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5-HYDROXYTRYPTAMINE ANTAGONISTS

LASZLO GYERMEK

Geigy Research Laboratories, Ardsley, New York

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I. INTRODUCTION

Numerous pharmacological studies have been conducted in recent years with the purpose of finding drugs which are antagonistic to 5-hydroxytryptamine (HT). These studies were of help in giving us some insight into its mechanism of action. Although the physiological and pathological role of HT in the mammalian organism has not been ascertained, the need for the possible therapeutic application of those agents which antagonize HT has also been discussed several times.

The first attempts at developing antagonists to HT started only about ten years ago, shortly after HT had been isolated and its structure determined. The number of drugs since reported to have antagonistic properties to HT is rather extensive. The presently known antagonists belong to several quite different chemical classes and a systematic enumeration of them appears to be indicated.

A. 5-Hydroxytryptamine (HT) receptors

Before discussing the role and characteristics of the receptors sensitive to HT, it would be worthwhile to look at the behavior of certain other receptors which are pharmacologically better known and have been extensively investigated. The different pharmacological characteristics of cholinergic receptor sites sensi-

tive to acetylcholine (ACh) are well known. These receptors show different degrees of sensitivity to various cholinergic blocking agents (*e.g.*, preference to atropine of the postganglionic parasympathetic receptors; affinity to hexamethonium of autonomic ganglia; sensitivity to tubocurarine of the myoneural receptors). This is but one of the classical examples of the heterogeneity of receptor sites responsive to a single neurotransmitter substance. The following additional examples can be mentioned: a) the resistant character of some epinephrine receptors to adrenergic blockade (*e.g.*, the dilator receptors of the blood vessels; receptors responsible for the positive chronotropic action on the heart); b) the resistance of some histamine receptors to antihistaminic agents (*e.g.*, those regulating gastric secretions). The examples indicate that several different receptor sites also might exist for a substance like HT. Studies which compared the actions of HT with those of tryptamine, epinephrine, norepinephrine, histamine, ACh, bradykinin, and oxytocin, have shown that HT has characteristic actions which differ from those of the compounds mentioned (102, 125). These findings provide a basis for the possible existence of pharmacologically different HT receptor sites in the different organs. However, the possibility that HT acts partly, or in some organs predominantly, on receptors sensitive to the common neurotransmitter substances and biogenic amines cannot be excluded.

B. Modes and types of action of antagonists

Our knowledge of HT receptors and their blockade is based almost entirely on the study of a few simple organs (*e.g.*, the rat uterus, the guinea pig ileum). But even the results obtained with smooth muscle preparations sometimes have proved to be difficult to interpret.

5-Hydroxytryptamine receptors, like other tissue receptors, can be investigated either by using a variety of antagonists or by stimulant drugs structurally related to the agonist.

Gaddum and Picarelli (58) stated that the guinea pig ileum contains two types of receptors sensitive to HT and differentiated them by the use of different antagonists. They demonstrated that one receptor-type, the "nervous receptor," could be blocked by morphine (M-receptors), atropine, cocaine, and methadone; the other type, the "smooth muscle receptor," was blocked by Dibenzyline (D-receptors), *d*-lysergic acid diethylamide (LSD), dihydroergotamine (DHE), and 5-benzyloxygramine. These studies originated as a result of the consideration of the action of HT on the rat uterus and the perfused rabbit ear which could easily be blocked by ergot derivatives (54), whereas the ergot derivatives were much less effective on the guinea pig ileum. From this it is obvious that the sensitivity of some organs to HT-blocking agents is markedly different; however, no general conclusion can be drawn as to the possible predominance of a certain type of HT receptor in the different organs. The "nervous receptors" of HT in the guinea pig ileum seem to differ from the ganglionic cholinergic receptors of this organ in that they are not suppressed by hexamethonium or by large blocking doses of nicotine (125). The HT receptors of the guinea pig ileum could also

be differentiated from other peripheral receptors of the gut which are sensitive to ACh, histamine, and bradykinin (125). The M-receptors are probably located in the nervous tissue of the intestine, and antagonism studies with morphine suggested that these sites are probably peripheral to the autonomic ganglia but central to the parasympathetic receptor sites (*cf.* 58). It is still possible, however, that the nervous receptors are located at the intramural autonomic ganglia of the guinea pig ileum although these receptors function differently from the cholinergic ganglionic receptors. This latter assumption is substantiated by recent studies on autonomic ganglia.

It was found that HT in small quantities produced facilitation (80a, 167) and also direct stimulation of the sympathetic ganglia of the cat, where the direct stimulant action of 5-HT differs from that of the typical cholinergic type of ganglionic stimulants (nicotine, DMPP) (7a, 167). The facilitatory effect of both HT and pilocarpine on preganglionic electrical stimulation on the superior cervical ganglion of the cat could be blocked by morphine and cocaine. Since the effect of HT cannot be blocked by atropine, it was concluded that its facilitatory action differs from that of pilocarpine (166, 167). There is also evidence that the isolated rabbit atria can be stimulated by 5-HT indirectly through certain nervous elements belonging to the sympathetic nervous system (167a). These receptors, like the M receptors of the gut, can be blocked by morphine and cocaine. Lysergic acid diethylamide (a D receptor-blocking agent) produces only a non-specific blocking action. In contrast to the rabbit atria, isolated atrial musculature of the cat is directly stimulated by HT (167a). This latter musculotropic effect of HT is highly susceptible to LSD blockade, indicating that in the feline species elements probably similar to the LSD sensitive D receptors of the gut are involved.

Further differentiation of the HT receptors in the gut and in other organs may be of great value in characterizing the type of action of HT, its different structural analogues, and its antagonists. It should be kept in mind, however, that we do not know how the HT receptors of the other organs, including the brain, compare with those of the few organs investigated. Therefore, it is important to determine whether the majority of the HT receptors in the organism belong to the M or D receptor types, or are entirely different from them.

The nature of the HT receptors can also be analyzed by using structural analogues of HT and tryptamine. Results obtained with these analogues indicate that the HT receptors of the rat uterus resemble D receptors of the guinea pig ileum, and the receptors of the rat fundus resemble M receptors of that organ (2a). Employing these analogues of HT, it was also possible to distinguish three different types of agents (173): 1) those like HT having a certain affinity for tissue receptors (rat stomach) and monoamineoxidase (MAO) prepared from the same organ (the action of this group could not be potentiated in the isolated organ preparation by inhibiting MAO); 2) those similar to 5-methyltryptamine, having a certain affinity for the tissue receptors and for MAO (however, the actions of this group could be potentiated in the isolated organ by MAO in-

hibitors); 3) those like 5-hydroxy-1-methyltryptamine which have an affinity for only the tissue receptors and not for MAO.

The above observations suggested that the tissue receptors for HT are located apart from the intracellular enzyme receptors. Some of the compounds, such as tryptamine, can penetrate into the cells and be attacked there by the intracellular enzyme, but some, like HT, in spite of their sensitivity to MAO preparations, cannot penetrate into the cells. Studies on the dissociation constants of the pharmacophore groups of HT and on the partition coefficients between oil and water of tryptamine and HT showed that HT did not penetrate into the lipoid phase, whereas tryptamine did (173). The demonstration of the different types of HT tissue receptors and the MAO receptors is of great importance in comparing HT with norepinephrine, because it has been suggested that the tissue receptors for norepinephrine are also responsible for its enzymatic destruction. The significance of these findings is that a) the inactivation processes should be strongly considered in analyzing the action of HT-like drugs, and b) antiHT agents may have a possible affinity for a second receptor site (*i.e.*, MAO). With the exception of chlorpromazine, LSD, hydrazinophthalazine, and harmine, which were shown to interfere a) with the tissue receptors of HT (51, 74, 108, 197) and b) with its deamination as well (104, 118, 134), almost nothing is known about the proportion of "tissue receptor-blocking" and "enzyme-inhibiting" properties of different blocking substances.

Such a second receptor site (*i.e.*, the inactivating enzyme) may be available not only for the agonist but also for the corresponding antagonist molecules. This has been demonstrated previously for a group of cholinergic blocking drugs (*e.g.*, higher alkyl and aralkyl quaternary derivatives of tropeines). In addition to their anti-cholinergic properties, these agents exhibit some degree of cholinesterase inhibition (70, 157). It is evident, therefore, that the overall spectrum of action of such a compound will be dependent upon the predominance of one or the other of these blocking properties.

