ileum was still responsive to initial injections of nicotine, choline, carbachol, and TMA. However, responses to the maximum doses of these agents gradually decreased; after repeated injections of maximum doses, the responses disappeared or were markedly reduced whereas the responses to ACh were not altered. It is important, therefore, to deplete the minute amount of endogenous ACh in the nerve tissue of the cooled ileum with ACh releasers before the bioassay is performed. The technique has been used to determine ACh released from synaptic vesicles by some cholinergic agents (6).

(1) C. Y. Chiou and J. P. Long, *Proc. Soc. Exptl. Biol. Med.*, to be published Nov. (1969).
(2) M. Day and J. R. Vane, *Brit. J. Pharmacol.*, **20**, 150(1963).
(3) R. L. Volle, *Pharmacol. Rev.*, **18**, 839(1966).
(4) P. Th. Henderson, E J. Ariens, and A. M. Simons, *European J. Pharmacol.*, **4**, 62(1968).
(5) J. H. Gaddum, *Brit. J. Pharmacol.*, **8**, 321(1953).
(6) C. Y. Chiou, J. P. Long, R. F. Potrepka, and J. L. Spratt, to be published (1969).

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Investigation of Adrenergic Beta-Receptor Blockade and Mescaline-Induced Bradycardia

Keyphrases ☐ Mescaline-induced bradycardia—adrenergic blockade effect ☐ Isoproterenol activity—mescaline effect ☐ Ethylnorepinephrine activity—mescaline effect

Sir:

Mescaline-induced bradycardia was first observed in frogs and cats by Grace in 1934 (1). This activity was not affected by vagotomy or by pretreatment with atropine in either *in vitro* or *in vivo* preparations. In 1955 Speck reported mescaline-induced bradycardia in rats, and suggested a possible mescaline competition for epinephrine receptors (2). Recently, in the course of studies concerned with the design and standardization of an autonomic-cardiovascular screen in dogs, mescaline-induced bradycardia was documented again (3). As shown in Table I, bradycardia was seen in the dosage range of 6.4–25.6 mg./kg. Dramatic changes in heart rate and pressor response to serial intravenous *l*-epinephrine challenge injections were also documented with dosages as low as 0.4 mg./kg. The decrease in the epinephrine challenge heart rate suggested that the resting bradycardia might be due to adrenergic beta-receptor blockade. The increased epinephrine pressor response also seemed to imply this through restricted adrenergic alpha-receptor-induced vasoconstriction. This postulation is supported by the report that another hallucinogen, lysergic acid diethylamide, possesses adrenergic beta-receptor-blocking activity in rabbits (4). In the present study, mescaline[1] was tested for adrenergic beta-blocking activity using specialized, qualitative *in vitro* and *in vivo* testing procedures.

Table I—Effects of Cumulative Intravenous Mescaline on the Resting Heart Rate and Epinephrine Challenge in an Intact Urethan-Anesthetized Dog

Cumulative Dosage, mg./kg.	Mean Percent Change from Pre-Mescaline Control Cycles[a]		
	Resting Heart Rate	Epinephrine Heart Rate	Epinephrine Pressor Response
0.1–0.2	−1	−18	−6
0.4–3.2	0	−36	+56
6.4–25.6	−26[b]	−52	+97
51.2 (lethal)	—	−38	+98

[a] During the control cycles (3), the mean stabilized pre-mescaline heart rate was 154/min. The mean pre-mescaline pressor response to a standardized injection of 4 mcg./kg. of epinephrine was a 44-mm. Hg elevation from the resting level of 134 mm. Hg. The heart rate slowed to 116/min. durnig the peak of the pressor response. The dog was not vagotomized. [b] A similar degree of bradycardia was induced by cumulative intravenous dosages of 0.08–1.28 mg./kg. of propranolol in a similar dog preparation.

The specific *in vitro* procedure of Levy and Tozzi (5) was used in which beta blocking agents are known to antagonize isoproterenol-induced relaxation of the spontaneously contracting rat uterus. The perfusate was Locke's solution, aerated with 95% O_2 and 5% CO_2 at 37.5°. Mescaline showed no isoproterenol[2] antagonism at tenfold increments between 0.005–5.0-mcg./ml. bath concentrations (Fig. 1). The 5.0-mcg./ml. mescaline bath concentration produced significant increases in uterine contraction rate and contracture without truly antagonizing isoproterenol (Fig. 1). These results, which were confirmed in another tissue preparation, indicated that mescaline, itself, does not possess adrenergic beta-blocking activity at concentrations without intrinsic activity. Propranolol[3] served as a standard reference beta blocker and was shown to be effective at bath concentrations of 0.1 mcg./ml. in antagonizing

[1] Mescaline HCl (lot D3303) was obtained from Mann Research Laboratories, Inc., New York, N. Y. All text references are expressed in terms of the salt.

[2] The HCl salt was obtained from the Special Chemicals Dept., Winthrop Laboratories, New York, N. Y. All text references are in terms of the salt (5).

[3] Propranolol (Inderal) was kindly supplied by the Medical Dept., Ayerst Laboratories, New York, N. Y.

