METHYLSEROTONINS AS POTENT ANTIMETABOLITES OF SEROTONIN ACTIVE BOTH IN VITRO AND IN VIVO

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The idea has arisen that antagonists of serotonin may be useful both as therapeutic agents and as tools with which to discover the physiological roles of this hormone (Woolley and Shaw, 1952a,b, 1953a). For example, the ability of two of these antagonists to control the hypertension caused by injection of serotonin has suggested that such agents might be useful in naturally occurring hypertensions or in other abnormalities resulting from an excess of this hormone. In the field of physiology, these antagonists have already been used to demonstrate a probable function for serotonin in the central nervous system (Woolley and Shaw, 1954a,b). For such reasons a further investigation of antiserotonins seems justifiable. We wish to describe in this paper some new antiserotonins which are distinguished by their high activity against the pressor-effects of the hormone when tested in anaesthetized dogs.

The trouble with existing antimetabolites of serotonin is that in living animals they are either weakly active or completely inactive as antipressor agents for serotonin.[2] These antimetabolites have been discovered because of their antagonism to serotonin when tested *in vitro* on isolated tissues (Woolley and Shaw, 1953b; Shaw and Woolley, 1954; Erspamer, 1953). Although compounds have been achieved which are quite potent *in vitro* in overcoming the contractions of smooth muscles which serotonin causes, they have been inactive (or only weakly active) as antipressor agents *in vivo* in dogs. That is, they frequently fail to protect dogs against the rise in blood pressure caused by intravenous injection of serotonin. Thus, 2-methyl-3-ethyl-5-aminoindole was relatively active in prevention of the serotonin-induced contraction of isolated artery rings (Woolley and Shaw, 1952a, 1953b) but was only partially effective as an antipressor agent when fed to dogs which were subsequently challenged with serotonin (Woolley and Shaw, 1952b, 1953a; Page and McCubbin, 1953a). Similarly, medmain (2-methyl-3-ethyl-5-dimethylaminoindole), which was extraordinarily potent in the artery ring test, was inactive[3] against the pressor effects of serotonin in dogs

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[2] This discussion is concerned only with the effects of serotonin on blood pressure. If one considers also the functions of this hormone in the central nervous system or in other systems, then a highly active antagonist to it is available in the form of lysergic acid diethylamide. Certain other analogs of serotonin likewise have been shown to affect the central nervous system when given orally (cf. Woolley and Shaw, 1954a,b). However, these substances usually do not antagonize the pressor effects of serotonin in dogs.

[3] One reason for this inactivity in the live animals has been found to be that medmain is adsorbed by, and inactivated by the globulins of the blood. Medmain was produced in an attempt to protect the amino-group of 2-methyl-3-ethyl-5-aminoindole from oxidative destruction by enzymes of the intestinal tract (cf. Woolley and Shaw, 1953a). However, this attempt to avoid one difficulty led only to another.

(Shaw and Woolley, 1954). More recent investigators (Erspamer, 1955; Gaddum et al., 1955) have made similar observations with their antiserotonins.[4] One can even see a refinement of this difference between in vivo and in vitro effects, for, although it has been possible to achieve compounds which are active in dogs if given intravenously, these have proved to be almost inert when fed. Examples of this are 2-methyl-3-ethyl-5-aminoindole (Woolley and Shaw, 1953a) and 6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole (Shaw and Woolley, unpublished). An orally effective compound is required for the reasons already given (Woolley and Shaw, 1952b, 1953a). The only effective compound of this class thus far described is 2-methyl-3-ethyl-5-nitroindole (Woolley and Shaw, 1952b, 1953a), but this one is so insoluble in water, that some (e.g. Page and McCubbin, 1953a) have had difficulty in using it. Even under the best circumstances, large doses of it were required.

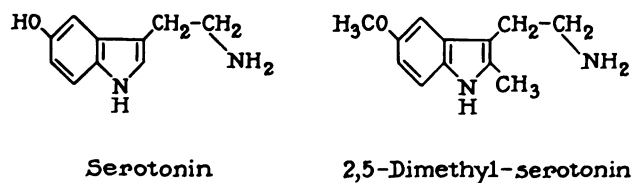Serotonin   2,5-Dimethyl-serotonin

Fig. 1

A water-soluble antiserotonin which is highly active in preventing the pressor effects of the hormone in live animals should thus be desirable. In this paper we wish to describe such agents, viz. 2,5-dimethylserotonin (see figure 1) and its derivatives. This is the 2-methyl analog of serotonin-methyl-ether. Some congeners having alkyl groups at positions 1, 2, and 5, or on the side chain-amino group, will also be described briefly. The 2,5-dimethylserotonin was so much more active than existing antimetabolites (cf. footnote 2) that it may be of use to others, even though it was less effective when fed than when administered intravenously. The 1-benzyl-2,5-dimethylserotonin was more active and was highly effective even when fed. It may therefore prove to be useful where oral administration is desired.