Of the many theoretical possibilities of drug-receptor interactions, the competitive type of antagonism is suggested for many HT antagonists (113), but sufficient evidence in support of this assumption is not yet available. So far, very little research has been done with the primary emphasis upon the type of interaction of HT and its antagonists on HT receptors. The complexity of the problem, from a theoretical as well as from a practical point of view, has been well emphasized by Gaddum *et al.* (55). Therefore, a classification of antiHT drugs into two groups, competitive and non-competitive (113), appears to be an oversimplification. When the blocking action of a given dose of antagonist can be overcome by a larger dose of the agonist, and this effect is, in turn, blocked by another dose of the antagonist, the blockade is called *surmountable*. This does not necessarily mean that the blockade is *competitive*. As is known, a surmountable antagonism can be competitive as well as non-competitive and also uncompetitive. Furthermore, surmountable antagonism can be derived from the interaction of two drugs in which they form an inactive complex with each other.

Many types of drug interactions in which two drugs (an agonist and an antagonist) are involved can be of a competitive nature, but this does not necessarily imply that the interaction takes place on a common receptor site. In contrast, several drug interactions between a single receptor and two drugs which are antagonistic to each other have been found to be non-competitive. The major difficulty, in the case of the HT, HT-antagonist relationship and in almost all cases of drug antagonisms, is that the isolated enzyme-type receptor systems are not available for investigation. Even the use of an isolated organ for antagonism studies is inadequate in that frequently it can only exclude the existence of one or another type of antagonism and, in most cases, is unable to define the exact type of antagonistic interaction or even the site of interaction. Such difficulties may arise in the case of the guinea pig ileum by using atropine as an antagonist to HT. The nervous receptors for HT of this organ are above the level of the parasympathetic nerve endings, consequently stimulation which manifests at these sites is likely to produce stimulation of the peripheral parasympathetic nerve endings which can be blocked by atropine. An adrenergically innervated organ system, such as the superior cervical ganglion-nictitating membrane preparation, or an exclusively ganglionic test organ (*e.g.*, the inferior mesenteric ganglion preparation of the cat) is therefore more suitable for investigating the blocking action to HT of atropine or of agents which may influence the postganglionic parasympathetic effector sites. Considering all the limitations of methods and the complexity of the problems, it is not surprising that investigations of HT antagonists have usually been restricted to determinations of potency and selectivity of the blocking agents. A thorough analysis of the action of some HT antagonists with some methodological innovations was published by Gaddum *et al.* (55). It was recommended that on the rat uterus preparation, instead of measuring the amount of antagonist necessary to elicit a given reduction (usually 50 %) of the effect produced by the agonist, the dose ratios or drug ratios could be used. In surmountable antagonism, which accounts for a large part of all biological antagonisms, there are two ways recommended for analyzing the interaction between the agonist and antagonist: 1) By using the *dose ratio*, which refers to a dose of antagonist capable of maintaining a pharmacological equilibrium with an increased, selected dose of the agonist. The pA_x value, introduced by Schild (135b), corresponds to the negative logarithm of a concentration of the antagonist which maintains an equilibrium with an x-fold increment of the agonist and produces an effect as large as the original dose of the agonist without any antagonist. For determining the pA_x, different doses of the antagonist should be tried against a constant, x times increased dose of the agonist. Although this procedure seems to be the most suitable for comparing the potency of different antagonists, it is often difficult to perform, primarily because the effectiveness of some antagonists is influenced markedly by the time of exposure. 2) By using the *drug ratio*, which was recommended for rapid screening of potency of antiHT agents (55). The drug ratio is based on a single dose of the

antagonist, and is equal to the ratio of the concentrations of the agonist and antagonist when the response is 50% of the original response previously elicited without the antagonist. The dose and drug ratios of several HT antagonists on the rat uterus were determined. The relationship between dose ratio and time was also studied (55); this procedure characterized the type of interaction between the antagonist and the receptors. In the case of LSD, the dose ratio showed a gradual increase with time. Dihydroergotamine and Dibenamine acted in a similar manner. The antiHT effect of gramine derivatives, however, had a more rapid onset; the dose ratio reached its maximum within 30 to 40 minutes after exposure and then remained at a constant level. With some of the indole-type HT antagonists, the dose-effect curves were parallel before and after the antagonist (*e.g.*, 6-methylgramine). It was not possible to obtain similar results with some of the more active compounds because the dose ratio continued to increase almost indefinitely. On the basis of these studies, specific antagonists of HT can be divided into two classes: 1) potent drugs (such as Dibenamine, LSD, and the benzyloxygramines) which act slowly and eventually produce irreversible and insurmountable effects, and 2) less potent drugs (*e.g.*, the methylgramines, tryptamines, 2-methyl-3-ethyl-5-aminoindole) which act rapidly and are easily reversible. With some antagonists, like Dibenamine, LSD, and dihydroergotamine, the drug ratios were more or less constant over a fairly wide range when relatively low concentrations were used, but with high concentrations the drug ratio increased suddenly, so that HT caused less than 50% of the maximum response even in the largest doses. Therefore, the applicability of the dose ratio technique is always limited when the agonist produces auto-inhibition in large doses. Of the drugs investigated (55), 5-methylgramine differed from the others in that its drug ratio showed no tendency to rise, but fell slightly with higher doses; in larger doses this drug actually stimulated the uterus.

Besides the problem of the possible existence of different receptors for HT in the same organ, one must account for the possible dual nature of the action of HT, that is, production of stimulation and, especially in larger doses, of self-blockade; furthermore, the frequently observed phenomenon of tachyphylaxis with HT may also play an important role. In addition, there are HT antagonists which not only block but also stimulate the receptor sites.

C. Selectivity of action of HT antagonists

The use of isolated organs for determining the selectivity of HT antagonists is apparently limited by the fact that besides HT, only a few stimulant drugs can be tested on the same organ in order to determine the degree of blockade. Acetylcholine is the drug which has been compared most frequently with HT since it produces stimulation of most of the organs used for HT assays. The use of various autonomic and other stimulants like epinephrine, nicotine, histamine, and oxytocine, is restricted to organs where their actions are stimulatory. In certain studies (21, 55) on the rat uterus, the antiHT action was considered specific if no blockade against acetylcholine occurred. Only a few gramine and indole derivatives were found to be specific on the uterus preparation; however,

even these compounds proved to be unspecific blocking agents against HT on the guinea pig ileum if the comparison of blockade was made between HT and histamine (55). Most of the indole compounds have shown either a lack of selectivity or have produced, besides the blockade, stimulation of the uterus (*e.g.*, some had an HT-like action). The degree of selectivity of different ergot alkaloids has also been studied extensively on the isolated rat uterus by using HT and acetylcholine as stimulant substances (21). All the ergot derivatives investigated were found to be highly specific. The lowest specificity index (ED50 antiacetylcholine/ED50 antiHT) was that of *d*-lysergic acid dibutylamide, 1.3. The other compounds, including LSD, dihydroergotamine, ergonovine, and several mono- and disubstituted lysergic acid amide derivatives, showed much higher degrees of specificity. Lysergic acid diethylamide and 1-methyl-2-bromolysergic acid diethylamide, for example, were over 5000 times more potent against HT than against acetylcholine. However, had these compounds been investigated employing HT and epinephrine as stimulant drugs, probably much lower ratios of selectivity—sometimes lower than one—might have been obtained. Specificity of many different antiHT compounds was studied on the perfused hindlegs of the rabbit (102). Although acetylcholine was found to be one of the most potent compounds antagonizing the HT induced vasoconstriction, its effect was obviously not specific. Acetylcholine antagonized epinephrine, norepinephrine, $BaCl_2$, histamine, and vasopressin, thus showing no selectivity against HT. Its antiHT action could be eliminated by atropine. Chlorpromazine, which was the most potent antagonist of HT of all drugs tried, was postulated to be unspecific, since it also had a strong blocking action against histamine and a less marked action against norepinephrine. Lysergic acid diethylamide was nearly as potent as chlorpromazine against HT and was more selective in that it had only mild antiepinephrine and antihistamine action. The other 23 compounds investigated proved to be either much less potent or less selective, or both. Some of these drugs blocked the actions of HT and histamine (*e.g.*, antihistaminic drugs and hydralazine), while others (*e.g.*, ergot derivatives, phentolamine) were effective against HT and sympathomimetic amines.

Selectivity of a few well-known HT blocking agents has also been studied on autonomic ganglia, which are highly sensitive to HT. Morphine and cocaine showed considerable selectivity against HT as compared to other ganglionic stimulants such as DMPP or nicotine (7a, 167). Atropine and LSD, however, were equally potent against the ganglionic stimulant effects of HT and DMPP. Hexamethonium characteristically blocked only the cholinergic type of ganglion stimulation but not the effect of HT (7a).

In contrast to LSD, which seems to be a relatively poor and non-specific antagonist at autonomic ganglia, some indole compounds are extremely potent and selective inhibitors of HT receptors of nervous tissues (ganglia, chemoreceptors); on isolated smooth muscles these compounds showed only very weak potency (73).

