J.Pharmacol.exp.Ther. 136, 59-67 (1962). PSI 92

DIFFERENTIAL ANTAGONISM BY BAS-PHENOL OF RESPONSES TO THE INDOLEALKYLAMINES

RUBEN D. BUÑAG[1] AND EDWARD J. WALASZEK[2]

Department of Pharmacology, University of Kansas Medical Center, Kansas City, Kansas

Received for publication October 2, 1961

It has been observed that under suitable experimental conditions, tryptamine produces a specific desensitization of the isolated guinea-pig ileum to serotonin and *vice versa*. On the basis of this finding, Gaddum (1953) suggested that in the guinea-pig ileum, serotonin and tryptamine act on the same receptors. On the other hand, Woolley and Shaw (1953) have shown that by aging carotid artery segments from sheep, the tissue loses sensitivity to tryptamine but remains responsive to serotonin. Furthermore, by using the serotonin antimetabolite, 1-benzyl-2-methyl-5-hydroxytryptamine (BAS-phenol), the latter investigators found that in anesthetized dogs, pressor responses to serotonin could be blocked selectively without affecting similar responses to tryptamine (Shaw and Woolley, 1957; Woolley and Shaw, 1957). More recently, Barlow and Khan (1959a) reported that on the isolated rat fundus strip preparation, contractions in response to serotonin could be blocked much more readily by 2-bromlysergic acid diethylamide (BOL) than those induced by tryptamine. It was, however, also reported that the differentiation in antagonism of serotonin and tryptamine could not be demonstrated in the isolated rat uterus (Barlow and Khan, 1959a,b). In the chicken, various lysergic acid derivatives have also been found to reverse arterial pressure responses to both serotonin and tryptamine without any apparent discrimination (Buñag and Walaszek, 1962a).

The difference in test objects used by the various investigators has been offered as an explanation for the divergent results which have been obtained (Woolley and Shaw, 1957). The present report is mainly concerned with an investigation of the arterial pressure effects of serotonin and tryptamine in various animal species. In order to establish a correlation between variations in indolealkylamine structure and the corresponding cardiovascular effects, arterial pressure responses to 4-hydroxytryptamine, dimethyltryptamine, bufotenine, psilocin and psilocybin were also studied. The effect of BAS-phenol on the responses to the indolealkylamines was determined not only on blood pressure of intact animals but also on isolated organ preparations.

METHODS AND MATERIALS. *Compounds.* The agonist drugs used were serotonin creatinine sulfate, tryptamine hydrochloride, 4-hydroxytryptamine oxalate, dimethyltryptamine, bufotenine, psilocin and psilocybin. In most experiments, control injections of acetylcholine bromide, histamine phosphate, epinephrine bitartrate or norepinephrine bitartrate were also given. The doses for all of these drugs are expressed in terms of the base. The antagonist used was 1-benzyl-2-methyl-5-hydroxytryptamine hydrochloride (BAS-phenol) and its doses are expressed in terms of the salt.

Blood pressure recordings. Fourteen dogs, ten cats, seven rabbits and twenty-four chickens were used in these studies. The animals were anesthetized as follows: the dogs with sodium pentobarbital (Nembutal), 30 mg/kg, intravenously; the cats with sodium pentobarbital, 30 mg/kg, intraperitoneally; the rabbits with urethane, 1.2 g/kg, intraperitoneally; and the chickens with sodium phenobarbital, 200 mg/kg, intramuscularly. Graphic tracings of blood pressure were made with a suitable mercury manometer from the femoral artery in dogs and cats, the carotid artery in rabbits and the ischiadic artery in chickens. To keep surgical procedures to a minimum, drug injections were made into cannulae inserted in ipsilateral veins exposed through the same incision; the femoral vein in cats and dogs, the external jugular vein in rabbits and the ischiadic vein in chickens. To study BAS-phenol antagonism, most of the agonist drugs were initially

[1] International Postdoctoral Research Fellow of the National Institutes of Health, 1960-1962. Permanent Address: Department of Pharmacology, UE-RM Memorial Medical Center, Quezon City, Philippines.

[2] This work was supported by U. S. Public Health Service Senior Research Fellowship SF-72 and Research Grant M-1902.

injected at 10- to 15-minute intervals and then repeated in gradually increasing amounts, 15 to 30 minutes after the administration of varying doses of BAS-phenol. Blood pressure responses to the dimethylated compounds were generally of longer duration, and in those animals in which these compounds were used the intervals of drug injection were adjusted accordingly. The doses of the various indolealkylamines used in the arterial pressure studies are given in table 1. The doses of BAS-phenol used in the different species are: 2.5 mg/kg in the dog, 1 to 2 mg/kg in the cat, 0.1 to 2.0 mg/kg in the rabbit and 1 to 12 mg/kg in the chicken.