EXPERIMENTAL. *Source of compounds.* All the analogs of serotonin were synthesized in this laboratory according to the directions given in a separate paper (Shaw, 1955). Serotonin was generously supplied by the Abbott Laboratories. The amounts of this compound mentioned in this paper represent weights of the double salt with creatinine sulfate.

Methods. Tests for serotonin-like and antiserotonin-activity on segments of sheep carotid arteries were conducted according to the method of Woolley and Shaw (1953b). Assays on isolated horns of rat uterus were carried out according to the directions of Shaw and Woolley (1954) except that the uteri were taken from animals which had been given estrogens 24 hours earlier. The test thus resembled that first used by Erspamer (1952) except that the rats were not castrated.

[4] The situation with the antiserotonins is thus quite similar to that with antihistamines and antiacetylcholines. With these latter classes of drugs, it is well known that the tests on isolated tissues may indicate high activity for a compound which subsequently proves to be worthless or of little value in whole animals.

Intravenous trials on dogs were done as follows. Relatively small, young, normal dogs (7-10 kgm.) were anesthetized with pentobarbital, and an 18 gauge needle was inserted into the femoral artery without surgical operation. A mercury manometer was then attached to this needle by means of a short section of Tygon tubing, which was filled with heparinized physiological saline solution. A reservoir of the same was included so that by turning suitable stopcocks, the needle could be flushed and more heparin introduced into the dog. Readings from the manometer were recorded every 5 seconds. Serotonin was then injected into the jugular vein. Care was taken to introduce this solution at uniform speed so that the entire dose was delivered in 10 seconds. The importance of this was described by Shaw and Woolley (1954, page 50). After each injection of serotonin, at least 15 minutes were allowed to elapse in order to avoid complications from tachyphylaxis (cf. Freyburger et al., 1952; Page, 1952). After the proper dose which would elicit a good rise in arterial pressure[5] had been determined, several challenges with the same dose of serotonin were made so that the uniformity of the response could be assured. When a dog had been thus calibrated, the analog to be tested was injected as a neutralized solution in physiological saline into the jugular vein (entire dose in 10 seconds). At least 15 minutes thereafter, the response to the standard dose of serotonin (0.5-1.0 mgm. per dog) was determined. The first dose of analog was usually 1 mgm. per dog. If this failed to prevent the rise in pressure elicited by the challenging dose of serotonin, the amount of analog was increased (after at least 15 minutes) and the challenging with serotonin was repeated. In this way the minimal amount of analog required to protect a dog from significant rise in pressure was determined. The experiment was then repeated with several new dogs.

For the trial of an analog by the oral route in dogs, an animal was calibrated with serotonin in the way just described. At least a week afterwards, when it had fully recovered from the anaesthetization, the feeding of analog was begun. The compound was mixed with the food (which contained no raw meat). This mixture was fed once daily for 4 days. About 1 hour after the last feeding, the dog was anaesthetized with pentobarbital, challenged with serotonin in the way described above, and the changes in arterial pressure were recorded. At least three challenges with the hormone were made, each one at least 15 minutes after its predecessor. Various doses of analog could be tested on the same dog by repetition of the experiment after a recovery period of about two weeks. When dogs were recalibrated with serotonin at intervals of a month or so the type and magnitude of their responses were found to be quite uniform and this inspired confidence in the methods.

RESULTS. *Antiserotonin action of 2,5-dimethylserotonin on artery rings.* 2,5-Dimethylserotonin was found to have an inhibition index of 10, i.e., the contraction action of 0.1 microgm. of serotonin was erased by 1 microgm. of the analog. On these carotid arteries, this analog by itself showed no serotonin-like activity.

2,5-Dimethylserotonin on isolated rat uterus. The tracing in figure 2 will show that the analog antagonized the action of serotonin, but that the inhibition index was markedly higher than in artery rings. Values for this index ranging from 100 to 1000 were found with different uterine horns.[6] In other words, the analog was from 10 to 100 times less effective on rat uterus than it was on sheep artery rings.