The above information concerning the various selectivities of different antiHT agents indicates that receptors may exist which are quite specific to HT and

TABLE 1

Methods for testing antiHT action

Isolated Organs	Notes	References
	I. DIRECT METHODS	
Heart of different molluscs	Highly sensitive to HT. Some blocking agents (ergot alkaloids, indoles) produce stimulation	36, 57, 179, 180
Isolated artery rings (sheep)	The first isolated organ used for testing HT antagonism. Extensively used in screening antiHT action of indole compounds	121, 122, 143, 146, 195
Isolated artery rings (rabbit)	Besides HT, it is sensitive to epinephrine, norepinephrine, isoproterenol, histamine, and ACh	47
Rat stomach fundus	Very sensitive to HT, but slowly reacting; was used in the evaluation of tryptamine derivatives	2, 172, 173
Rat ileum	LSD, besides blocking the HT action, produces stimulation	96
Rat colon	Sympathomimetic amines are most potent group of blocking agents, but sufficient selectivity has not been observed. LSD, chlorpromazine are also very effective	4, 6, 88
Rat uterus	The most frequently used isolated organ for HT antagonism studies. Highest blocking activity: cyproheptadine, phenothiazines, LSD derivatives	2, 22, 28, 35, 39, 48, 50, 74, 113, 128, 156, 160
Rat kidney (perfused)	LSD, bromo-LSD, and acetyl-LSD have been studied	22, 128
Guinea pig ileum	Extensively used, relatively low sensitivity to LSD and chlorpromazine. The existence of two receptor types (M and D) in this organ has been established	2a, 3, 18, 34, 58, 120, 125
Guinea pig colon	Used for the evaluation of gramine derivatives	119
Guinea pig lung (perfused)	LSD and sympathomimetic amines are highly potent. Antihistaminic agents and atropine are only slightly potent or inactive	7, 91, 161
Guinea pig auricle	Depending on the dose of HT, negative and positive chrono- and inotropic actions can be studied	96
Rabbit ileum	Only LSD, bromo-LSD, and some local anesthetics have been studied as antagonists	151, 156
Rabbit auricle	HT may produce dual effect, acceleration and deceleration. Morphine, cocaine are potent antagonists. LSD is not specific	96, 98a, 167a
Rabbit ear (perfused)	Besides HT, it is highly sensitive to epinephrine, ACh, and histamine	53, 54, 135
Rabbit hindleg (perfused)	The blocking action of several different types of drugs has been studied	102
Cat lung (perfused)	Only LSD and DHE were tested	56
Cat hindleg (perfused)	Only LSD was studied	65
Cat renal vessels (perfused)	Blocking potencies of LSD derivatives parallel those obtained on other isolated organs	65
Cat pulmonary vessels (perfused)	Only LSD and ergotamine were tested	65
Dog hindleg (perfused)	Only LSD was studied	65
Aneural smooth muscle preparation of chick amnion	Suitable for determining the direct muscular action of HT and its antagonism	41
In Vivo Preparations	Notes	References
Mouse, behavioral changes on intraventricular injection	LSD and its derivatives were studied	77
Mouse, antagonism of the HT-induced narcosis potentiation	Positive results do not necessarily indicate that the site of action is the CNS, or that the awakening agent is an HT antagonist	22, 61, 73, 129, 133, 150, 162, 199
Mouse, depression of spontaneous motility	LSD is a potent antagonist. Antagonism can be produced by CNS stimulants which are not antagonistic to HT	13
Mouse, antagonism against HT toxicity	Administration of the histamine releasing agent 48/80 is recommended to potentiate the toxic effects of HT	40, 165
Mouse brain edema produced by HT	Reserpine is a potent antagonist	14

TABLE 1—*Continued*

In Vivo Preparations	Notes	References
Rat, conditioned response; depression of	Only LSD was studied	27
Rat, antidiuretic action	Many of the blocking agents also produce antidiuretic effect	30, 35, 36, 38, 39, 171
Rat, BP	Pithed or ganglionically blocked animals are needed	31, 132
Rat, ulcer of the stomach	All except the LSD type blocking agents are weak antagonists	185, 186
Rat, defecation	Dibenamine was found to be effective	38
Rat, paw edema	Most active blocking agents are LSD and congeners	4, 33, 90, 103, 115, 116, 163, 164, 176
Guinea pig bronchospasm	HT administered in 1% aerosol or i.v. Most potent antagonists were the LSD derivatives	83, 84a, 88, 92
Rabbit BP	Biphasic response to HT. Only *BAS* (1-benzyl,2-methyl,5-methoxytryptamine) was studied	87
Cat, spinal, BP	Three phases of the HT blood pressure reaction can be distinguished. LSD and phenothiazines have been studied	74, 132, 178
Cat, BP under ganglionic blockade	Mostly phenothiazines were studied	74, 140, 189
Cat, superior cervical ganglion-nictitating membrane preparation	Actions on the nictitating membrane and on the ganglion can be differentiated by the injection technique	95, 166, 167
Cat, inferior mesenteric ganglion preparation	Morphine, cocaine are potent and selective antagonists. LSD is not selective and relatively weak	7a
Cat, behavioral and EEG changes on intraventricular injection	LSD, ergotamine, morphine, and indole derivatives were studied. No antagonism between HT and LSD was observed	11, 12, 141
Dog, BP	Action of HT is usually biphasic. In order to produce pure pressor response ganglionic blockade is required. LSD, cyproheptadine were the most potent antagonists	35, 114, 139, 145, 146, 160
Dog, pulmonary BP	The pulmonary vascular system is very sensitive to HT and may offer certain advantages in testing antiHT agents	127
Dog, urinary bladder (*in situ*)	Similarly to the guinea pig ileum, two receptor sites can be distinguished. Actions of HT on the tonic changes produced by pelvic nerve stimulation can also be studied	38, 72
Dog, gut villi (*in situ*)	Most active antagonist: LSD	98
II. INDIRECT METHODS		
Mouse, antagonism against 5-HTP-induced defecation	BAS and phenoxyethylamine derivatives were tested	190, 191
Mouse, antagonism against reserpine-induced narcosis potentiation	Probably more specific for centrally acting HT-antagonists than the HT-narcosis potentiation method. LSD potent, bromo-LSD inactive	73, 162
Mouse, cat, dog antagonism against 5-HTP-induced excitement in iproniazid treated animals	Most potent antagonist: chlorpromazine. General depressants of the CNS should be excluded when analyzing antiHT agents	24, 45
Mouse, rat and rabbit, antagonism against the excitement produced by reserpine plus iproniazid	Chlorpromazine and phenoxybenzamine were potent antagonists	24, 45, 149

vary markedly from organ to organ. This heterogeneity of the HT receptors might be used as a tool for establishing groups of HT antagonists classified according to their type and sites of antiHT action. Since, at present, no such classification of antagonists to HT exists, the only way to enumerate and describe these agents is to group them according to their chemical structures.

II. METHODS FOR TESTING ANTI-HT ACTION

Almost as many pharmacological methods have been employed in measuring antiHT action as for assaying the actions of HT. Studies dealing with the mechanism of action of HT have often entailed the use of the HT blocking substances for characterizing the HT receptors of the organs. Unfortunately, primary emphasis was usually directed to qualitative rather than quantitative aspects of antagonism. Since the currently employed methods have afforded little insight into the exact mechanism of the antagonism, it is doubtful whether these methods will remain the methods of choice. There is great interest in the possible role of HT in mental functions and the actions of its antagonists on the central nervous system. It is obvious that an almost exclusive use of isolated smooth muscle organs for testing antiHT action is inadequate in this regard.

Since injected HT does not produce very characteristic changes in the function of the CNS (112, 113), the majority of methods used for investigating the antagonism of "central" HT effects usually employ endogenous HT which is formed in excess when large doses of 5-hydroxytryptophane (5-HTP) are injected. The HT content of certain organs, in particular the brain, can be increased by two methods: 1) 5-HTP treatment, and 2) inhibiting the oxidative deamination of HT by administration of MAO inhibitors, and mobilizing the HT from its tissue depots (24, 45, 148). Therefore, the methods used for investigating the actions of HT and its antagonists in the CNS can be divided into two groups: 1) direct methods, using HT, and 2) indirect methods, employing 5-HTP, MAO inhibitors, HT liberators, and their combinations.

The approach chosen for the selection of a method has been to consider all of the methods hitherto used for testing antiHT agents. Most of the available biological methods are enumerated in Table 1.