In vitro procedures. The antagonistic potency of BAS-phenol on responses to serotonin and tryptamine was tested on the isolated guinea-pig ileum and rabbit ear preparations. For the former, pieces of guinea-pig ileum were suspended in oxygenated Tyrode's solution at 35°C in a 7-ml organ bath. The rabbit ear preparation was set up according to the procedure described by Gaddum and Kwiatkowski (1938), such that the height of the tracings in the records indicates the time interval between drops. The perfusion fluid used for the rabbit ear was that recommended by Page and Green (1948). The experimental design employed in the *in vitro* experiments is essentially the same as that which is described for the blood pressure studies. Two reservoirs were used to allow addition or perfusion of alternate solutions, one containing BAS-phenol. The concentrations of BAS-phenol used were 2 to 5 μg/ml for the guinea-pig ileum and 2 to 10 μg/ml for the rabbit ear.

TABLE 1

Doses (μg/kg) of indolealkylamines used in the blood pressure studies

Indolealkylamine	Animal Species			
	Dog	Cat	Rabbit	Chicken
Serotonin	50–120	20–40	5–20	5–25
Tryptamine	125–1000	125–500	125–500	75–250
4-Hydroxytryptamine	200–300	—	—	50–100
Bufotenine	50–200	100–200	50–100	50–100
Dimethyltryptamine	250–500	500–1000	125–250	300–750
Psilocin	100–200	—	—	50–100
Psilocybin	200–400	—	—	100–200

RESULTS. *Effects of the indolealkylamines on blood pressure.* In the dog the usual response to serotonin was triphasic as described by Page (1957), consisting of an initial transient fall in pressure concurrent with slowing of the heart rate, followed by a rise and then finally a more prolonged fall. The response to 4-hydroxytryptamine was biphasic, consisting of an initial sharp drop in pressure followed by a slight but more prolonged rise in pressure. The response to all the other indolealkylamines tested, namely, tryptamine, dimethyltryptamine, bufotenine, psilocin and psilocybin, was predominantly pressor although occasionally the major response was preceded or followed by slight depressor effects. Blood pressure responses recorded in our

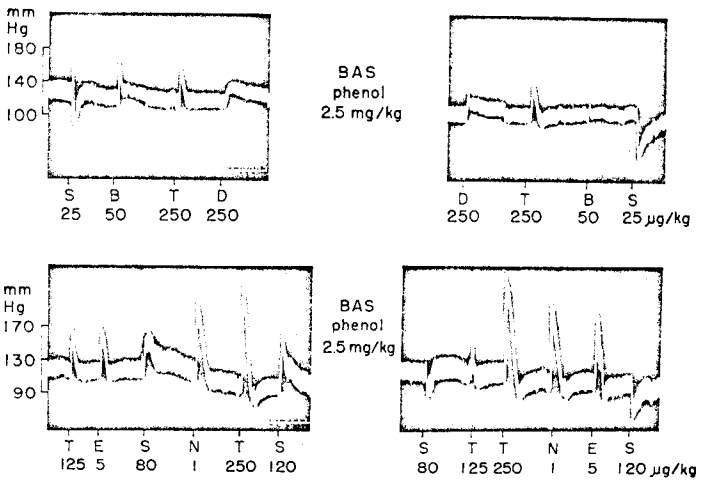


FIG. 1. The effects of BAS-phenol on blood pressure responses of the anesthetized dog to the indolealkylamines.

Upper tracings taken from a dog, 13.2 kg, under pentobarbital anesthesia. S, serotonin; B, bufotenine; T, tryptamine; and D, dimethyltryptamine. Lower tracings taken from another dog, 19.5 kg, also under pentobarbital anesthesia. E, epinephrine; and N, norepinephrine. Time signal: 1 minute.

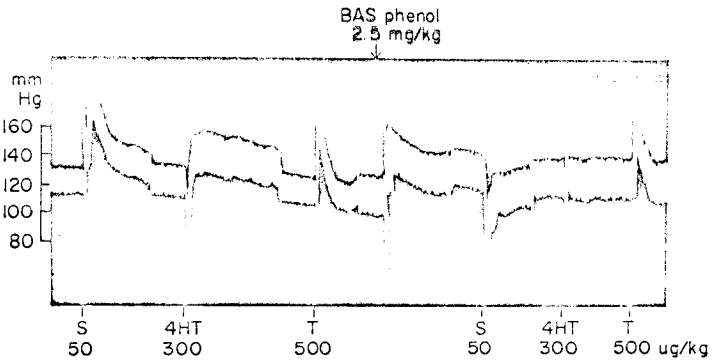


FIG. 2. Blood pressure responses of an anesthetized dog to the primary indolealkylamines before and after administration of BAS-phenol.
Dog, 8.6 kg, under pentobarbital anesthesia. S, serotonin; 4HT, 4-hydroxytryptamine; and T, tryptamine. Time signal: 1 minute.

