

continuous interaction of narcotic drugs with their receptors may inactivate the receptors. Thus, a decreased response to the narcotic drugs may develop as a result of unavailability of receptor sites (10).

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#### References and Note

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### Apomorphine Test for Tranquilizing Drugs: Effect of Dibenamine

When a minimal emetic dose of apomorphine is carefully established in a group of dogs, it is possible to detect the inhibiting effect on emesis of a second drug, such as diphenhydramine (1), chlorpromazine (2), or reserpine (3). These findings indicate that the apomorphine test may have utility in selecting tranquilizing agents and imply a link between central emetic mechanisms and activities effecting tranquil behavior.

The rationale for the apomorphine test lies in the drug's established site of action at the chemoreceptor trigger zone in the area postrema, an area afferent to the emetic center which lies more deeply in the lateral reticular formation of the

medulla. This center may be excited reflexly from the periphery, through the chemoreceptor trigger area or from rostral neural sites (4). It is adjacent to areas integrating and mediating vasomotor, respiratory, and postural responses and functionally related to adjacent and rostral brain-stem areas involved in extrapyramidal, visceral, and "alerting" functions. The emetic integrating mechanisms are thus linked with a complex of brain-stem operations that bring the individual physiologically into contact with both his internal and external environment. This complex of operations may mediate the change in level and quality of psychomotor and autonomic reactivity which characterizes tranquil behavior. The link between emetic mechanisms and tranquilization is thus a neural one.

Apomorphine has central effects other than an emetic action. These apomorphine actions implicate the adjacent neural systems—for example, a hypotonic effect on spasticity produced either by decerebration or anterior cerebellar section (5) and, in the human, with subemetic doses, a tranquilizing action (6). It is entirely possible that drugs inhibiting the action of apomorphine at the chemotrigger area do so in part by action on these adjacent systems, which in turn may affect the reactivity of the emetic center.

One cannot use tests of emetic reactivity indiscriminately to infer tranquilizing or antiemetic clinical utility. Reserpine, for example, antagonizes apomorphine emesis in the dog but in the pigeon and in man may produce nausea and vomiting (7). Interpreting apomorphine tests, one may infer a brain-stem site of action; this is indicated by positive results and not at all ruled out by negative findings.

This report describes a centrally mediated antiapomorphine effect of dibenamine. A powerful adrenergic blocking agent, the drug acts peripherally on the effector cell to block chiefly the excitatory effects of epinephrine. Nickerson (8) has cited two phases in dibenamine activity: an initial epinephrine-dibenamine antagonism for the first 2 hours, and, with the binding of dibenamine to the peripheral effector cell, the onset of true adrenergic blockade enduring for 3 or 4 days. During the first phase, a brief period of central excitation may be noted, presumably affecting temporal lobe, as well as hypothalamic and medullary, function. Since a hydrolysis product of dibenamine which lacks adrenergic blocking properties produces the central effects of the first phase, the initial central effects may not be attributed to alteration of central adrenergic systems. Since no central effects had been experimentally demonstrable for the second phase, the finding of a prolonged tranquilizing action in anxiety states had to be ascribed to the peripheral blockade of adrenergic sub-

stances related to tension states (9), and the finding that catatonic patients were brought tranquilly into contact for a period of 18 to 72 hours was attributed to a possible action on central blood vessels (10). It would therefore be important to demonstrate an alteration of central neural activity that would be coincident with the behavioral effects and the peripheral adrenergic blockade of the second phase. Results of dibenamine inhibition of apomorphine emesis are indicated in Table 1.

With chlorpromazine and diphenhydramine, antiemetic potency is apparent during the peak period of pharmacologic activity (1, 2). With dibenamine, however, antiemetic potency is not demonstrable during the first 2 hours after administration. Following this initial period, and for a period up to 24 hours (the longest interval tested), a definite inhibition of apomorphine-induced emesis has been observed. The prolonged action thus establishes a central neural basis for the noted behavioral effects. This action is related neither to the adrenergic blockade (sympathectomy does not alter apomorphine emesis) nor to a clinical antiemetic effect. Both the excitatory phase and the local gastric irritation can produce nausea or vomiting.