III. CLASSES OF DRUGS HAVING ANTI-HT PROPERTIES

A. Ergot alkaloids and derivatives

1. Ergot alkaloids. Ergot derivatives were among the first compounds used as antiHT agents. The antagonistic action of ergotoxine on isolated sheep artery rings (195) and the same action of dihydroergotamine (DHE) on the isolated rat uterus and perfused rabbit ear (35, 42) were first recognized eight years ago. Later, a comparison of the actions of a few additional ergot alkaloids was made (55). A complete study of the antiHT potency of natural and dihydrogenated ergot alkaloids has only recently been published (21). Most of these alkaloids show a highly selective action against HT on the isolated rat uterus. Ergonovine and methylergonovine have been found to be about three thousand times, and DHE (21) three hundred times more potent against HT than against ACh. The most potent ergot alkaloids belonged to the ergonovine group. Methylergonovine and dihydromethylergonovine approached the potency of LSD; ergonovine and dihydroergonovine also exhibited considerable efficacy. Members of the ergotamine group were weaker and showed only 3 to 11 % of the potency of LSD. The natural and dihydrogenated alkaloids of the ergotoxine group were the weakest with less than 5 % of the potency of LSD (21).

On the rabbit ear preparation, DHE and ergotamine were found to be somewhat less potent than LSD (54). Reports on the potency of ergonovine on this preparation are ambiguous (135, 142).

Dihydroergotamine behaves similarly to LSD on the isolated guinea pig ileum. Each has a relatively slight potency and blocks the muscular (D) but not the nervous (M) receptors (58). Dihydroergotamine was found highly effective on the perfused cat lung preparation (55) but only slightly active *in vivo* against HT aerosol-induced bronchoconstriction in guinea pigs (83). In addition, it was unable to antagonize the positive inotropic action of HT on the isolated rabbit auricle (98a).

Many antiHT compounds which are potent *in vitro* are only slightly potent against the HT-induced BP rise, but ergotamine is an exception. It is very potent in blocking and reversing the BP rise produced by HT in cats and dogs (132, 114). Its antiHT action on the pulmonary vessels of the cat is, however, not specific (65). The antidiuretic effect of HT, which is probably due to its action on renal arteries, is effectively inhibited by DHE and by the hydrogenated alkaloids of the ergotoxine group (35, 38). Dihydroergotamine and ergotamine were very weak antagonists of HT as compared to LSD on the rat paw edema test (33).

As far as the central effects of HT are concerned, some ergot alkaloids showed interesting antagonistic properties. Ergonovine, although less potent than LSD on isolated organs, effectively antagonized the CNS actions of HT (59). Unlike LSD, the mixture of hydrogenated ergotoxine alkaloids (Hydergine) offered no antagonism against the narcosis-potentiating effect of HT on mice (16). Ergotamine and LSD were found to be ineffective against the excitatory actions of the reserpine-iproniazid combination (26). The excitatory actions of this drug combination were attributed to HT which is liberated by reserpine and potentiated by iproniazid. Ergotamine, like some other known antiHT agents, was found to be ineffective against the flushing attacks in carcinoid patients (155).

Elymoclavine and Agroclavine, two recently developed derivatives of lysergic acid, merit attention because they are at least ten times more potent than LSD in awakening mice from reserpine sedation; at the same time they exhibit weaker antiHT action than LSD (198).

2. d-Lysergic acid diethylamide (LSD). Isolated organs. The intensive antiHT action of LSD has been known since 1953 when this action was first investigated because of its structural similarity to HT (48). Lysergic acid diethylamide is a potent antagonist on many isolated organs—its pA_2 value on the isolated rat uterus has been found to be 8.7, but the degree of blockade changes appreciably with the exposure time (54). Because of the fairly high specificity of LSD on the rat uterus, it has been used extensively by many investigators as a reference standard for evaluating the relative potency of other antiHT drugs (21, 22, 40, 59, 135, 160, 176). It was reported to have not only HT blocking action on the rat uterus but, in minute amounts, it also potentiated the effect of HT (28). On some molluscan hearts both LSD and HT have stimulant properties, whereas on some others (*e.g.*, *Cordium edule* and *Spisula solida*) a blockade occurs (57). The uterus of the mouse became extremely sensitive to HT after the ani-

mals were pre-treated with egg white; LSD blocked the action of HT on these sensitized mouse uteri in concentrations of 1 to 3 μg/l (43). Although it is fairly potent in inhibiting the HT-induced spasm of the isolated ileum of the guinea pig, duodenum of the rat (19), and the isolated ureter of the pig (25), its action is less specific and weaker on these organs than on the uterus of the rat (53, 55). It is highly active in preventing the smooth muscle spasm produced by HT in different isolated bronchial and lung preparations (7, 56, 91). In somewhat higher concentrations (in the 10^{-6} to 10^{-7} range), LSD has been found to inhibit the positive chrono- and inotropic actions of HT on isolated rabbit and guinea pig auricles (96, 98a, 167a).

Cardiovascular actions. On the rabbit ear preparation, LSD was found to be effective in 1 to 10 μg/l concentrations, thus being one of the most potent and probably most selective antiHT agents (55, 102, 135). It prevents the vasoconstrictor action of HT on many other vascular systems such as the perfused hindleg preparations of the dog and cat (22, 65, 128); it is somewhat less potent on the renal and pulmonary vessels (22). The antidiuretic action of HT, which is attributed to its renal vasoconstrictor action, is effectively blocked by LSD (31). The increased capillary permeability induced by HT was also antagonized by it (79). Lysergic acid diethylamide exhibits a wide range of potency on the systemic arterial blood pressure of different animals. On pithed rats and on ganglionically blocked dogs, doses of 5 to 10 μg/kg, i.v., were reported to be effective in blocking the pressor action of HT (132, 160), whereas on the same type of cat preparation doses up to 0.4 mg/kg were ineffective (132). Only relatively high doses of LSD were effective against the HT-induced rise of pulmonary pressure in dogs (127). The BP drop and respiratory stimulation produced by HT as a carotid sinus reflex are also fairly resistant to LSD (64). This is one of the examples that LSD is a relatively poor antagonist of nervous receptors sensitive to HT.

Effects of LSD on the nervous system. The most extensively studied facet of the pharmacology of LSD deals with its action on the central nervous system. Lysergic acid diethylamide was found to be an extremely potent hallucinogenic drug. Only later was its antiHT action discovered, and investigations were undertaken to correlate these two different effects; however, no satisfactory relationship has been obtained (53, 113). It is questionable whether the biological techniques employed for testing the antiHT action of LSD *in vitro* were suitable for elucidating such a relationship.

5-Hydroxytryptamine, when given intraventricularly to mice, produced excitatory actions followed by stupor. Lysergic acid diethylamide and some of its derivatives prevented these actions of HT (77). Hydroxytryptamine in large doses produced catalepsy and depression in rats, cats, and dogs; these effects were antagonized by LSD (13, 59, 131). This antidepressant action of LSD, however, can hardly account for its antiHT and hallucinogenic actions, because drugs which do not have appreciable antiHT or hallucinogenic actions, such as ergotamine, morphine, and amphetamine, were also potent in this respect (59). On the other hand, some fairly potent antiHT drugs like bromo-

LSD, methyl-medmain, and 5-benzyloxygramine were ineffective against the HT stupor (59). The conditioned pole climbing response of rats, which is depressed by HT, could be restored by LSD (27). In studies of the EEG and behavioral changes in cats produced by HT, LSD, and a combination of the two, no antagonism has been found between them (11, 141). The results obtained were rather suggestive of a synergism between LSD and HT (11). Hydroxytryptamine in large doses potentiates the effect of different hypnotic drugs (*e.g.*, hexobarbital, pentobarbital, ethanol) probably by a central mechanism, and LSD is capable of antagonizing this narcosis-potentiating effect (61, 73, 123, 133, 150, 162). Although both the mechanism of potentiation of HT and its antagonism by LSD have been studied intensively, these phenomena are not well understood (16, 23, 129, 133, 150, 199). The hallucinogenic action of LSD cannot be ascribed fully to its antiHT action alone because: a) not only LSD, but other hallucinogenic and non-hallucinogenic LSD derivatives were found to be potent in antagonizing the action of HT on sleeping time (128, 133, 162), b) although LSD shortens the HT-potentiated hypnosis time it also shortens the duration of hypnosis elicited by hexobarbital alone (199), and c) certain CNS stimulants (*e.g.*, tetrahydronaphthylamine) antagonize the prolongation of sleeping time by HT (51, 117, 128). In general, it seems that the potentiation of narcosis by HT is not specific and can be antagonized by a fairly large variety of drugs. Furthermore, certain restrictions must be placed upon the value of the above findings because: 1) the blood-brain barrier was found to be practically impermeable to HT (*cf.* 113), and 2) HT, even when given intraventricularly, failed to produce significant changes in the EEG recordings and did not markedly influence the behavior pattern of animals (10), whereas many antiHT drugs do have definite influence on the EEG and behavior (12, *cf.* 113). In view of the above statements, it seemed to be more appropriate to investigate the actions of endogenous rather than of exogenous HT with respect to antagonism by LSD.