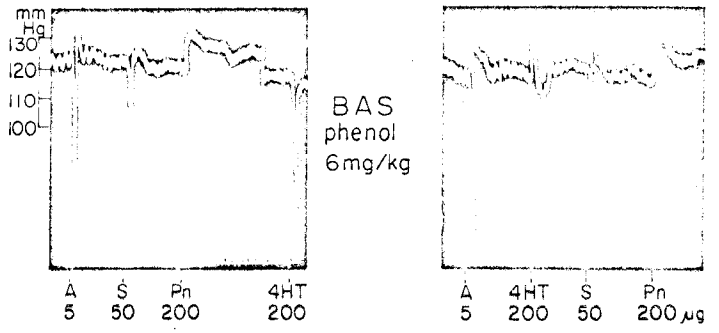


FIG. 3. Blood pressure responses of an anesthetized chicken to the indolealkylamines before and after administration of BAS-phenol.
Chicken, 1.75 kg, under phenobarbital anesthesia. A, acetylcholine; S, serotonin; 4HT, 4-hydroxytryptamine; and Pn, psilocin. Time signal: 1 minute.

dogs to the different indolealkylamines mentioned are represented in figures 1 and 2. With regard to the duration of these pressor effects, the response to tryptamine usually lasted for 2 to 3 minutes; the response to bufotenine and dimethyltryptamine, 5 to 10 minutes; and upon administration of psilocin or psilocybin, the pressure remained elevated even 1 to 1½ hours after injection.

The usual cardiovascular effect of serotonin and tryptamine in the chicken is an abrupt and short-lived fall in arterial pressure (Buñag and Walaszek, 1961a). As shown in figure 3, the other primary amine employed in the present studies, 4-hydroxytryptamine, also produced a sharp and transient depressor effect upon intravenous injection. On the other hand, the tertiary amines, dimethyltryptamine, bufotenine, psilocin and psilocybin, produced an elevation of blood pressure which was of relatively long duration and occasionally preceded by transient vasodepression, particularly in the case of bufotenine (see fig. 4).

In the cat, the predominant cardiovascular effect of serotonin observed was a fall in arterial pressure. Tryptamine, on the other hand, was pressor. Bufotenine elicited a biphasic response consisting of a transient fall followed by a rise of greater magnitude and duration. The response to dimethyltryptamine in the cat consisted of a sustained elevation in blood pressure lasting for 8 to 10 minutes. Cardiovascular responses to the indolealkylamines in this species are exemplified in figure 5. These responses were, however, rarely purely pressor or depressor, the major phase usually being preceded or followed by a change in pressure in the opposite direction.

In the rabbit cardiovascular responses to the

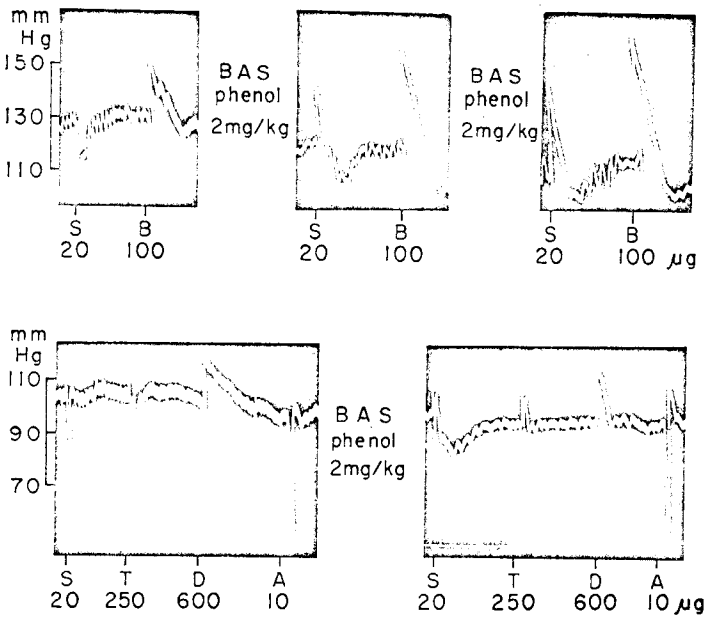


FIG. 4. The effects of BAS-phenol on blood pressure responses of the anesthetized chicken, to the indolealkylamines.

