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Pressor Response to Acetaldehyde and Its Potentiation by Cocaine.*

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In view of the reports of the occurrence of acetaldehyde in the body and in urine, its pharmacodynamic action would seem to have merited serious investigation. Actually very little is known of its action. The only extensive study of its pharmacology is that of Handovsky, whose findings have been reported only in condensed form.[1] As pointed out by this author most of the few studies have been carried out with the use of such large doses that they have been essentially studies of the toxicology of acetaldehyde. Handovsky found that the intravenous administration of small amounts in anesthetized dogs (chloralosane) induced a sharp rise in blood pressure and a cardiac acceleration. The cardiac action was induced after removal of the stellate ganglia, ligation of the adrenals, and administration of atropine. The pressor effect was believed to be in part a direct vascular action, in part a reflex due to stimulation of chemoreceptors in the carotid body. It was suggested that acetaldehyde might be motor to non-voluntary muscle, since it was necessary only to triple the concentration normally present in blood to induce cardiac acceleration. It appears from the context that by non-voluntary muscle, Handovsky had cardiac rather than smooth muscle in mind.

The findings of Handovsky have been confirmed so far as examined, and considerably extended. Doses of the order of 5 to 15 mg per kg, given in solution in Ringer's intravenously to dogs under dial-urethane or morphine and urethane, result in a definite but transitory rise in pressure. Pithed cats and cats under dial-urethane respond similarly. The rise is frequently not quite as abrupt as that of epinephrine, but is of about the same duration. It can be obtained repeatedly, there being no evidence of tachyphylaxis. The combination of clamping both carotids and sectioning both vagi does not appreciably modify the pressor response. The same may be said of ligation of the adrenals. (Apparently Handovsky was concerned more with the cardiac action than the pressor effect in his experiments on adrenal ligation). When nicotine is given in large and repeated doses until its pressor action is lost and the blood pressure is at a low level, acetaldehyde still induces a rise. These findings indicate that most if not all of the action is peripheral and that epinephrine liberation from the adrenals is not involved. Studies to reveal the particular area of the vascular tree involved in the rise in pressure are incomplete. However, the picture is almost identical with that following injection of equi-pressor doses of epinephrine. The volume of the nose vessels and those of the kidney usually decrease, while the volume of the hind leg may increase, decrease, or first increase and then fall, resembling in detail the various effects one may get from epinephrine.[2] The differences here as in the case of the rise in pressure, are chiefly in the somewhat slower rate of development.

Since these actions resemble so closely those following sympathetic stimulation or epinephrine injection, the sympathomimetic action has been examined further. The reaction of the nictitating membrane of the cat, after acute denervation, is one of contraction to acetaldehyde. In preliminary experiments made approximately 3 weeks after removal of the superior cervical ganglion the nictitating membrane seems to have become more sensitive to acetaldehyde stimulation. Further, it has been shown clearly that cocaine increases the response to acetaldehyde in

* Aided by a grant from the Winthrop Chemical Company.

1 Handovsky, H., *Compt. Rend. Soc. Biol.*, 1936, **123**, 1242.

2 Woods, G. G., Nelson, V. E., and Nelson, E. E., *J. Pharm. and Exp. Therap.*, 1932, **45**, 403.

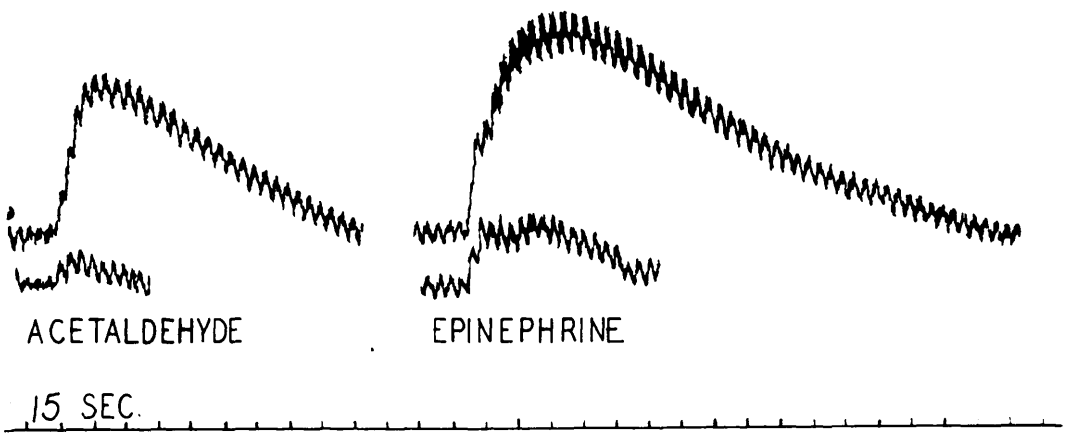

FIG. 1.
The potentiation of acetaldehyde by cocaine. Dog. Dial-Urethane. Both adrenals tied off. Each record actually started from the same level of pressure. Acetaldehyde dose 2 mg per kg. Epinephrine dose 0.00125 mg per kg. Ten minutes were allowed for absorption of the cocaine.

both acute and chronic experiments.

The most striking observation, and the one to which attention is particularly directed, is the potentiation of the pressor action by cocaine. (Fig. 1). After the intramuscular injection of cocaine hydrochloride, 10 mg per kg, this potentiation has invariably been demonstrated, regardless of other previous experimental procedures, including ligation of the adrenal vessels. The degree of effect has been quite parallel to that on control injections of epinephrine. There are obviously several mechanisms which might be involved in this response. Acetaldehyde, a very unstable substance, might persist in the blood stream in larger amounts after cocaine. Preliminary experiments on the blood concentrations reveal no differences before and after cocaine. Blood concentrations do not however necessarily give an index to the amounts diffusing into the cell. Conceivably acetaldehyde does not act *per se* but by liberation of some other substance such as epinephrine or sympathin. The adrenals as a source of the stimulant have been eliminated by ligation. Other humoral mechanisms are under investigation.

Summary. Acetaldehyde, given intravenously, has a pressor action resembling epinephrine. This action is peripheral, and resembles that of sympathetic stimulation in that it is markedly potentiated by cocaine. It is not due to liberation of epinephrine from the adrenal glands.