In contrast to the findings with injected HT, reserpine-produced potentiation of hypnosis is not antagonized by peripherally acting antiHT drugs (23, 73). Antagonism against this latter type of narcosis potentiation can be obtained by certain central stimulants and only by those antiHT drugs which have, besides their antiHT properties, a characteristic (*i.e.*, hallucinogenic or antidepressant) central action. Thus, within the group of lysergic acid derivatives, LSD was potent in counteracting the reserpine-hexobarbital narcosis potentiation, whereas bromo-LSD, which did not share the hallucinogenic property of LSD, was inactive (22, 23, 162). In the Siamese fighting fish, both reserpine and LSD produced sedation; the two compounds, when given together, acted synergetically (169). Hydroxytryptamine produced a decrease in the O_2 consumption of the rat brain, but this was not influenced by LSD (159). Initially, LSD potentiated, and later antagonized the effects of HT on the flexor reflex of spinal cats (153). Its blocking action against HT on the inferior mesenteric ganglion of the cat is not specific (7a).

Other organs. Lysergic acid diethylamide was found to be one of the most

effective of the antiHT agents studied on the following test objects: 1) prevention of HT-bronchospasm in the guinea pig and cat (83, 92); 2) intestinal villi of the dog (98); 3) rat paw edema test (33, 103); 4) HT-induced stomach ulcer of the rat (34, 185). An antagonistic interaction between LSD, or its derivatives, and HT, has been reported on the pigment cells of the guppy fish. In this test, HT antagonized the pigment cell-expanding effect of LSD and of certain other LSD derivatives (5, 20). A study of the anti-tumor action of LSD and some of its derivatives showed that this effect is proportional to the antiHT potency of these agents (142). Although in man it inhibited the output of HT in the urine (126), it did not influence any of the symptoms in carcinoid tumor patients due to increased HT production (155).

3. LSD derivatives. About 40 derivatives of LSD have been synthesized and investigated. A few of these surpass LSD in antiHT potency but none has more pronounced psychotomimetic effects. The best known derivative of LSD is one of its bromo analogues, 2-bromo LSD (BOL), which is approximately as potent as LSD on isolated organ preparations (3, 22, 128, 156, 173). It blocked the pressor and vasoconstrictor effects of HT (31, 127, 132) about as effectively as LSD, although marked variations between different species were reported (32). In the perfused rabbit ear preparation, BOL proved to be about ten times weaker than LSD (135). It was also considerably less potent in the rat paw edema test (33, 115, 116). Bromo lysergic acid diethylamide, in spite of its potent peripheral antiHT action, is frequently inactive in tests measuring its action on the CNS; for example, the depressant action of HT on cats is not antagonized by BOL but only by LSD (59). Although the potentiation by HT of hexobarbital narcosis was antagonized by BOL (132), reserpine-hexobarbital narcosis was unaffected by it (23, 73); but the opposite effect was also reported (132). These contradictory results may well be explained by the variation in the dosage schedule employed by the different investigators. The negative results with BOL on the CNS are consistent with the absence of hallucinogenic properties (128). Bromo lysergic acid diethylamide inhibits the ascorbic acid-depleting effect of HT on the adrenals, this effect probably being mediated through the hypothalamic-hypophyseal system by preventing ACTH mobilization (105). In spite of its powerful antiHT effects, BOL was completely inactive against the clinical symptoms of carcinoid tumors which were due to increased HT secretion (155). Of the other derivatives of LSD, five more (*i.e.*, acetyl-LSD, 1-methyl LSD, 1-methyl,2-bromo LSD, *d*-lysergic acid cyclobutylamide, and 1-methyl-*d*-lysergic acid butanolamide) were found to be very potent antagonists of HT on isolated organs (rat uterus and duodenum) (21, 40, 129, 175). The sizable number of LSD derivatives recently synthesized has offered the opportunity for SAR studies. Most of these compounds were investigated on the rat uterus and rat paw edema test. From these studies it can be concluded that: a) lysergic acid monoalkyl amides are generally slightly less potent than LSD (21); lysergic acid cycloalkylamides are about as active as LSD on the rat uterus but are weaker in the paw edema test (176); b) among the dialkylamides of lysergic acid, the diethylamide has the peak potency; other dialkylamides are

3 to 4 times less potent; compounds in which the amino group is a member of a cycloalkyl ring are considerably less effective than LSD (21, 22, 66); c) *l*-lysergic acid derivatives are much less potent than the corresponding dextrorotatory compounds; d) substitutions on the ring system of the lysergic acid derivatives, such as bromination at the 2-position or methylation at the 1-position, or both, resulted in compounds more potent than LSD, whereas other substitutions yielded less potent compounds; e) saturation of a part of the ring of lysergic acid resulted in weaker compounds (21, 128).

In the rat paw edema test, a few lysergic acid oxyalkylamides (lysergic acid butanolamide, 1-methyl-*d*-lysergic acid propanolamide, and 1-methyl-*d*-lysergic acid butanolamide) were more potent than LSD (33, 40). Some compounds showed a marked difference in potency when their antiHT actions were compared on the isolated rat uterus and in the rat paw edema test (33). Acetyl-lysergic acid diethylamide was found to be as potent an antiHT agent as LSD *in vitro* and *in vivo* (22, 77); it also produced psychic effects in man similar to that of LSD (128). 1-Methyl lysergic acid diethylamide exhibited a potency two hundred times that of LSD in antagonizing the HT-potentiated hexobarbital hypnosis (21). 1-Methyl-*d*-lysergic acid butanolamide also was considerably more potent than LSD in this respect (40). The pyretogenic action of 1-methyl LSD was, however, weaker than that of LSD (21).

B. Indole and related compounds

Indole compounds. A large number of different indole derivatives has been found to have antiHT action. These derivatives of indole can be divided into three subgroups: 1) derivatives of indole (37, 39, 55, 93, 119, 143, 144, 186), 2) derivatives of gramine (3-(aminomethyl)-indole) (2, 37, 39, 55, 57, 58, 119), and 3) derivatives of tryptamine (3-(2-aminoethyl)-indole) (2, 37, 55, 87, 145, 146, 150, 160, 161). In the first group the following four proved to be the most active: 5-methylamino indole; 2-methyl,3-ethyl,5-methylamino indole; 2-methyl,3-ethyl,5-dimethylamino indole (medmain), and 1,2 dimethyl,3-ethyl, 5-dimethylamino indole (methyl medmain). These compounds were among the first antiHT drugs synthesized with the aim of producing antimetabolites which are structurally related to HT (144). All members of this series, however, are less potent than the alkaloids of the ergot type which also have the indole nucleus as a part of their molecular structure.

Reports concerning the activities *in vitro* of some of these indole derivatives were not consistent (39, 144). Of the compounds mentioned, medmain and methyl medmain have been subjected to the most intensive investigations. The action of the former was found to be competitive against HT, but it was also reported that its action was not reversible on isolated sheep artery rings (144). Medmain in large doses exhibited stimulant properties on the isolated rat uterus, whereas its methyl derivative did not show such action (144). *In vivo*, large doses of medmain were needed to antagonize the cardiovascular effects of HT in the dog. Methyl medmain offered some advantages over medmain (144). Two compounds structurally similar to medmain (2,3 dimethyl-5-aminoindole

and 2-methyl-3-ethyl-5-aminoindole) have been found to be ineffective in man as hypotensive agents (86).

The most potent members of the gramine group were 2-methyl,5-chloro gramine, 2-methyl,5-bromo gramine, and benzyloxygramine (119, 174). These active gramine derivatives were more potent on isolated organs than the most active members of the previously discussed indole group (39). Gramines were compared for their actions on the rat uterus *in vitro* and against the antidiuretic effect of HT *in vivo*, but there was no correlation between the *in vitro* and *in vivo* potencies (39). 2-Methyl,5-chloro gramine, which was promising on the basis of studies on isolated organs, showed only a slight blocking effect on HT-induced hypertension in the dog (39).

Tryptamine is capable of interfering with HT by rendering the HT receptors insensitive to HT (49, 172). Since HT is similarly antagonistic to tryptamine, it was postulated that they affect the same receptors (49).