Upper tracings taken from a chicken, 1.8 kg, under phenobarbital anesthesia. S, serotonin; and B, bufotenine. Lower tracings taken from another chicken, 1.9 kg, also under phenobarbital anesthesia. T, tryptamine; D, dimethyltryptamine; and A, acetylcholine. Time signal: 1 minute.

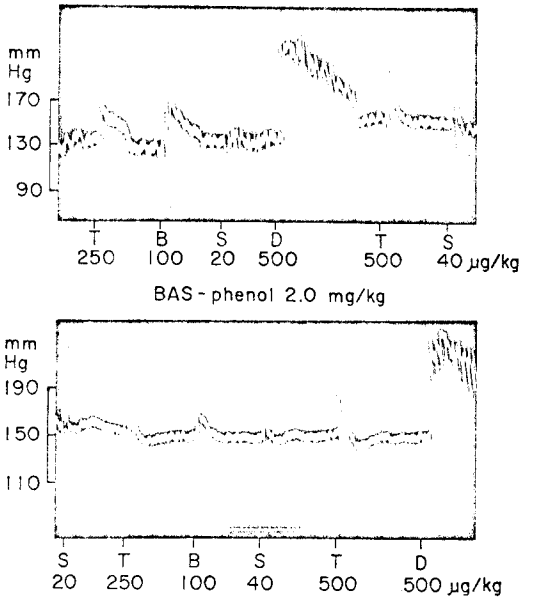


FIG. 5. The effect of BAS-phenol on blood pressure responses of the anesthetized cat to the indolealkylamines.

Cat, 3.9 kg, under pentobarbital anesthesia. T, tryptamine; B, bufotenine; S, serotonin; and D, dimethyltryptamine. Time signal: 1 minute.

indolealkylamines were even more inconsistent than in the other species. The response to serotonin was usually depressor, although pressor responses to this drug were observed in two of the rabbits used. Tryptamine was pressor; bufotenine was biphasic, depressor-pressor, while dimethyltryptamine elicited a prolonged pressor response occasionally preceded by a transient fall (see fig. 6).

Effects of BAS-phenol on arterial pressure responses to the indolealkylamines. The original observation of Woolley and Shaw (1957) concerning the serotonin specificity of BAS-phenol blockade in the dog was confirmed in the present studies. In figure 1, the lower tracings show the responses of an anesthetized dog to serotonin and tryptamine together with control responses to epinephrine and norepinephrine, before and after administration of BAS-phenol. The record is essentially a reproduction of Woolley and Shaw's findings. In addition, however, the upper tracing in the same figure shows the responses of another dog to the dimethylated analogues of serotonin and tryptamine, bufotenine and dimethyltryptamine, respectively. It is evident that

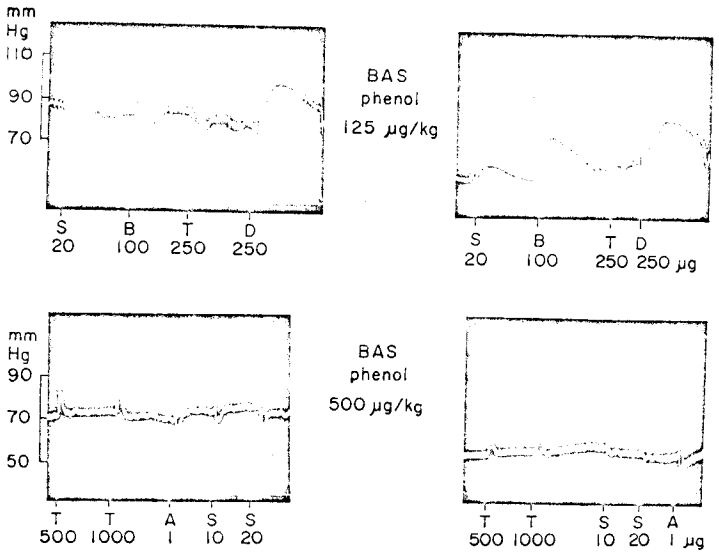


FIG. 6. The effect of BAS-phenol on blood pressure responses of the anesthetized rabbit to the indolealkylamines.

Upper tracings taken from a rabbit, 2.9 kg, under urethane anesthesia. S, serotonin; B, bufotenine; T, tryptamine; and D, dimethyltryptamine. Lower tracings taken from another rabbit, 2 kg, also under urethane anesthesia. A, acetylcholine; control injections given to test specificity of BAS-phenol antagonism. Time signal: 1 minute.