The demonstration of prolonged central neuronal alteration does raise the possibility that less toxic agents with greater tranquilizing potency may be found among some of the interesting chemical analogs of dibenamine (8). From the experimental viewpoint, several clues point to particular receptor systems altered by dibenamine (6, 8, 11), so that the drug may now prove useful as a tool to study central drug-enzyme systems.

The fact that a drug may induce long-enduring central changes the neural bases for which are masked, stresses the importance in neuropharmacology of searching for such latent actions. In this respect, the apomorphine test of medullary vomiting mechanisms may be but one of several possibilities for studying brain-stem reactivity in attempting to develop drugs that affect psychic function.

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Table 1. Proportion of dogs protected from emesis by dibenamine.\*

Time to emetic challenge	Apomorphine dose ( $\mu$ g/kg)	
	2 $\times$ M.E.D. (60)	4 $\times$ M.E.D. (100)
20 min	0/4	0/4
2½ to 6 hr	3/3	3/6
24 hr	7/7	2/3

\* In acid alcohol solution (0.4 percent), at a dose of 2 mg/kg intraperitoneally; apomorphine minimal emetic dose (M.E.D.) established at 25  $\mu$ g/kg.

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## Self-Stimulation of the Brain Used as a Screening Method for Tranquilizing Drugs

Behavioral effects of reserpine and chlorpromazine in animals and man have led to the search for an adequate screening method that would relate both to behavior in animals and site of action in the brain. Such a screening method is described here on the basis of the finding (1) that electric stimulation applied to specific hypothalamic and paleocortical structures of the rat brain has an effect on behavior tantamount to primary reward.

In these experiments (2), a bipolar electrode was chronically implanted in the brain of each animal. The pair stimulates only at the tip, and thus it affects only a small area of the brain. For testing, the animal was placed in a lever box (Skinner box), and an electric circuit was set up so that each bar-press produced a train of electric stimulation 0.6 sec in duration through the implanted electrode. The stimulus used was a 60-cy/sec sine wave of from 1 to 1.5 v applied through a resistance of about 10,000 ohms. In tests, the animal was never stimulated by the experimenter but was allowed to stimulate itself by pressing the lever.

The reinforcing value of an electrode placement is assessed in terms of the frequency of the lever-pressing response. When electrodes are placed in the anterior or middle hypothalamus, extremely high response rates can be achieved, often rising above 5000 responses per hour. When electrodes are placed in the region of the septal area or the amygdaloid complex, rates range from 200 to 2000 per hour. Rates of 200 responses per hour are also achieved from all structures of the rhinencephalic cortex. Other parts of the brain do not produce this positive reinforcing effect.

The size and anatomical differentiation of this "rewarding" system suggested that its parts might be differentially sensitive to neuropharmacological agents. Experiments were therefore designed to determine whether different agents would affect self-stimulation rates for some electrode loci more than for others.

In the series reported here, electrodes were implanted in the middle hypothalamus, the septal region of the forebrain, or the amygdaloid area. Each animal had an electrode pair in only one of these

regions. Animals were allowed 4 days to recover from the operation and then were given 6 to 14 days of pretraining at self-stimulation in the test boxes. In training and tests, the animals were run for 80 minutes per day. The electric stimulus was the only reinforcing agent used in these experiments. Under these conditions, all animals showed day-to-day improvement during pretraining and achieved stable response prior to drug tests. The stable response rate of animals that were stimulated in the septal region of the forebrain or the amygdaloid area was about 500 per hour, and the stable response rate of animals that were stimulated in the middle hypothalamus was about 2500 per hour.

After stable rates had been achieved, drugs were introduced on the basis of a modified Latin square with crossing over of drugs between animals and control runs on intervening days to measure carry-over effects.