Of the *tryptamine* derivatives, the best known are BAS (1-benzyl, 2-methyl, 5-methoxytryptamine) and BAS phenol (the corresponding 5-OH derivative). They did not exhibit high potency on isolated organs (146, 161), although BAS selectively blocked HT (2, 160). 1-Benzyl,2-methyl,5-hydroxytryptamine characteristically inhibits only HT-induced effects on blood pressure in the dog, and does not modify the actions of tryptamine, epinephrine, and norepinephrine (148). It also could be used to distinguish between the effects of two stimulant compounds: the HT-like 5-hydroxy 3-indoleacetamidine and the tryptamine-like 3-indoleacetamidine; it blocked selectively the effect of the first more than that of the second (196). Although BAS was found to be effective against the HT-induced rise of blood pressure in dogs, it generally was much less potent than LSD or chlorpromazine (160). BAS phenol was effective in small doses when given orally to dogs (148), but it also had significant HT-like stimulant action on the blood pressure. This action was antagonized by BAS (148). The diarrhea in mice produced by 5-HT was inhibited by BAS and BAS phenol. Like reserpine, BAS was capable of mobilizing HT from blood platelets. This effect led to the suggestion that antiHT and HT-releasing actions may parallel each other (193). Because of the enthusiastic reports on BAS in animal experiments, it has also been studied clinically; a tranquillizing action was found, but it was accompanied by marked side-effects (130). Although BAS produced convulsive-like, non-spreading electric discharges in the hypothalamus of the rabbit, it did not influence human EEG patterns (123). When given continuously (i.v. or orally), BAS reduced the cardiovascular and respiratory effects of HT in patients, but antihistaminic agents with a very low antiHT action were also found as effective (85). Reserpine, which has been found potent against HT in certain isolated organs (6, 28), was ineffective in human beings (85). When BAS was tried in hypertensive patients, a mild, reserpine-like, hypotensive effect was observed (187, 188). The question of whether its clinical action was due to its antiHT properties is still unsolved. It was ineffective against the flushing reaction produced by HT in normal individuals and in carcinoid tumor patients (138). The only drugs which offered some relief from the symptoms of

these patients were chlorpromazine and 1-methyl-*d*-lysergic acid butanolamide (methysergid) (40, 138).

A bufotenine derivative, benzyl-dimethyl-bufotenine (BAB), which is very similar in structure to BAS, was reported to be highly active on the isolated rat uterus and on 5 HT-induced diarrhea in mice (145, 191). When fed to dogs for four days or given i.v., BAB prevented the BP rise produced by HT (145). Although it had approximately the same type and degree of antiHT properties as BAS (145), it produced different changes in the EEG pattern of the rabbit (123). Little or no activity against HT has been found with BAS or BAB on the isolated guinea pig lung and on the rabbit auricle (106, 161). A recently investigated derivative of HT, 1-(*p*-methoxybenzyl)-2-methyl-5-hydroxytryptamine, which is the *p*-methoxy analogue of BAS, had a significantly higher potency than BAS on the isolated rat uterus and dog blood pressure responses; it was also relatively potent in the rat paw edema test (160). Among a new series of derivatives of 1-benzyl-2-methyl tryptamine, the 1,10-decamethylene-bis-5-oxy-, the 5-oxyacethydrazide-, and the 5-(*p*-methoxybenzyloxy)-derivatives had higher potencies than BAS (192).

Carbazol derivatives. Of this group (55, 133, 147), 6-N,N-dimethylaminoethylcarbazol was found to be most active *in vitro*. In dog experiments, another member of this series, 6-N-phenyl carboxamidino-1,2,3,4-tetrahydrocarbazole, showed the highest potency in blocking the HT-induced blood pressure rise in doses as low as 0.14 mg/kg, i.v. It is worthy to mention that 9-benzyl,6-N,N-dimethylamino-methyl-carbazole, which did not show significant antiHT action, proved to be potent in evoking behavioral effects in dogs (147).

Carboline derivatives. Of the naturally occurring carboline alkaloids, harmine, harmane, harmaline, harmol, and harmalol have been studied. While harmane was reported to be quite potent, harmine showed considerably lower activity on isolated artery strips (143, 197). On the isolated rat uterus the order of activity was the following: harmine, harmane, harmaline, harmalol (73). These compounds did not show appreciable antiHT potency against diuresis in the rat or on the isolated rat uterus (37). In spite of its moderate action *in vitro*, harmine was highly potent in antagonizing the potentiation of narcosis produced by reserpine (73). Harmine, like bromo-LSD, illustrates that antiHT action and the action against the potentiated hypnosis produced by reserpine are phenomena not necessarily related to each other.

C. Antihistaminic agents

The structural resemblance between histamine, tryptamine, and HT initiated the first attempts to investigate blockade of HT action by using antihistaminic agents (69, 120). Although a few commonly known antihistaminic agents were shown to have antiHT and antitryptamine potency, the findings were not utilized in the search for new antiHT agents. Systematic studies concerning the antiHT spectrum of antihistaminic drugs have only recently been accomplished (32, 137). The most common types of antihistaminic agents, the substituted ethylenediamines, have generally been found to be moderately potent (7, 32,

33, 54, 68, 82, 102, 120, 137). However, antihistaminic agents belonging to the phenothiazine type showed pronounced activity (but some members of this group are only very weak antihistaminic agents). Some compounds of the iminostilbene, iminodibenzyl, and dibenzothiazepine groups, which were originally studied for antihistaminic action, exhibited significant antiHT potency (Table 2). In general, antihistaminics are potent against HT only in tests *in vitro* and they exhibit little or no activity *in vivo* against the bronchoconstrictor and paw edema-producing effects of HT (32, 83, 116). It is interesting that although these agents do not prevent the action of histamine on gastric secretion, some of them (*i.e.*, antazoline, pyrilamine) inhibit the HT-induced increased secretion and acidity (17), whereas others (*i.e.*, meparine) do not (34). A recent comparison between the antihistaminic and antiHT actions of different drugs showed that the ratio between the two potencies (based upon isolated gut experiments) may vary markedly. Certain antihistaminic agents are almost as potent against HT as against histamine (137). A recently developed compound, cyproheptadine (1-methyl-4,5-dibenzo[a,e]cycloheptatrienylidine piperidine HCl), exhibits these blocking properties in an extremely high degree (160). Its antiHT action is equal to, and in a few tests even surpasses, that of LSD. The antihistaminic potency is also very marked on the dog blood pressure responses and against bronchoconstriction in the guinea pig (160). This compound was tested clinically and found to be a potent antihistaminic agent in dermatological patients (89a, 99). In spite of its intensive antiHT properties in animal experiments, no major effects on human behavioral and mental status (9) except somnolence (89a) have been reported.

D. Phenothiazines and related drugs

Of this group of compounds, chlorpromazine (CPZ) was the most extensively studied. Because of its manifold pharmacological actions it is generally not considered to act primarily as an HT antagonist; it must be taken into account, however, that in some organs its HT blocking capacity is extremely high and usually more pronounced against HT than against any other biogenic amine. The high degree of HT antagonism elicited by CPZ (4, 28, 60, 71, 74), and the correlation between the intensity of psycho-sedative and antiHT actions of certain phenothiazines (29a, 74) suggest that the antiHT effect should be considered in the mechanism of its pharmacological actions. Chlorpromazine was found to be the most potent of the HT antagonists on the isolated rat uterus (74) and on the perfused peripheral vessels of the rabbit (102). It was active also on the rat colon (4, 6, 60), but much less potent on the guinea pig ileum (34). In the spinal cat and the cat under ganglionic blockade, CPZ was effective against HT but its action was not specific (74). The action of HT on the nictitating membrane of the cat is antagonized by CPZ administered either locally (95) or systemically (73, 74). It has been reported to prevent HT-induced myocardial infarct formation (15) and brain edema in mice (14). In contrast to its potency on isolated organs, in intact animals CPZ was relatively weak and quite inferior to LSD. It was only slightly potent against HT-induced rat paw edema

(33, 116, 160), bronchospasm in the guinea pig (91, 102, 137), and antidiuresis in the rat. It was ineffective against the hypothermic effect of HT on rats (84).

Certain pharmacological actions of CPZ have been attributed to antagonism of endogenous HT (24). Endogenous HT can either be liberated from its tissue depots by certain drugs (*e.g.*, reserpine), or be formed by administering 5-hydroxytryptophane (5-HTP) in large doses. Although CPZ did not change the amount of HT in the tissues of rabbits after 5-HTP administration (29), it blocked the behavioral (148) and EEG changes (29) produced by 5-HTP. Likewise, CPZ proved to be highly potent in preventing the iproniazid-reserpine induced excitation of mice, rats, and rabbits (24, 45, 148). It is important to note that CPZ was the only compound which produced relief of some symptoms in patients with carcinoid tumor (152, 155), in whom signs of an excessive HT-output occur. Other compounds, such as BOL and BAS, previously claimed to be specific and potent antiHT drugs (21, 197), proved to be less so or not at all effective clinically (155). The depressant effect of HT on the body temperature of rats was not prevented by CPZ (84). On some isolated organs, promethazine (Phenergan) was about as potent as (74, 102), or even more potent than CPZ (32, 34), but in tests *in vivo* (33, 185) it proved to be inferior to CPZ. There were marked differences in the potencies of promethazine, Diethazine [10-(2-diethylaminoethyl) phenothiazine], and Thiazinamium (trimethyl-[1-methyl-2-(10-phenothiazinyl) ethyl] ammonium methyl sulfate) on the rat uterus and guinea pig ileum tests. In the rat uterus test, several phenothiazine derivatives were slightly or considerably less potent than CPZ (73), whereas in the guinea pig ileum test all these agents were more potent than CPZ (34). Since the guinea pig ileum seems to be less specific for HT than the rat uterus, a non-specific spasmolytic action or another blocking property (antihistamine, antiacetylcholine) of these compounds may have contributed to the apparent blockade. Promethazine was not specific in blocking the increased capillary permeability produced by HT, whereas CPZ blocked it more selectively. Lysergic acid diethylamide showed a higher degree of specificity in this test than did any of the phenothiazines (97).