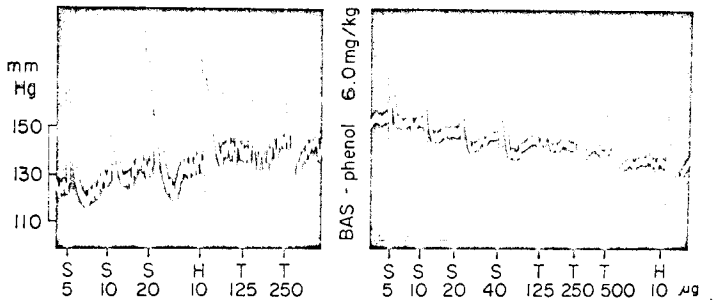


FIG. 7. The effect of BAS-phenol on the pressor response to serotonin and tryptamine in the atropinized chicken.

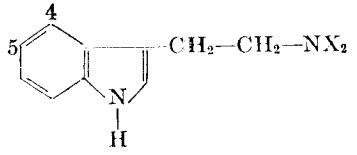
Atropine sulfate, 6 mg/kg, was injected intravenously prior to the start of the experiment. Chicken, 1.6 kg, under phenobarbital anesthesia. S, serotonin; H, histamine; and T, tryptamine. Time signal: 1 minute.

BAS-phenol antagonism is not limited only to serotonin induced responses but also extends to responses to bufotenine. The responses to compounds without any substituents other than the ethylamine chain on the indole nucleus, *i.e.*, tryptamine and dimethyltryptamine, were not affected. Furthermore, BAS-phenol also blocked the arterial pressure effects of 4-hydroxytryptamine (see fig. 2) and those of its dimethylated analogues, psilocin and psilocybin. BAS-phenol itself produced cardiovascular effects which simulate those of the indole compounds being tested. As shown in figure 2, the predominate response to BAS-phenol is a rise in pressure, which in this instance is preceded by a fall. A finding which was singularly unique for serotonin was its prolonged depressor effect in the dog pretreated with BAS-phenol. Since this prolonged depressor response can be blocked with antihistaminic drugs, the involvement of a histamine mediated mechanism has been suggested (Buñag and Walaszek, 1961b).

In the chicken, the depressor responses elicited by the primary amines, serotonin, tryptamine

TABLE 2

Blood pressure effects of various indolealkylamines before and after administration of BAS-phenol



Compound	Structure			Effects on Arterial Pressure							
				Control responses				Responses after BAS-phenol			
	X_2	4	5	Dog	Cat	Rabbit	Chicken	Dog	Cat	Rabbit	Chicken
Tryptamine	H	H	H	Pressor	Pressor	Pressor	Depressor	Same response as control	Same response as control	Same response as control	Reversed
Serotonin	H	H	OH	Triphasic major phase pressor	Depressor	Depressor	Depressor	Purely depressor	Blocked	Blocked	Reversed
4-Hydroxy-tryptamine	H	OH	H	Biphasic major phase depressor	—	—	Depressor	Blocked	—	—	Reversed
Dimethyl-tryptamine	CH_3	H	H	Pressor	Prolonged pressor	Prolonged pressor	Prolonged pressor	Same response as control	Same response as control	Same response as control	Same response as control
Bufotenine	CH_3	H	OH	Pressor	Biphasic depressor pressor	Biphasic depressor pressor	Biphasic depressor pressor	Blocked	Blocked	Depressor blocked	Depressor blocked
Psilocin	CH_3	OH	H	Prolonged pressor	—	—	Prolonged pressor	Blocked	—	—	Same response as control
Psilocybin	CH_3	OH_2PO_4	H	Prolonged pressor	—	—	Prolonged pressor	Blocked	—	—	Same response as

and 4-hydro
reversed after
On the other
tertiary amine
psilocin and p
phenol. Howe
present in th
then BAS-pl
augmented th
of the chicke
before and af
represented ir
Shaw's differ
tryptamine r
selective bloc
phenol, exper
in which resp

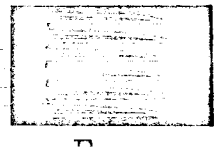


Fig. 8. Gui
Concentrat
0.25 and 0.5;
T1 and T2, tr
Between A a
phenol, 2 μg/
by all three
serotonin and
greater degre
dose, respon
height of con
tryptamine r
pressed. Bet
solution with

