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12. For example, since in some earlier experiments (*6*, *7*) error-corrective feedback was available to the subject, it was suggested that this "cognitive" factor was responsible for the intermanual transfer. However, in other studies (*9*, *10*) employing what Howard (*9*) termed a "prism-shaping procedure," this argument was disproved by the demonstration that intermanual transfer can occur with terminal display even though the subject is not aware that he has made any errors.
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15. Duncan's new multiple-range test. All statistical analyses are for the data from the first minute after prism removal only. Analysis of variance indicated that the effect of prism base was not significant ($P > .05$). The data are, therefore, combined for presentation here.
16. The present results should not be interpreted as indicating that intermanual transfer could never be demonstrated to occur with massed practice in a continuous-display situation, nor is this suggested by the position that prism adaptation is a learning phenomenon. It seems quite possible that some change in training or stimulus conditions, perhaps one which served to increase the massed-ipsilateral effect, might result in some transfer.
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Histamine: Effect on Self-Stimulation

Abstract. *When injected discretely into the lateral hypothalamus of rats, histamine inhibited electrical self-stimulation at the injection site without affecting self-stimulation in the contralateral lateral hypothalamus. This effect was blocked by prior treatment with antihistaminics. Histidine, the amino acid precursor of histamine, produced a similar effect after a delay of 6 to 10 minutes.*

In the course of screening substances whose intracranial administration might affect electrical self-stimulation or stimulus-bound eating, we have found histamine to be capable of influencing both behavioral modalities. The presence of histamine in the mammalian central nervous system has been known for some time (*1*), although its role in behavioral homeostasis is currently obscure. The regional distribution of histamine in the brain is virtually identical to that of noradrenalin and serotonin (*2*), and its subcellular localization is predominantly synaptosomal (*3*). The brain also contains abundant quantities of the enzymes that govern histamine metabolism: histidine decarboxylase, histimine *N*-methyltransferase, diamine oxidase, and monoamine oxidase (*4*). At least one of these enzymes, the *N*-methyltransferase, is predominantly synaptosomal (*3*).

We examined the effects of small intracranial doses of histamine on self-stimulation in rats and found it to be a potent inhibitor of this phenomenon. Intracranial cannula electrodes were implanted in 20 250-g male Sprague-Dawley rats with the use of a Kopf stereotaxic apparatus. Nembutal was the anesthetic. Cannula electrodes, made from No. 23 hypodermic electrodes insulated except for the tip of the cannula insert, were placed in the left perifornical region of the lateral hypothalamus. With the tooth bar set 3.1 mm above the ear bar, the electrodes were implanted 0.0 mm posterior to bregma, 1.3 mm lateral to the midline, and 8.5 mm below the skull. A bipolar electrode of comparable diameter was placed in the contralateral perifornical area. After the experiment half of the animals were perfused with formalin and prepared for histological examination. Sections 50 μm thick were cut and stained with cresyl violet. Placements were verified to be in the perifornical area.

The cannula electrode permitted injection of compounds into the site of electrical self-stimulation. The contralateral electrode was used as a control. Cannula electrodes in the septum were 3.0 mm anterior to bregma, 0.0 mm lateral to the midline, and 6.0 mm perpendicular to the skull. Electrodes in the lateral ventricle were 1.0 mm posterior to bregma, 2.0 mm lateral to the midline, and 5.1 mm perpendicular to the skull.

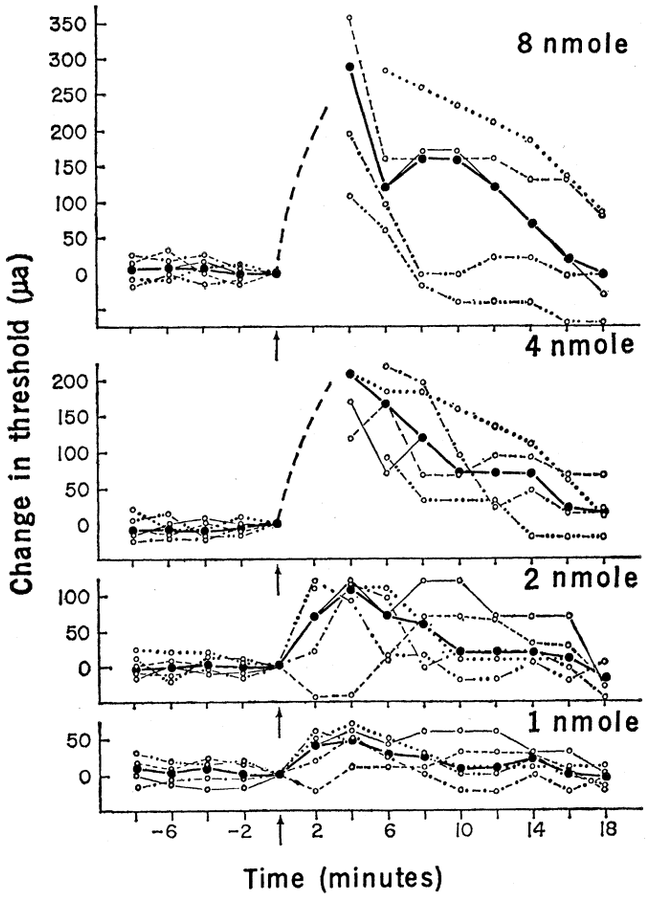
Thresholds for self-stimulation were obtained by determining that amount of current which would maintain lever-pressing for 30 seconds. Whenever an animal failed to reach this criterion the current was raised 10 percent. When the animal met the criterion the current was lowered 10 percent.