The preliminary series reported here consisted of a limited range of doses of reserpine, chlorpromazine, and pento-

barbital. The effectiveness of a given dose was gauged by evaluating the response rate following drug administration as a percentage of the average response rate for all days when no drug was administered.

In three animals with electrodes placed ventromedially in the hypothalamus, reserpine at 1 mg/kg depressed response rates to 7 to 45 percent of normal. In two rats with electrodes implanted in the amygdala, the same dose of reserpine reduced the response rates to 1 and 22 percent of normal. In contrast, the response rates of four rats in which the electrodes were placed in the septal region of the forebrain were depressed to a mean of 75 percent of normal (range, 67 to 83 percent.) Thus, there was marked depression in rats that were stimulated in the hypothalamus or in the amygdala but only a minor depression produced in the rats that were stimulated in the septal region. Typical data are presented in Fig. 1.

Chlorpromazine (2.5 mg/kg) depressed response rates in rats that were

## SELF STIMULATION IN FOREBRAIN AND HYPOTHALAMUS AS AFFECTED BY RESERPINE (R), CHLORPROMAZINE (C), AND PENTOBARBITAL SODIUM (A)

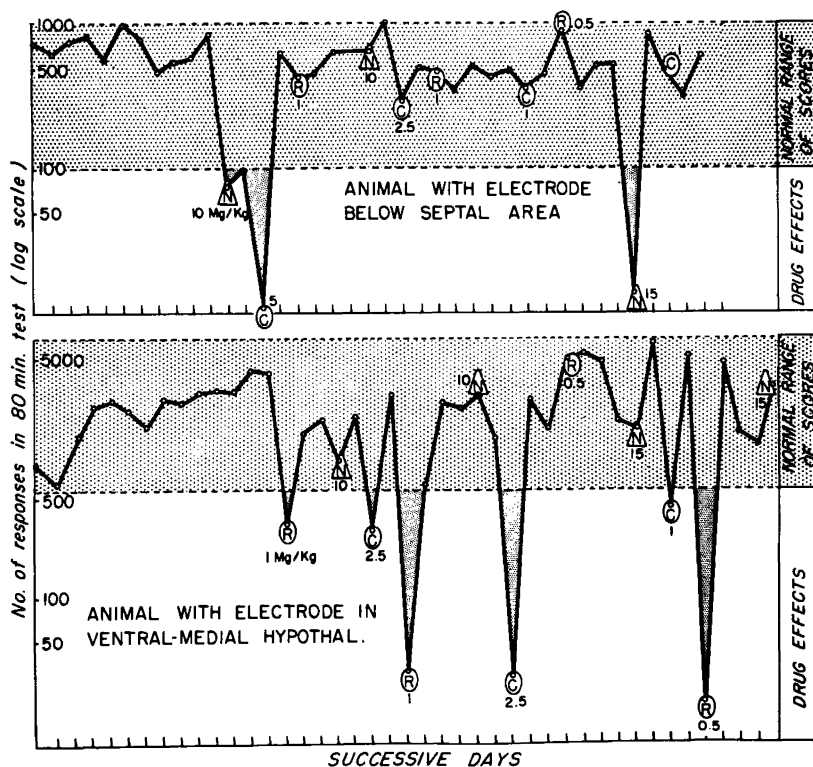


Fig. 1. The number of responses in 80-minute test periods plotted for each day of the experiment for two representative rats. The top graph presents data for a typical rat with an electrode implanted in the region below the septal area. Reserpine at 1 mg/kg and 0.5 mg/kg and chlorpromazine at 2.5 mg/kg and 1 mg/kg produce no major change in response rate; pentobarbital at 10 mg/kg slightly depresses responding on first, but not on second, administration. The lower graph presents data for a typical rat with an electrode placed in the posterior ventromedial hypothalamus. Doses of reserpine (1 mg/kg) and chlorpromazine (2.5 mg/kg) produce sharp falls in response rates; pentobarbital has little effect. Both rats were responding for a 1 v, 60 cy/sec sine wave stimulus.