T, tryptam
both serotoni

Psilocin	CH_3	OH	H	Prolonged pressor	—	—	Blocked	—	Same response as control
Psilocybin	CH_3	OH_2PO_4	H	Prolonged pressor	—	Prolonged pressor	Blocked	—	Same response as control

and 4-hydroxytryptamine, were completely reversed after the administration of BAS-phenol. On the other hand, the pressor response to the tertiary amines, dimethyltryptamine, bufotenine, psilocin and psilocybin, was not affected by BAS-phenol. However, whenever a depressor phase was present in the response to the tertiary amines, then BAS-phenol blocked the depressor and augmented the pressor component. The responses of the chicken to the various indolealkylamines before and after BAS-phenol administration are represented in figures 3 and 4. Since Woolley and Shaw's differentiation between serotonin and tryptamine receptors in the dog was based on a selective blockade of pressor responses by BAS-phenol, experiments were also done on chickens in which responses to serotonin and tryptamine were rendered pressor by pretreatment with atropine. In figure 7 the tracings were taken from an atropinized chicken and as previously reported, following atropine administration, the effects of serotonin and tryptamine on blood pressure are reversed (Buñag and Walaszek, 1961a) and injections of these agents now produce pressor instead of the usual depressor responses. Upon administration of BAS-phenol in such an animal, pressor responses to both serotonin and tryptamine were diminished without any perceptible differentiation.

The effects of BAS-phenol on the arterial pressure responses of the cat to the indolealkylamines are shown in figure 5. The depressor responses to serotonin and bufotenine were completely blocked while the predominantly pressor responses to tryptamine and dimethyltryptamine were not. Representative tracings for the rabbit are shown in figure 6. In this species, the administration of BAS-phenol apparently favors the pressor component of the cardiovascular response to the indolealkylamines. When serotonin was depressor, as is the case in most rabbits, BAS-phenol converted the response to a pressor one. However, in those rabbits in which the response to serotonin was initially pressor, BAS-phenol was without any significant effect. Interpretation of antagonism of BAS-phenol on blood pressure responses of the cat and the rabbit to the various indolealkylamines is relatively more difficult than in the other two species studied because of the highly variable nature of the responses. In the rabbit, an added complication is the marked diminution in baseline pressure consistently produced by the intravenous injection of BAS-phenol.

The results obtained in our blood pressure studies are summarized in table 2. From an examination of the table and the data just

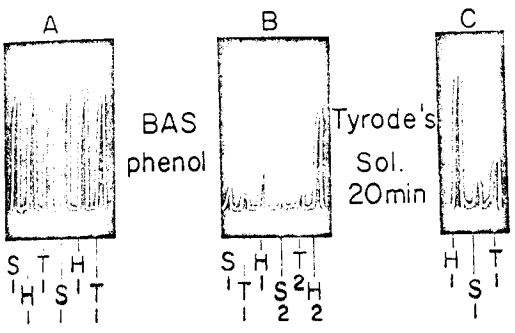


FIG. 8. Guinea-pig ileum in 7-ml organ bath.
Concentrations in μg: S1 and S2, serotonin, 0.25 and 0.5; H1 and H2, histamine, 0.02 and 0.04; T1 and T2, tryptamine, 100 and 200, respectively. Between A and B, the solution containing BAS-phenol, 2 μg/ml, was used. Contractions induced by all three agonists are markedly depressed, serotonin and tryptamine being antagonized to a greater degree than histamine. Upon doubling the dose, responses to histamine approximate the height of control contractions but serotonin and tryptamine responses still remain markedly depressed. Between B and C, control Tyrode's solution without any BAS-phenol was resumed.

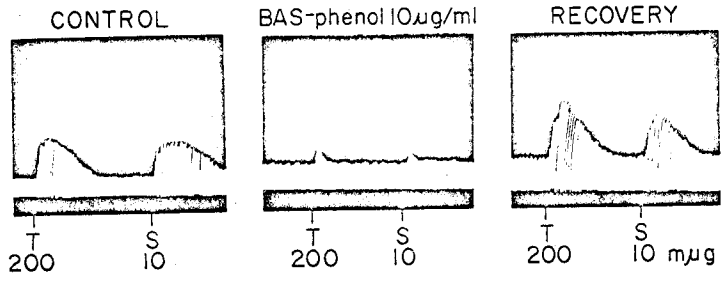


FIG. 9. Isolated rabbit ear.
T, tryptamine; and S, serotonin. Upon addition of BAS-phenol to the perfusion medium, responses to both serotonin and tryptamine are depressed.

presented, the following general statements can be made: (1) In all the species studied, except the chicken, tryptamine is a pressor agent while serotonin and 4-hydroxytryptamine are predominantly depressor. (2) On comparing the effects of the three primary amines studied on chicken blood pressure, larger amounts of tryptamine than of serotonin or 4-hydroxytryptamine are required in order to produce the same degree of vasodepression. (3) In the chicken the tertiary amines, dimethyltryptamine, bufotenine, psilocin and psilocybin, possess stronger pressor activity and a relatively longer duration of action than the other indolealkylamines studied. (4) In the dog, BAS-phenol blocks not only serotonin but also other compounds with hydroxy substituents on the indole ring whether at position 4 or 5. This antagonism is not affected by dimethylation of the terminal nitrogen.

