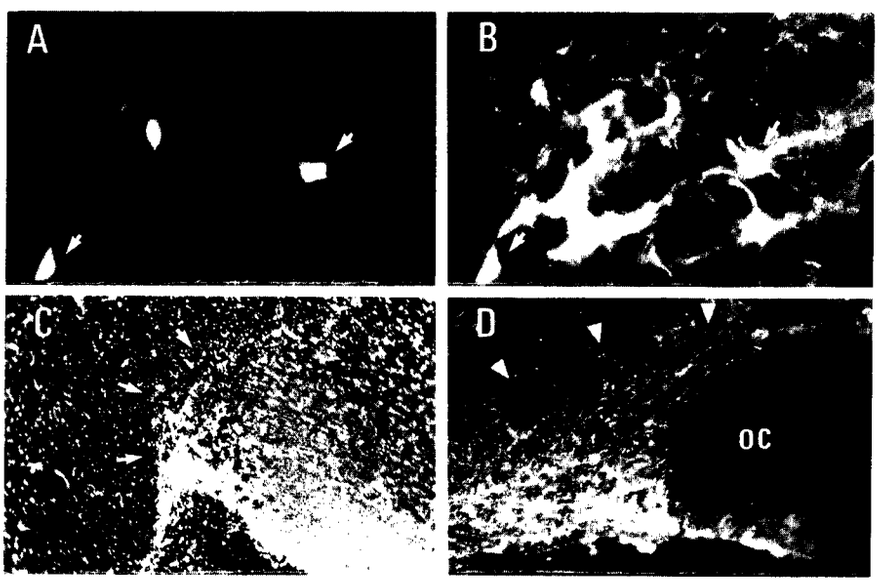

Fig. 1. (A and B) High-power fluorescence photomicrographs of the same field in the ventrolateral medulla, taken with different excitation wavelengths. (A) Cells retrogradely labeled after an injection of True Blue into the PVN. (B) A cluster of dopamine-β-hydroxylase–stained cells in the A1 catecholaminergic cell group. Two cells (arrowheads) clearly contain both dyes and are, therefore, dopamine-β-hydroxylase–containing neurons that project to the region of the PVN (× 250). (C and D) Photomicrographs showing (C) the distribution of anterogradely transported tritiated amino acids in the SON after an injection in the A1 region of the ventrolateral medulla and (D) the distribution of dopamine-β-hydroxylase–stained fibers in the SON of a normal rat brain. The injection was centered in the region of retrogradely labeled cells shown in (A). Note that the labeled terminal field in (C) and the noradrenergic fibers in (D) are both concentrated in the ventral part of the nucleus (arrowheads indicate nuclear borders) which contains predominantly vasopressinergic neurons (× 70). Abbreviation: *oc*, optic chiasm (lateral border).

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