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Quantitative Comparison of Responses of Isolated and of Intact Intestine to Seven Sympathomimetic Amines.

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Quantitative studies have been made concerning the isolated rabbit intestine inhibiting potency of the series of sympathomimetic amines which have been previously investigated with regard to inhibition of innervated and denervated intestinal fistulæ in unmedicated dogs.[1]

The motility of isolated segments of the duodenum and jejunum of rabbits was recorded by a modification of the technic used by Stewart.[2] The compounds studied were l-adrenalin (Parke, Davis & Co.), dl-arterenol (Winthrop Chemical Co.), cobefrin (Winthrop Chemical Co.), epinine (Burroughs-Wellcome & Co.), kephrine (Alba Pharmaceutical Co.), l-neosynephrin (Frederick Stearns & Co.), and dl-synephrin (Frederick Stearns & Co.). The effect on the isolated rabbit intestine of a certain dilution of adrenalin was determined, and a dilution of each of the other drugs was found that would duplicate the inhibitory effect of the test dilution of adrenalin. The test dilution of adrenalin was usually one part in 20 million or one part in 40 million. The compounds were tested in various orders and in some cases the entire series, except synephrin, was tested on the same intestinal segment.

Qualitatively, all of the compounds had effects on the isolated rabbit intestine similar to those resulting from adrenalin. There was inhibition of rhythmic contractions and a decrease in tonus. Hyperactivity was sometimes observed following the inhibition. The hyperactive recovery phase was most marked following neosynephrin, adrenalin and arterenol, and has been previously reported for the latter 2 compounds.[3]

The potency of the compounds as inhibitors of the isolated intestine relative to that of adrenalin is shown in Table I. The figures are given for the extremes obtained from comparisons on segments from nine rabbits, and each compound was assayed at least 8 times.

1 Youmans, W. B., Aumann, K. W., and Haney, H. F., *Am. J. Physiol.*, 1939, **126**, 237.

2 Stewart, G. N., *J. Exp. Med.*, 1911, **14**, 377.

3 Greer, C. M., Pinkston, J. O., Baxter, J. H., Jr., and Brannon, E. S., *J. Pharm. Exp. Therap.*, 1938, **62**, 189.

TABLE I.

Comparison of the relative potency of 7 amines as inhibitors of the isolated rabbit intestine with their potency as inhibitors of the dog intestine *in situ*. Figures indicate the increased concentration of the compound necessary to duplicate the inhibitory effect of a test concentration of adrenalin. The reciprocal of any figure in the table indicates the potency of the corresponding compound as compared to that of adrenalin.

	Formula	Isolated rabbit intestine	Intestinal fistulæ in unmedicated dogs
l-adrenalin	$(OH)_2C_6H_3 . CHOH . CH_2NHCH_3$	1	1
dl-arterenol	$(OH)_2C_6H_3 . CHOH . CH_2NH_2$	1½-2	1½-4
Cobefrin	$(OH)_2C_6H_3 . CHOH . CHNH_2 . CH_3$	3-5	2½-10
l-neosynephrin	$m\text{-}(OH)C_6H_4 . CHOH . CH_2NHCH_3$	4-10	25-100
Epinine	$(OH)_2C_6H_3 . CH_2 . CH_2NHCH_3$	10-20	10-25
Kephrine	$(OH)_2C_6H_3 . CO . CH_2NHCH_3$	20-50	25-100
dl-synephrin	$p\text{-}(OH)C_6H_4 . CHOH . CH_2NHCH_3$	500-1000	660-2500

The lower isolated rabbit intestine inhibiting potency of arterenol[3, 4] and neosynephrin[5] as compared with that of adrenalin has been previously reported.

Since the effect of a compound on the isolated intestine may be the reverse of that obtained in the denervated intestine *in situ* following an intravenous injection of the compound, some facts may be learned by utilization of both technics which may not be learned from one alone. Effects on the intestine *in situ* may be the result of reflexly liberated neurohormones and alterations in circulation produced by the injected compound. These factors are eliminated by the isolated intestine technic. However, the 7 compounds studied all had effects on the isolated rabbit intestine which were qualitatively similar to the effects on the innervated or denervated dog intestine *in situ*. With one exception there was correspondence both in the order of potency and the potency relative to that of adrenalin. Neosynephrin ranked higher as an inhibitor of the isolated rabbit intestine than as an inhibitor of the dog intestine *in situ*.

Conclusions. The similarity of the effects of 7 sympathomimetic amines on the isolated rabbit intestine and on the intact dog intestine indicates the physiological similarity of the smooth muscle used and demonstrates the peripheral and direct inhibitory action of these amines on the smooth muscle of the intestinal wall.

4 Barger, G., and Dale, H. H., *J. Physiol.*, 1910, **41**, 19.

5 Boyd, E. M., *J. Pharm. Exp. Therap.*, 1937, **60**, 174.