The inhibition index in any single specimen of isolated rat uterus depended on the time elapsed between administration of the analog and of serotonin. In the experiments described above, this interval was about one minute. When this interval was increased to twenty minutes, the analog appeared much more active and inhibition indices of 10-20 were found.

[5] Usually 0.5 mgm. per dog, occasionally 1 mgm. per dog.

[6] In some tissue specimens, the analog itself caused a slight contraction but this was never maximal nor proportional to increasing doses and was found in less than half of the specimens.
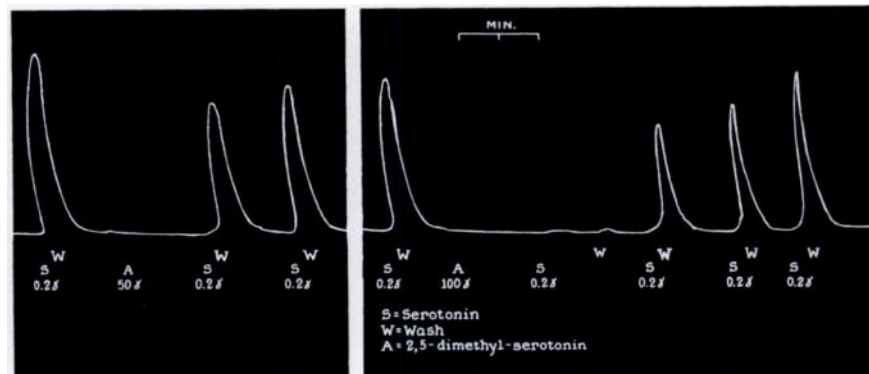
Fig. 2. Antagonism between serotonin and 2,5-dimethylserotonin on isolated rat uterus

Antagonism between serotonin and 2,5-dimethylserotonin given intravenously to dogs. Typical effects seen when a dog was given separately serotonin and various amounts of 2,5-dimethylserotonin intravenously are shown in figure 3. Note that the analog by itself caused some rise in pressure. However, as the dose was increased, it was never found possible to achieve a rise as great as that which had been produced by serotonin. In fact, increasing doses of the analog resulted in diminishing pressor responses (cf. figure 3). Nevertheless, in those dogs in which a polyphasic pressure curve developed after injection of serotonin (Page and McCubbin, 1953b) (of which the one shown in figure 3 is not an example), all the features of the serotonin curve were reproduced qualitatively in the response to 2,5-dimethylserotonin. The differences were that the original fall was somewhat greater, and the subsequent rises were quantitatively considerably less.

When the dose of analog had been great enough to afford protection against the pressor effects of serotonin, then the initial fall in pressure following injection of serotonin became very prominent. This was true even in dogs which had
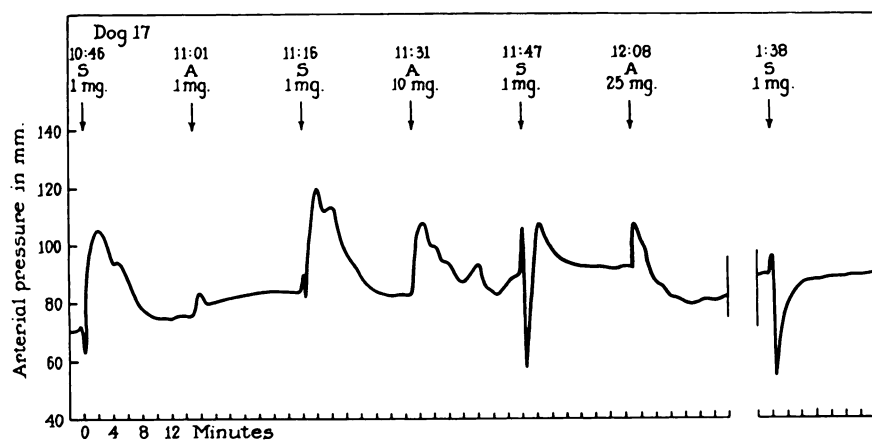

Fig. 3. Changes in arterial pressure in a 9.5 kgm. dog given serotonin or 2,5-dimethyl-serotonin intravenously.

TABLE 1

Variation in the amount of 2,5-dimethylserotonin required to protect an individual dog against the rise in arterial blood pressure caused by serotonin

The analog was given intravenously at gradually increasing dosage and after each injection a challenge with a constant amount of serotonin was made.