On the assumption that the antiHT effect of the phenothiazines interferes with the "central" actions of HT, some of these compounds were tested against HT-induced narcotic potentiation in the mouse. No significant antagonism with CPZ, promethazine (73), or diethazine (16, 73) could be demonstrated. It is difficult to assess the antiHT action of CPZ in such a test because of the intensive narcosis-potentiation induced by CPZ itself. In spite of this obstacle, however, some authors could demonstrate a certain degree of antagonism (162) or lack of additive synergism (73) between reserpine and CPZ in the mouse narcosis potentiation test.

Among the newer, recently developed phenothiazine derivatives there are some which have been reported to have marked antiHT potency (78, 116, 137, 160, 163, 184, 189). But the antiHT actions of these and of other chemically related groups of compounds (*i.e.*, iminodibenzyl, iminostilbene (34, 103, 185), and dibenzothiazepine (84) derivatives) were only superficially investigated.

In the tests *in vitro* or *in vivo* or both, some members of these series showed antiHT potencies comparable to or even stronger than that of CPZ (Table 2).

E. Adrenolytic and hypotensive drugs

Of this group of agents, excluding dihydroergotamine which was discussed with the ergot alkaloids, Dibenamine has been studied most extensively. Since HT shows structural similarity to epinephrine and histamine, it is not surprising that Dibenamine, a member of the β-haloethylamine group which is known for its adrenolytic and antihistaminic potencies, also shows antagonism to HT. It must be noted, however, that the antiepinephrine and antiHT potencies do not necessarily parallel each other. There are certain members of this series which are much more potent against epinephrine and norepinephrine than against HT, whereas others block norepinephrine and HT equally well (*cf.* 53). In their specificity, the β-haloethylamines resemble ergotamine and tolazoline, and they differ from piperoxan, which is active against epinephrine and norepinephrine but ineffective against HT (111).

On isolated organs (including the rat uterus (38, 42, 54, 55), rat duodenum (38), rat stomach (172), rat colon (102), rabbit ileum (42), isolated rabbit aorta (47), and isolated hind leg arteries (102)) Dibenamine was found to be highly potent. Its antiHT and adrenolytic actions were both long lasting and difficult to reverse (55). On the other hand, Dibenamine was only moderately potent on the isolated guinea pig lung (7). In some organs it blocked the effect of epinephrine and norepinephrine as much as, or even more than that of HT (47, 55). On the rat uterus it was found to be less selective than DHE (42). *In vivo*, it offered protection against HT aerosol-induced defecation and antidiuretic action in rats (36, 38, 171). Certain cardiovascular effects of HT were resistant to Dibenamine (*e.g.*, the positive inotropic action of HT in the rabbit (56) and the hypertensive effects in cats (46)). The hypotensive effect of HT, however, was effectively blocked by it (154). That Dibenamine may influence certain nervous receptors sensitive to HT is suggested by the observation that it prevents fixation of HT to brain cell mitochondria (177). Yet it was found ineffective *in vivo* in counteracting iproniazid-reserpine induced CNS stimulation in mice (24).

Congeners of Dibenamine have not been systematically investigated. N-(2-bromoethyl)-N-ethyl-1-naphthylmethylamine HBr showed a reduction but not a complete blockade of the BP rise produced by HT (46); it was ineffective against HT-induced tachycardia (100a). Phenoxybenzamine (Dibenzyline), which is known to have stronger adrenolytic potency than Dibenamine, proved to be very potent in the rat stomach and guinea pig ileum preparations (58, 172). On the guinea pig ileum it blocked only the muscular D-type receptors, while the nervous M receptors remained practically uninfluenced by it. Similarly, Dibenzyline showed only very slight antiHT potency on the inferior mesenteric ganglion of the cat, which presumably contains only nervous receptors (7a). In this respect, Dibenzyline resembles LSD and benzyloxygramine; it differs from morphine, cocaine, and atropine which block the M rather than the D receptors.

Yohimbine was one of the first known antagonists of HT. It inhibited reversibly HT-induced vasoconstriction of isolated artery rings (121, 195). Although on other isolated organs (rat uterus (55), rat duodenum (96), rat colon (102), isolated guinea pig ileum (102), and rabbit vessels (102)) it was found to be fairly potent, its action was not usually selective (55). It showed antagonistic actions against the BP fall and rise produced by HT (38, 114, 154), the degree of which, however, varied markedly (114). Yohimbine did not influence the inhibition of diuresis produced by HT in rats (38). It offered no protection, except in large doses, against the bronchoconstrictor effect of HT in the guinea pig (82, 102) and did not block the CNS excitation produced by combined iproniazid-reserpine treatment (24).

Other adrenolytic compounds have been studied less extensively. *Phentolamine* was found to be fairly potent (102) in antagonizing the rise in blood pressure produced by HT (8, 114) and the vasoconstrictor action of HT on perfused rabbit arteries (102). It was fairly inactive against the effects of HT on the isolated rabbit auricle (98a) and against HT-bronchoconstriction in guinea pigs (7, 102). *Tolazoline* showed no antiHT action on the renal vessels of the cat; it inhibited only the actions of epinephrine and norepinephrine (65). *Piperoxan* was one of the least potent HT antagonists of the adrenolytic drugs. Large doses were found to be either ineffective or only slightly effective on isolated organs (38, 42, 54, 68) and in the rat diuresis test (38). Although it reduced the rise in blood pressure in normal, anesthetized dogs, it augmented this response in spinal animals (114). *Azapetine* (Ilidar) was tested only on the rat duodenum, and was found to be only moderately effective (96).

Reserpine is the most extensively studied of the non-adrenolytic hypotensive agents. It was only slightly potent or inactive on isolated organs in comparison with some of the well-known antiHT drugs (6, 19, 28, 102, 107). In relatively low doses it showed long lasting protection against HT-induced bronchoconstriction (102), but it was ineffective in the rat paw edema test (115), against the HT-induced stomach ulcer (185), and also against the hypertensive effect of HT in normal, anesthetized dogs (139). Surprisingly, it was reported to antagonize the cerebral edema produced by HT in mice (14) and the rise in blood pressure induced by HT in spinal, bivagotomized dogs (139). It also counteracted the antidiuretic action of HT (61). *1-Hydrazinophthalazine* was either inactive or only moderately potent on isolated organs (35, 102, 108). It increased the depressor and decreased the pressor action of HT in dogs (114); its inhibitory action seemed to be non-specific (35). In contrast to LSD, it did not block the action of HT on the spinal reflexes (153).

A few ganglionic blocking agents (*i.e.*, tetraethylammonium, pentamethonium, and hexamethonium) were found to be uniformly ineffective against HT (35, 41, 96, 181).

F. Atropine and atropine-like drugs

Atropine exhibited a high degree of blockade against HT (124, 125) almost as marked as against acetylcholine (18, 120) on the guinea pig ileum. In the case of HT-atropine interaction, the characteristic linear dose-response relation-

ship was not observed but a hyperbolic curve was obtained (18). This observation and the difference in the response to atropine of preparations in which HT acts at ganglionic and postganglionic sites, strongly suggest that the interaction between atropine and the receptors sensitive to HT, directly or indirectly, is a complex one; for example, in organs with parasympathetic motor innervation, such as the guinea pig ileum, an inhibition by atropine of a peripheral cholinergic mechanism, activated by HT at the level of ganglia or of viscerosensory receptors, may contribute to the overall effect observed. Therefore, especially in the case of atropine-like agents, the use of isolated ganglia or aneural smooth muscles for studying the nervous and muscular receptors sensitive to HT is of prime importance. It was suggested that on the guinea pig ileum the action of atropine is directed to the M receptors (59). The ileum of the rabbit was much less sensitive to the blocking action of atropine (124). On the aneural smooth muscle preparation of the amnion of the chick embryo, atropine was relatively slightly active, but it was highly potent in blocking the action of acetylcholine (41). On the rat uterus the effective dose of atropine against HT was relatively high (54, 55); atropine and methantheline have been found to be about equipotent on this test organ (110). The actions of HT on the smooth muscle of the respiratory tract are affected differently by atropine: on the isolated guinea pig lung it is a very weak antagonist (7), whereas in anesthetized guinea pigs and cats, moderate doses diminish the bronchoconstrictor effect of HT (84a, 92). In the guinea pig, atropine inhibits HT aerosol-induced bronchoconstriction, but it is much less effective and specific than some other antiHT agents (*e.g.*, LSD (83)). It is highly potent against the negative chrono- and inotropic actions of HT on isolated guinea pig auricles (96). Atropine is ineffective against HT-induced tachycardia (100a) and apnea (181) in the dog, stomach ulcer formation in the rat (185), and against the increased motility of intestinal villi induced by HT (98). On the guinea pig ileum preparation, atropine, in its strong inhibitory action, shows a similarity to cocaine and morphine; but, on the superior cervical and inferior mesenteric ganglia of the cat and in the pelvic nerve bladder preparation of the dog, unlike morphine and cocaine, it was found to be either not specific or inactive against the stimulant actions of HT (7a, 72, 167). That atropine may interfere with some of the actions of HT in the central nervous system is indicated by the finding that it is capable of antagonizing the HT and pentothal-induced potentiated narcosis in rats (16).