Chemicals were obtained from commercial sources and were of the highest quality available. All substances were dissolved in physiologic buffer and injected with Hamilton syringes in volumes no greater than 1 μl. Repeat injections were made only after thresholds had returned to the level before treatment. Control injections were appropriate volumes of physiologic buffer alone, with osmolarity appropriately adjusted for drug concentration with NaCl.

Over the range of 1 to 8 nmole, histamine injected into the perifornical area caused an immediate dose-related elevation of self-stimulation thresholds, which returned over the next 20 minutes to within 10 percent of the level before treatment (Fig. 1). No change in threshold was obtained with buffer alone. All changes were independent of the order of administered dosages. Thresholds to self-stimulation on the contralateral perifornical electrode were unchanged by the ipsilateral injection.

Prior treatment with cannula injections of 1 μl of an antihistaminic (either diphenhydramine, 40 nmole; or chlorpheniramine, 36.5 nmole) completely prevented the effect of 8 nmole of histamine injected 5 minutes later. At these dosages the antihistaminics alone did not alter thresholds. At higher dosages, chlorpheniramine (60 to 200 nmole) consistently lowered thresholds whereas diphenhydramine (45 to 180 nmole) consistently elevated thresholds, both in a dose-related fashion.

Injection of 100 nmole of histidine, the amino acid precursor of histamine, elevated the threshold to self-stimulation but only after an initial delay of 6 to 10 minutes (Fig. 2). Prior treatment with either antihistaminic prevented this effect. The histamine metabolite imidazoleacetic acid (30 nmole) failed to alter self-stimulation thresholds, whereas the metabolites methylimidazoleacetic acid (30 nmole) and



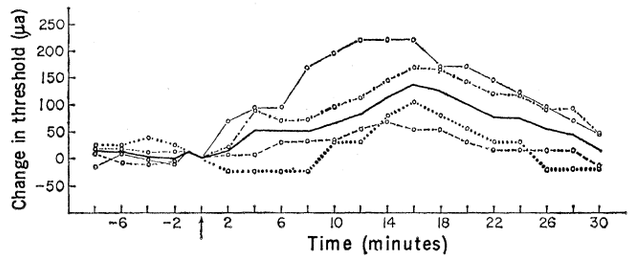


Fig. 1 (left). Effect of histamine on self-stimulation thresholds. Elevation of self-stimulation thresholds is shown for five animals self-stimulating on lateral hypothalamic cannula electrodes in response to four histamine dosages ranging from 1 to 8 nmole. The dark line is the median for the five animals. Histamine was injected in Krebs-Ringer solution, *p*H 7.4. Control injections, which had no effect, were made with buffer alone to which had been added appropriate quantities of NaCl to achieve osmolarities the same as histamine-containing solutions. Tests were run daily for no more than 90 minutes. Effects were independent of order of administered dosage. Training of animals was conducted during 1-hour sessions over 4 to 7 days. Experiments were begun when an animal demonstrated a stable threshold for 1 hour on three consecutive days. Thresholds ranged from 50 to 450 μa. Fig. 2 (right). Effects of histidine on self-stimulation thresholds. Cannula injections of histidine (100 nmole) were made in four animals self-stimulating on lateral hypothalamic cannula electrodes. The dark line is the median for the four animals. Controls were the same as for Fig. 1.

methylhistamine (30 nmole) were only one-sixth as potent as histamine. The metabolically unrelated congener 2-methylimidazole (30 nmole) was without effect. Other neuronally active substances were examined for their effect on self-stimulation thresholds. Glycine or γ-aminobutyric acid (30 nmole) had no effect, whereas equimolar concentrations of glutamate, glutamine, or carbachol all lowered thresholds. Noradrenalin (30 nmole) lowered thresholds in two animals and elevated the threshold in three others. Prostaglandin E_1 was without effect. The local anesthetic Xylocaine (75 nmole) elevated the threshold for more than 30 minutes, and the effect was not prevented by prior treatment with antihistaminics.

Similar effects were obtained, usually with a 1- to 2-minute delay, if the histamine was injected directly into the lateral ventricle in animals self-stimulating on a bipolar electrode in the lateral hypothalamus. In addition, animals self-stimulating on cannula electrodes in the septum also showed marked inhibition in response to cannula histamine injections. At similar dosages histamine also inhibited stimulus-bound eating, elevating the threshold for eating by exactly the same amount as that for self-stimulation.

The effects of small doses of histamine and the production of a similar effect with the precursor histidine (with a time-delay appropriate for its possible conversion to histamine) suggest that this mechanism may be physiologically functional. The doses of histamine used are considerably larger than endogenous levels (*5*). However, this has been a common problem when bioamines have been studied in similar situations. The immediate onset and rapid termination of the effect is consistent with transmitter-like function. The complex pharmacologic actions of antihistaminics (*6*) renders the interpretation of their action in antagonizing the histamine effect difficult. However, it is tempting to speculate that the effect may derive from antagonism at specific histamine receptors. It is possible that histamine may be acting through a secondary transmitter. However, the extreme rapidity of the onset of its action mitigates against this argument. Alternatively, but much less likely, histamine could be causing an extremely transient lesion unrelated to physiologic action. If this were so, it is surprising that antihistaminics so readily oppose histamine action. It is hoped that further elucidation of the mechanism will sort out these possibilities.

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