Dog	Weight	Analog Required for Half-Maximal Protection	Analog Required for Complete Protection
	kgm.	*mgm. per kgm.*	*mgm. per kgm.*
20	7.5	less than 0.1	0.1
19	7.0	0.3	1.5
16	7.8	less than 1.2	1.2
22	10.5	1.0	—
17	9.5	1.0	2.5
7	9.3	1.1	—
21	7.5	1.3	—

shown no initial fall after serotonin in their unprotected state. In a fully protected dog the initial fall in pressure after serotonin injection was both large and persistent. Almost always several minutes elapsed before the pressure climbed to its normal level. No rise in pressure then ensued. If the fall in pressure caused by serotonin is due to excitation of neuroreceptors rather than of those in smooth muscle (Page, 1952; Woolley and Shaw, 1954b), then 2,5-dimethylserotonin must be ineffective in blocking this action.

The amount of 2,5-dimethylserotonin required to protect a dog against the pressor effects of 0.5 mgm. of serotonin varied greatly among individuals. Some required more than 10 times the quantity which sufficed for others, but most animals could be protected completely by 1–2 mgm. of the analog per kgm. Some of the data on this point are summarized in table 1.

Duration of the protection after intravenous administration. No exact determination was made of how long the protection given by intravenous 2,5-dimethylserotonin would last. In three dogs, however, challenged with serotonin two hours after administration of the analog, there was no appreciable rise in pressure, so that the protection was of considerable duration.

Protection of dogs against serotonin with 2,5-dimethylserotonin administered orally. When the analog was given orally as described above, some protection against the pressor effects of serotonin were observed. The responses varied considerably from individual to individual as can be seen from the data in fig. 4. Some animals were completely protected by 20 mgm. of analog per kgm. per day (e.g., dog 17). Others, however, were unprotected to the first challenge with serotonin, but succeeding challenges gave only small increases in pressure (e.g., dogs 19 and 21 in fig. 4). In several animals the rise in pressure occasioned by the first challenge consisted principally of a rising baseline (e.g., dog 21). Sometimes the rise in pressure following injection of serotonin consisted of a sharp increase which lasted only 15–20 seconds and was not followed by the usual type of pressor response. This sharp and transient rise was coincident with the respiratory stimulation and cardiac changes caused by serotonin and may not have reflected any change in the vascular system. Seven dogs were tested in the manner described,

four of them with 20 or 25 mgm. of analog per kgm. per day and three of them with 6 or 7 mgm. per kgm. per day. Some protection against the pressor effect of serotonin was observed in six of these. As can be seen in fig. 4, this protection was sometimes rather striking.

Because several of the dogs used in the oral trials had been standardized pre-
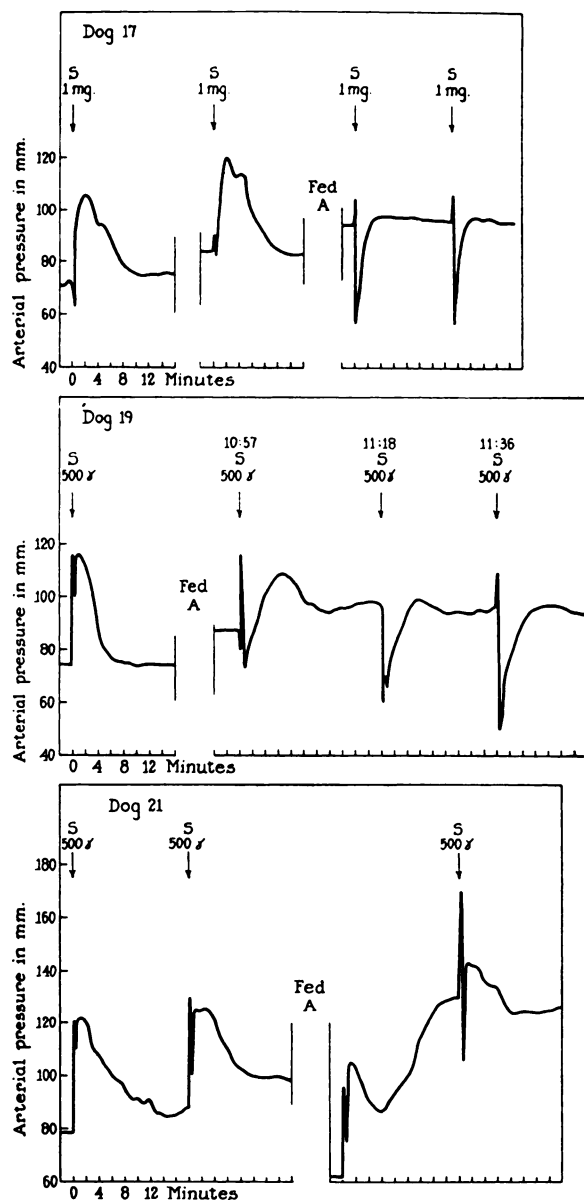