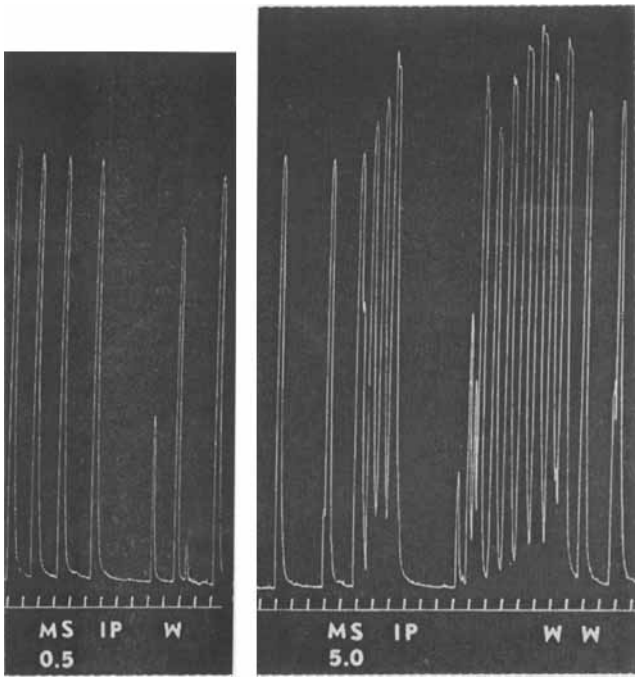

Figure 1—*Effects of mescaline (MS) on isoproterenol (IP) blockade of spontaneous contractions of the rat uterus. Key: Left, 0.5 mcg./ml. bath concentration of MS* versus *0.001 mcg./ml. of IP; Right, 5.0 mcg./ml. of MS* versus *0.001 mcg./ml. of IP; tissue washings(W). Time markings: 1 min.*

Table II—Effects of Cumulative Intravenous Propranolol and Mescaline on the Resting Heart Rate and Isoproterenol and Ethylnorepinephrine Challenges in Intact Urethan-Anesthetized Dogs

Compound	Cumulative Dosage, mg./kg.	Mean Percent Change from Pre-Drug Control Cycles: Resting Heart Rate	Isoproterenol Depressor	Ethylnorepinephrine Depressor	Ethylnorepinephrine Pressor
Propranolol	0.005–0.160[a]	−14	−43	−51	—
Propranolol	0.320–2.560	−28	−99	—	+3
Mescaline	0.10–3.20[b]	−11	+6	+29	—
Mescaline	6.40–12.8	−21	+2	+38	—
Mescaline	25.6 (lethal)	—	—	—	—

[a] During the pre-propranolol control cycles, the mean stabilized heart rate was 136/min. The pre-propranolol mean depressor response to a standardized injection of 4 mcg./kg. of isoproterenol intravenously was a 23-mm. Hg fall and to 50 mcg./kg. of ethylnorepinephrine a 16-mm. Hg fall. [b] During the pre-mescaline control cycles in the second dog, the mean stabilized heart rate was 180/min. The pre-mescaline mean depressor response to a standardized intravenous injection of 4 mcg./kg. of isoproterenol was a 49-mm. Hg fall and to 25 mcg./kg. of ethylnorepinephrine a 33-mm. Hg fall.

the uterine relaxant activity of isoproterenol without having any intrinsic activity of its own (Fig. 2).

The *in vivo* cardiovascular test of Levy and Ahlquist (6) was then used in order to test the possibility of beta blockade by mescaline through its conversion into a pharmacologically active metabolite. In this test, adrenergic beta-blocking agents have been shown to produce a loss and reversal of the blood pressure depressor responses of dogs to isoproterenol and ethylnorepinephrine[2] challenges, respectively. As shown in Table II, a characteristic propranolol-induced bradycardia was demonstrated along with a loss of the isoproterenol depressor responses and a small, but definite, reversal of the ethylnorepinephrine depressor responses. Mescaline-induced bradycardia was confirmed (Table II), but this activity did not involve either isoproterenol antagonism or ethylnorepinephrine reversal.

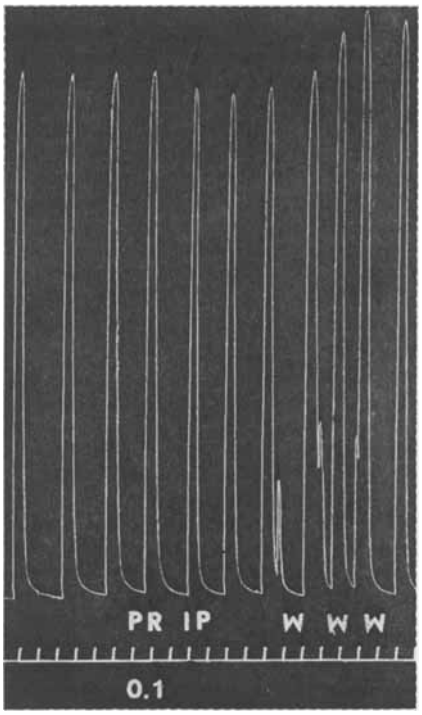

Figure 2—*Propranolol antagonism of isoproterenol blockade of spontaneous contractions of the rat uterus. Key: 0.1 mcg./ml. bath concentration of propranolol (PR)* versus *0.01 mcg./ml. of isoproterenol (IP); tissue washings (W). Time markings: 1 min. Typical isoproterenol controls are not shown here, but were documented both before propranolol incubation and after propranolol had been washed from the tissue (5).*

On the basis of these results it is concluded that the bradycardia produced by mescaline (*in vitro* and *in vivo* testing) or its metabolites (*in vivo* testing) is not due to simple adrenergic beta-receptor blockade.

(1) G. S. Grace, *J. Pharmacol. Exptl. Therap.*, **50**, 359(1934).
(2) L. B. Speck, *ibid.*, **119**, 78(1957).
(3) J. J. P. Morton and M. H. Malone, *Lloydia*, **30**, 269(1967).
(4) L. Goldstein, *Federation Proc.*, **21**, 337(1962).
(5) B. Levy and S. Tozzi, *J. Pharmacol. Exptl. Therap.*, **142**, 178 (1963).
(6) B. Levy and R. P. Ahlquist, *ibid.*, **133**, 202(1960).

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