Effects of BAS-phenol on responses of isolated organ preparations to serotonin and tryptamine. Figure 8 represents the responses of the guinea-pig ileum to serotonin and tryptamine, before, during and after addition of BAS-phenol to the bath. BAS-phenol antagonized contractions induced by serotonin and tryptamine to a greater degree than those due to histamine. Twenty minutes after the removal of BAS-phenol from the bath, the gut had completely recovered insofar as its responses to histamine were concerned, but its responses to serotonin and tryptamine still remained markedly depressed. Figure 9 shows the tracings taken from a rabbit ear preparation before, during and after the perfusion of the solution containing BAS-phenol. No difference could be discerned in the antagonism of BAS-phenol against responses to serotonin and tryptamine since both agents were blocked equally well. Our *in vitro* findings are in agreement with those of Gaddum (1953) and would support his contention that the receptors in the guinea-pig ileum are common to both serotonin and tryptamine. Furthermore, a similar situation apparently also exists in the rabbit ear vessels.

Discussion. The variability of the effects of serotonin on arterial pressure is well known and widely documented (Page, 1958). Upon intravenous injection of serotonin into animals of the same species, or even the same animal at different periods of time, a broad spectrum of blood pressure responses can be observed, sometimes purely pressor or depressor, but more often a confusing medley of both. The numerous mechanisms which contribute to the diversified cardiovascular activities of serotonin may arbitrarily be classified under two main groups, those which increase and those that diminish arterial pressure. Among the influences which would elevate blood pressure, peripheral vasoconstriction, myocardial stimulation and chemoreceptor stimulation have been mentioned (Page, 1957) and of these, the widespread vasoconstriction induced by serotonin appears to be the most important mechanism (Reid, 1952). The mechanisms which have been proposed to explain the depressor components of the response to serotonin have previously been enumerated (Buñag and Walaszek, 1961a) and they include the Bezold-Jarisch reflex, histamine release, ganglionic blockade, and an inhibition of vasomotor tone, both central and peripheral. Of these depressor mechanisms, the Bezold-Jarisch effect and the release of endogenous histamine appear to be the most dominant and consistent (Page, 1958; Buñag and Walaszek, 1961b, 1962b).

In view of the multitude of variables which may be operative to a greater or lesser degree in any given animal, it is therefore not at all surprising to find marked species differences in the cardiovascular response to serotonin (Page and McCubbin, 1953; Schneider and Yonkman, 1954). The complex pattern is even more magnified when the character of the response is examined in the light of changes in chemical configuration of the basic indolealkylamine structure. The presence of hydroxyl groups on the indole nucleus, as in serotonin and 4-hydroxytryptamine, favors depressor activity. In terms of the mechanism of action, this would imply that a hydroxyl radical on position 4 or 5 of the indole ring strengthens the compound's affinity for the receptors concerned with histamine release and the Bezold-Jarisch reflex. On the other hand, dimethylation of the terminal nitrogen, as in dimethyltryptamine, bufotenine, psilocin and psilocybin, favors pressor activity with the implication that dimethylation strengthens the compound's affinity for the receptors responsible for vasoconstriction. Another effect of dimethylation which is even more consistent is a prolongation of the compound's duration of action. The relatively longer duration of action of the dimethylated compounds has been ascribed to their greater resistance to inactivation by monoamine oxidase (Gessner *et al.*, 1960).

In the anesthetized dog, Woolley and Shaw

(1957) found that BAS-phenol blocks pressor responses to serotonin and serotonamidine (5-hydroxy-3-indoleacetamidine) but not those to tryptamine and tryptamidine (3-indoleacetamidine). The common presence of a hydroxyl group at position 5 of the indole ring in serotonin, serotonamidine and BAS-phenol may lead one to suspect that it is the key structure on which the selective antagonism is based. That this is not the case is shown by the fact that BAS-phenol antagonism also extends to the 4-hydroxy analogues, 4-hydroxytryptamine, psilocin and psilocybin. In the cat and the rabbit, it is difficult and probably unnecessary to use BAS-phenol blockade as a means of differentiating between serotonin and tryptamine, since the effects of the two compounds on blood pressure in these species are usually diametrically opposed to begin with. In the chicken, both compounds are depressor and their effects are reversed equally well by BAS-phenol. On the basis of the present findings, Woolley and Shaw's hypothesis on separate receptors for serotonin and tryptamine could well be extended to include the cat and the rabbit but not the chicken.