Fig. 4. Changes in arterial pressure caused by serotonin in dogs before and after feeding with 2,5-dimethylserotonin. Dog 17 was fed 20 mgm. per kgm. per day; dog 19 was fed 25 mgm. per kgm. per day; and dog 21 was fed 6 mgm. per kgm. per day.

TABLE 2

Arterial pressures of normal dogs and of these same animals following feeding with 2,5-dimethylserotonin

The individual values are the ones found at various time intervals in the normal dogs.

Normal Pressures	Analog	Pressures after Analog
mm.	*mgm. per kgm. per day*	*mm.*
80, 80	6	66
66, 88, 66	7	66
100, 90	7	90
98	20	114
84, 94, 80	20	94
86	25	90
60, 74	25	90

viously with 2,5-dimethylserotonin by the intravenous route, it was possible to compare the relative efficiency of the two methods of administration. The comparison showed that at least ten times as much was required by the oral route.

Protection of dogs against the pressor effects of serotonin with serotonin itself (tachyphylaxis, self-inhibition). Serotonin itself when given in sufficient amount intravenously was able to protect a dog completely from the pressor effects of a subsequent challenge with serotonin. This effect differed from the similar action of 2,5-dimethylserotonin in that it was short-lived, but otherwise it was similar. The data in fig. 5 will show that the large dose of serotonin called forth a smaller rise in pressure than did the usual challenging dose. Fifteen minutes later the dog was immune to the pressor action of serotonin, but after an hour had completely recovered its responsiveness. This self-protection by serotonin has been observed earlier in isolated smooth muscle preparations (Gaddum, 1953). The present experiment demonstrated a similar effect in the whole animal. Evidence for a more short-lived tachyphylaxis in cats has been presented (Freyburger *et al.*, 1952).

Hypotensive effects of 2,5-dimethylserotonin. In dogs treated with protective doses of 2,5-dimethylserotonin by the intravenous route, some fall in arterial pressure followed the transient rise. However, this effect was fleeting, and the pressure was back to its normal value within 10 minutes. No persistent hypotension was found even though the antiserotonin action was evident for at least two hours. In the seven dogs which had been fed the analog for 3–4 days, one showed arterial pressure below that observed before it was treated with the compound. The others were approximately the same or slightly higher after treatment (see table 2). Because of daily fluctuations in pressures, especially in animals anesthetized before the measurements were made, there was no convincing evidence of a hypotensive effect in these normal animals fed the analog. However, it should be noted that all of these dogs had relatively low blood pressures.[7]

[7] Although the low normal pressures of the dogs used in this study may occasion some surprise, they should not be construed as a sign of inadequacy of the method used for measuring pressure. We have observed dogs with pressures of 160–190 mm. but these animals
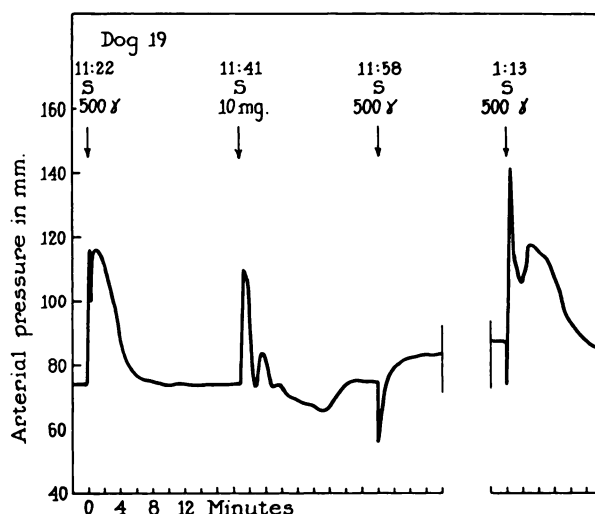
Fig. 5. Protection of a dog against the pressor effect of serotonin with serotonin itself. The 10 mgm. dose of serotonin was injected at constant rate during two minutes.

Toxicity of 2,5-dimethylserotonin for mice. Acute toxicity trials in adult mice by intraperitoneal injection showed that these animals withstood 80 mgm. per kgm. without ill effects which could be noted grossly. Six mice given 80 mgm. per kgm. daily for seven days showed no noticeable signs of toxicity and did not lose weight.

2,5-Dimethylbufotenine in dogs. Because 2,5-dimethylserotonin was so much less effective orally than it was intravenously, the hypothesis arose that much of it was being destroyed by amine oxidase in the digestive tract. If the amino-group in the side chain were protected against this enzyme, one might then expect to form an analog which would be more active when fed. To this end, 2,5-dimethylbufotenine (N,N-dimethyl-2,5-dimethylserotonin) was prepared and tested in dogs by both oral and intravenous routes. The results, however, showed that this analog was less potent than 2,5-dimethylserotonin. Thus, dog 20 had been partially protected by 7 mgm. per kgm. per day of 2,5-dimethylserotonin. When the same animal was tested with 7 mgm. per kgm. per day of 2,5-dimethylbufotenine given orally, there was no protection against the pressor effect of serotonin. In intravenous trials with 2,5-dimethylbufotenine, partial protection against the serotonin pressor effect was found, but the dose required was about ten times greater than that of 2,5-dimethylserotonin in the same animals.

Serotonin-like action of 1,5-dimethylserotonin in rat uterus. In contrast to 2,5-dimethylserotonin which was an antiserotonin in the isolated rat uterus, 1,5-

were not in the present series. Their existence, and even more the reproducibility of the pressures found in the same dog on different occasions would indicate that the pressures recorded were real. It may be that the depth of anaesthesia contributed to somewhat low pressures. The dogs were maintained at a plane of anaesthesia in which there was no eye reflex.
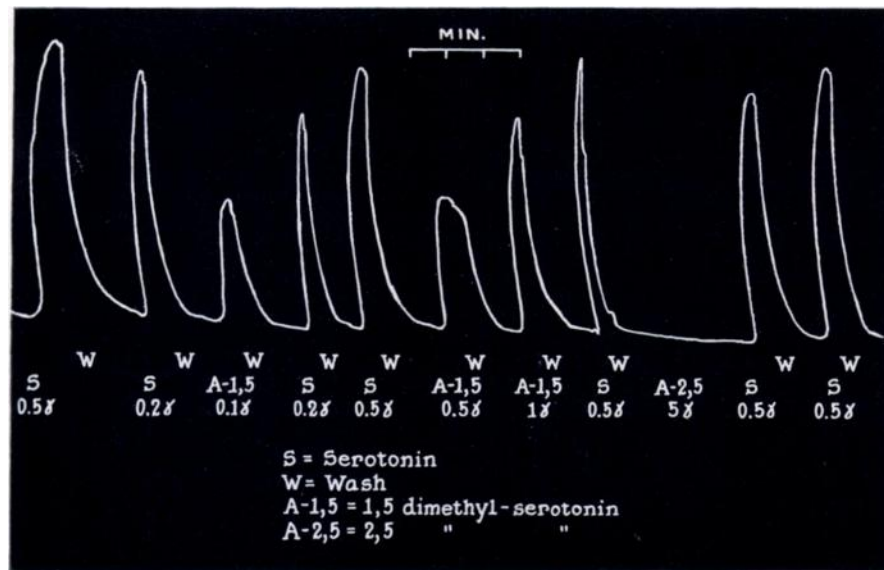
Fig. 6. Serotonin-like action of 1,5-dimethylserotonin (A-1,5) on isolated rat uterus. A-2,5 = 2,5-dimethylserotonin.

dimethylserotonin showed a rather high activity like the hormone itself, i.e., by itself the analog caused contraction of the muscles. From the data in fig. 6 and similar experiments, one would infer that the 1,5-analog was 10–20 per cent as active as serotonin (molecular basis). This high pro-serotonin potency prevented any measurement of a possible antagonistic effect.

In the anesthetized dog, 1,5-dimethylserotonin showed a serotonin-like pressure wave when given intravenously. When compared to serotonin in the same dog, about ten times as much of the analog was needed for comparable pressor effects. Just as with the similar effect from 2,5-dimethylserotonin, the resemblance was only qualitative, because large doses of the analog gave diminished responses (self-inhibition). Fifteen minutes after the injection of 1,5-dimethylserotonin, when the alterations in pressure had died away, challenge with serotonin failed to elicit the usual rise in pressure. From this and similar experiments in dogs one must conclude that 1,5-dimethylserotonin shows some of the pressor effects of serotonin, but is able to act also as an antiserotonin which is somewhat weaker than 2,5-dimethylserotonin.