From studies conducted on isolated organ preparations, a greater antagonism of serotonin than of tryptamine has thus far been demonstrable only in the isolated rat stomach (Barlow and Khan, 1959a,b). In this preparation and on cat blood pressure, iproniazid, a monoamine oxidase inhibitor, potentiates tryptamine but not serotonin (Vane, 1959). Since tissue homogenates of the rat stomach showed an amine oxidase activity which inactivated serotonin and tryptamine to the same degree, Vane suggested that the difference was due to the presence of a cellular diffusion barrier which allows passage of tryptamine but not of serotonin, and since amine oxidase is located intracellularly, only agents which could penetrate the barrier would be subject to inactivation. On this basis, the alternative possibility has therefore been brought up that the receptors involved are common to both tryptamine and serotonin and that differential antagonists act by interfering with the transport of tryptamine (but not of serotonin) across the cell wall (Barlow, 1961).

SUMMARY

Studies were made on the antagonistic effect of BAS-phenol on blood pressure responses of different animal species to various indolealkylamines. In the dog, BAS-phenol selectively blocks responses to serotonin, bufotenine, 4-hydroxytryptamine, psilocin and psilocybin but not those to tryptamine or dimethyltryptamine. A similar differentiation could usually be shown in the cat and the rabbit but not in the chicken. Differentiation between serotonin and tryptamine by selective specificity of BAS-phenol antagonism could not be demonstrated in the isolated guinea-pig ileum and rabbit ear preparations.

ACKNOWLEDGMENTS. We wish to thank the following individuals for their generous supplies of the respective drugs mentioned. Dr. Karl Pfister of Merck Sharp & Dohme, Rahway, New Jersey, for BAS-phenol hydrochloride; Dr. J. H. Trapold of Sandoz Pharmaceuticals, Hanover, New Jersey, for 4-hydroxytryptamine oxalate, psilocin and psilocybin; Dr. Joseph P. Webb of the Upjohn Company, Kalamazoo, Michigan, for bufotenine and dimethyltryptamine.

REFERENCES

BARLOW, R. B.: Brit. J. Pharmacol. **16:** 153, 1961.
BARLOW, R. B. AND KHAN, I.: Brit. J. Pharmacol. **14:** 99, 1959a.
BARLOW, R. B. AND KHAN, I.: Brit. J. Pharmacol. **14:** 265, 1959b.
BUÑAG, R. D. AND WALASZEK, E. J.: THIS JOURNAL **133:** 52, 1961a.
BUÑAG, R. D. AND WALASZEK, E. J.: Experientia **17:** 503, 1961b.
BUÑAG, R. D. AND WALASZEK, E. J.: Arch. int. Pharmacodyn. **135:** 142, 1962a.
BUÑAG, R. D. AND WALASZEK, E. J.: THIS JOURNAL **135:** 151, 1962b.
GADDUM, J. H.: J. Physiol. **119:** 363, 1953.
GADDUM, J. H. AND KWIATKOWSKI, H.: J. Physiol. **94:** 87, 1938.
GESSNER, P. K., KHAIRALLAH, P. A., MCISAAC, W. M. AND PAGE, I. H.: THIS JOURNAL **130:** 126, 1960.
PAGE, I. H.: in 5-Hydroxytryptamine, ed. by G. P. Lewis, Pergamon Press, New York, 1957.
PAGE, I. H.: Physiol. Rev. **38:** 277, 1958.
PAGE, I. H. AND GREEN, A. A.: Meth. med. Res. **1:** 123, 1948.
PAGE, I. H. AND MCCUBBIN, J. W.: Circulation Res. **1:** 354, 1953.
REID, G.: J. Physiol. **118:** 435, 1952.
SCHNEIDER, J. A. AND YONKMAN, F. F.: THIS JOURNAL **111:** 84, 1954.
SHAW, E. AND WOOLLEY, D. W.: Proc. Soc. exp. Biol., N. Y. **96:** 439, 1957.
VANE, J. R.: Brit. J. Pharmacol. **14:** 87, 1959.
WOOLLEY, D. W. AND SHAW, E.: J. biol. Chem. **203:** 69, 1953.
WOOLLEY, D. W. AND SHAW, E.: THIS JOURNAL **121:** 13, 1957.