Relative potency of other alkylserotonins in rat uterus. Several other analogs of serotonin, bearing methyl or other alkyl groups in positions 1, 2, and 5 were tested for anti- and pro-activity on isolated rat uterus. Tests were conducted in the manner described for 2,5-dimethylserotonin. The results are summarized in table 3. Compounds like 1-benzyl-5-methylserotonin and 1-benzyl-2,5-dimethylserotonin were of special interest because, once the tissue had been exposed to them, neither washing with Ringer's solution, nor treatment with serotonin served to restore completely the ability to respond to serotonin (cf. fig. 7).

TABLE 3

Antiserotonin activity of alkyl serotonins on isolated rat uterus

Compound	Inhibition Index
2-Methylserotonin	1000
2,5-Dimethylserotonin	300
1,2,5-Trimethylserotonin	200
1,5-Dimethylbufotenine	300
1-Benzyl-5-methylserotonin	40
1-Benzyl-2,5-dimethylserotonin	30
5-Methoxytryptophanol	300

All values represent averages. No delay occurred between application of analog and serotonin. As explained earlier, the values for inhibition index decreased when the analog was applied some time before the serotonin.

Inhibition Index represents the amount of analog required to prevent the effect of a unit weight of serotonin. The values were determined in the usual way from the estimation of half-maximal inhibition.

In fact, succeeding doses of serotonin gave decreasing responses as if time and exposure to serotonin were being required for the full effect. The analog was not merely a general tissue poison because responsiveness to acetylcholine was still retained. The 1-benzyl methylated analogs of serotonin were thus specific but irreversible antagonists of the hormone.

The 1,2,5-trimethylserotonin by itself occasionally caused partial contraction of the tissue. It thus had some serotonin-like activity (less than 1 per cent on a molar basis). In addition, it was a good antagonist to the hormone subsequently applied.
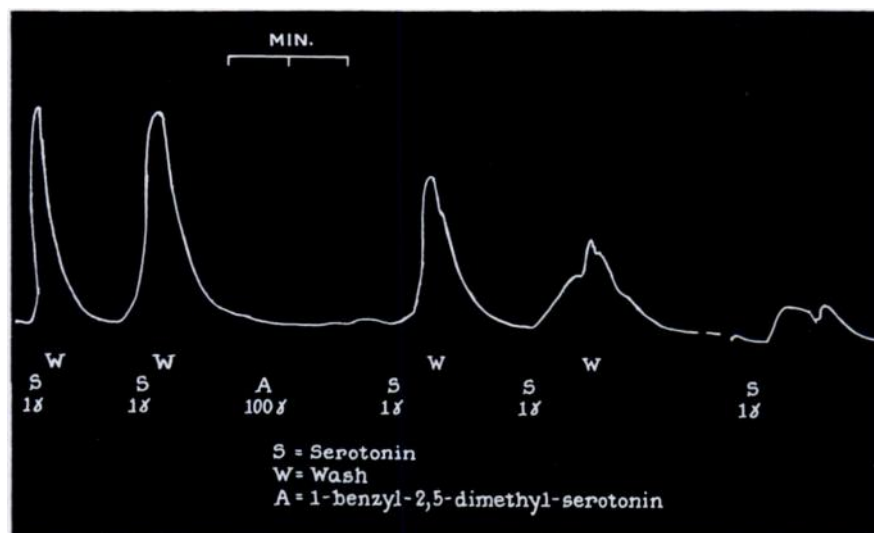

Fig. 7. Irreversible antagonism to serotonin exhibited by 1-benzyl-2,5-dimethylserotonin in rat uterus.

TABLE 4

Pressure changes in dogs given serotonin before and after oral administration of
1-benzyl-2,5-dimethylserotonin hydrochloride

Dog	Oral Dose of Analog	Serotonin Challenge	Changes in Arterial Pressure*			
			Before feeding		After feeding	
			Max. fall	Max. rise	Max. fall	Max. rise
	mgm. per kgm. per day	*mgm. per dog*	*mm.*	*mm.*	*mm.*	*mm.*
7	1	0.5	0	45, 42	50, 40	20, 10
17	1	1.0	8, 0	37, 38	6, 18	14, 2
20	6.5	0.5	4, 4	44, 34	10, 6	4, 4
24	1.3	0.5	0	60, 45	10, 18	12, 15, 13

* Replicate readings represent responses to repeated challenges with serotonin at 15 min. intervals.

High oral effectiveness of 1-benzyl-2,5-dimethylserotonin in dogs. Four dogs were fed 1-benzyl-2,5-dimethylserotonin hydrochloride and tested with serotonin as described above. Results in table 4 showed that this compound was extraordinarily active in protecting against the pressor effects of serotonin. These animals were rather well protected by approximately 1 mgm. of the analog per kgm. per day. Note that the protected animals showed a considerable fall in pressure when challenged with serotonin just as did those which had been protected by intravenous 2,5-dimethylserotonin.

Toxicity of 1-benzyl-2,5-dimethylserotonin. Acute toxicity trials in mice by the intraperitoneal route showed that 5 of 6 adult females died within 24 hours after they had received 100 mgm. per kgm. Of 12 mice given 20 mgm. per kgm. per day, one died after two weeks. The others were injected daily with this amount of the analog for four weeks. They maintained their weight and showed no external or internal signs of toxicity which could be noted grossly.

A trial of chronic toxicity by the oral route was made with mice which were fed Purina fox chow plus 1 gm. of 1-benzyl-2,5-dimethylserotonin hydrochloride per kgm. of ration (120 mgm. per kgm. of mouse per day). Six animals ate this ration for two months. During this time they gained weight and when autopsied showed no signs of toxicity which could be noted grossly. The analog was therefore considerably less toxic by the oral route.

The mice which had died following intraperitoneal injection of 100 mgm. of the analog per kgm. showed uniformly stomachs greatly distended by a clear fluid. When one remembers the high content of serotonin in gastric mucosa the occurrence of this sign produced by a powerful antiserotonin takes on significance.

DISCUSSION. Interpretation of the action of 2,5-dimethylserotonin cannot ignore two facts. (a) The analog causes serotonin-like effects on blood pressure, even though increasing doses of the analog result in decreasing response (cf. fig. 2). (b) Serotonin itself in large doses will protect against the pressor action of the hormone. This antiserotonin action is of shorter duration than is the similar effect of the analog.

One can picture the self-inhibition caused by serotonin in the same fashion as has been done for the same property of indoleacetic acid acting as a growth hormone in plants (Foster et al., 1952), or for the well-known general case of inhibition of an enzyme by an excess of its substrate. Instead of the serotonin attaching itself to its receptor by two or more points in the hormone, one molecule of serotonin combines with the receptor at, let us say, the amino-group, and a second molecule combines at, let us say, the indole nitrogen atom. Because the receptor is now saturated, *but not with a single molecule of the hormone*, the normal physiological role is not fulfilled, i.e., a single molecule of the hormone is excluded from a many-sited attachment to the receptor. The analog would only have to be less readily destroyed than serotonin itself in order to account for its longer action. The other possibility is that the analog acts in the usual way pictured for other antimetabolites.

The high potency of 1-benzyl-2,5-dimethylserotonin both in the isolated uterus and when fed to dogs was noteworthy. The increase in potency achieved by insertion of the benzyl group may possibly be associated with the fact that this insertion conferred on the compound an irreversible type of action.

SUMMARY

2,5-Dimethylserotonin was a water-soluble and rather active antiserotonin which was effective not only on isolated artery rings and isolated uteri, but also as an antagonist to the pressor action of serotonin in dogs. In these animals most individuals were protected against the pressor effects of 0.5–1.0 mgm. of serotonin by approximately 1 mgm. of the analog per kgm. The compound was effective either intravenously or orally, but was considerably less efficient by the oral route. Other pharmacological properties of it were recorded. A series of other methylserotonins, including 1,5-dimethylserotonin, 2,5-dimethylbufotenine, 1,2,5-trimethylserotonin and 1-benzyl-2,5-dimethylserotonin were studied both in isolated rat uterus and in living dogs. By the intravenous route in dogs, these (except the 1-benzyl compound) were less active than 2,5-dimethylserotonin as an antagonist to the pressor effect, but some had other interesting properties. Thus, 1,5-dimethylserotonin showed a considerable amount of serotonin-like activity on the rat uterus, and the benzyl compound exerted an irreversible antagonism in this tissue. 1-Benzyl-2,5-dimethylserotonin was extraordinarily active when fed to dogs and at 1 mgm. per kgm. per day by the oral route it protected them. It was therefore the most powerful known antiserotonin which was orally effective against the pressor action of the hormone.

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