The few other cholinergic blocking agents (Table 2) which have been investigated as possible antagonists for HT were about as potent as or less potent than atropine on isolated organs.

G. Local anesthetics

Procaine. On different test organs (rabbit ileum, guinea pig ileum, cat trachea, rat uterus, and rabbit auricle), procaine had only a moderate degree of blocking action; the EC50 for these isolated organs varied between 2×10^{-4} and 5×10^{-7}, with the cat tracheal chain preparation the least sensitive and the rabbit auricle the most sensitive (151). In another comprehensive study including

several isolated organs, procaine was found to be ineffective (96). The main site of procaine action was assumed to be at the preganglionic portion of the autonomic nerves. According to this theory, procaine does not act on those organs where the action of HT is ganglionic or postganglionic (96). On the perfused rabbit leg vessels, procaine proved to be inactive (102); *in vivo*, it inhibited the bradycardiac effect of HT in different species (140).

Other local anesthetic agents. Comparison of procaine with some of the other well-known local anesthetics on different isolated organs proved that the antiHT potency was proportional to their local anesthetic activity (151). Of these agents, cocaine was the most intensively investigated. It showed no blocking action, but only potentiated the response to HT on isolated artery rings (121), and on the nictitating membrane of the cat *in vitro* (164a) as well as *in vivo* (76). Large doses (5 to 10 mg) blocked the HT effect on the nictitating membrane and on the superior cervical ganglion (166). On intraarterial administration, 40 to 200 μg doses of cocaine blocked the stimulant action of 5-HT, but not that of DMPP, on the inferior mesenteric ganglia of the cat (7a). Even in very high doses, it was unable to inhibit the pressor action of HT in the dog (114). Tetracaine inhibited the reflex apnea produced by HT (181), but, like procaine and dibucaine, did not prevent the direct bronchoconstrictor effects of HT in the guinea pig (88, 181); in the same test, tetracaine was also effective against histamine (44).

The latter results point to the fact that local anesthetic drugs do not have significant inhibitory action against HT at the peripheral HT receptors; they interfere only with those actions of HT which are of reflex origin or are elicited by stimulation of certain nervous elements sensitive to HT. These elements, however, are usually sensitive also to other stimulants, the actions of which are similarly inhibited by the paralyzing properties of local anesthetics. Thus, the only possible conclusion is that the blockade against HT elicited by most of these drugs is not specific.

H. Morphine-type analgesics

The belief that morphine does not possess an inhibitory action against HT (129) is probably based on findings obtained with preparations such as the perfused rabbit ear (51, 135, 168) and rat uterus (51, 101), where morphine is, in fact, ineffective. It is highly potent on other test objects, such as the guinea pig ileum (53), the superior cervical and inferior mesenteric ganglia of the cat, and the dog bladder (7a, 72, 101, 167). There is convincing evidence that certain nervous receptors in the guinea pig ileum are blocked by morphine (M-receptors). These receptors are unaffected by drugs which are capable of blocking another type of receptor in smooth muscle (D-receptors), such as LSD, Dibenzyline, and bromo-LSD. It was demonstrated that morphine did not block the smooth muscle of the nictitating membrane, but strongly blocked the actions of HT on the superior cervical (167) and inferior mesenteric ganglia (7a); similar findings were obtained on the pelvic nerve-bladder preparation of the dog: morphine was capable of blocking those HT receptors which were uninfluenced by the D-

receptor-blocking bromo-LSD (72). Studies of the influence of morphine on the central effects of HT (59) have also confirmed the theory that morphine acts at certain HT-sensitive nervous receptors. The overall picture of the blocking action of morphine is still obscure; for example, Gaddum and Vogt (59) found that LSD, which in its peripheral antiHT effects differs from morphine, is also active against the HT-induced CNS depression in cats. Other agents which act peripherally similarly to LSD (*e.g.*, benzyloxygramine, methyl-medmain) are entirely inactive on the CNS. On the other hand, experiments attempting to prevent fixation of HT to brain mitochondria by morphine and LSD showed no effect (177).

Alkaloids of the morphine group and synthetic morphine-like analgesics in most cases have been tested against HT on isolated organs only. On the ileum of the guinea pig, dihydromorphine and methadone proved to be more potent, and meperidine, codeine, and ethylmorphine (Dionin) less potent than morphine (101). Methadone, like morphine, acted mainly but not entirely on the M-receptors (58). Narcotine showed only a slight antagonism against HT on the perfused guinea pig lung preparation (91).

I. Sympathomimetic amines

These compounds also merit attention as HT antagonists. Their action against HT has been tested mostly on isolated organs (7, 88, 172), but there are also observations which show that they may be potent *in vivo* as well (36, 88, 116). Of the catecholamines, isoproterenol (*iso*propylnorepinephrine) proved to be the most effective (61, 88). On isolated rat and guinea pig intestines it was about two hundred times more potent than LSD (88). Minute doses were found to be effective on the isolated rat stomach preparation (19, 172). In larger doses it was capable of preventing the potentiation of nembutal narcosis in mice (61). Epinephrine and norepinephrine were usually less potent than *iso*propylnorepinephrine (88, 172); ephedrine, *d*-desoxyephedrine, amphetamine, and a series of substituted phenoxyethylamines (190) showed negligible antiHT potency (88, 96).

Because of the well-known smooth muscle relaxant properties of sympathomimetic amines, the question arises whether their antiHT effects on isolated smooth muscle organs are due to a pharmacologic antagonism between oppositely acting amines or due to a specific antagonism. This question has not yet been analyzed, but the effectiveness of *iso*propylnorepinephrine against HT *in vivo* suggests that besides a possible pharmacologic antagonism, a specific blocking action may also share in the interaction between sympathomimetic amines and HT.

It is also possible that some physiologically occurring catecholamines, with marked antiHT action on certain smooth muscles, may have a physiologic regulatory role on HT in the organism. It is unfortunate that there are no data available to demonstrate whether catecholamines can influence the action of HT on the CNS. Thus, the very intriguing question of a possible functional

interaction between catecholamines and HT in the CNS remains unanswered at present.

J. Miscellaneous compounds

Members of the following group of compounds do not belong to any of the previously discussed chemical classes. They elicited, in a variety of tests, moderate to marked antiHT potency; the action usually was found to be non-specific. The group includes: acetylcholine (102), acetylsalicylic acid, aminopyrine (164), azacyclonol (28), bulbocapnine (177a), caramiphen (88, 102), cinchophen, cortisone acetate (164), *gamma*-amino-butyric acid (83), heparin (154), kallikrein (102), antipyrine (phenazone), phenylbutazone (164), prednisolone derivatives (200), quinine sulfate (164), sodium salicylate (90, 164), theophylline (88), tyramine (102), and 4-phenyl,2-butyl-hydrazide (67).

Miscellaneous compounds which have been found to be inactive as antiHT agents by the following tests include a) dog blood pressure experiments: colycanthine, lysergic acid, pentamethonium, piperoxan, quinamine, sempervirine, serpentine, TEA, trimethadione (Tridione), and 5-hydroxyindoleacetic acid (111, 114); b) rat uterus and guinea pig ileum: decamethonium, eserine, hexamethonium, mescaline, *p*-phenylbenzylatropinium bromide, piperoxan, and yohimbine (42, 54, 75, 125); c) various other isolated organs: hexamethonium, nicotine, nikethamide, chlorisondamine, pentamethonium, and TEA (88, 96, 102); d) perfused rabbit hindleg: adenosine, caffeine, ephedrine, isoniazid, mescaline, methamphetamine (Desoxyephedrine), methylhydantoin, methylphenidate, neostigmine, pipradrol, phenobarbital, sodium bromide, and *dl*-tryptophan (102, 168); e) rat, against the antidiuretic effect of HT: piperoxan, tolazoline, yohimbine (38); f) against HT bronchospasm in guinea pigs: amphetamine, azamethonium, cocaine, hydralazine, nikethamide, and procaine (88).

K. Potencies of various antiHT agents

Table 2 supplies information concerning the pharmacological potencies of the best known or most potent representative of each chemical group of antiHT agents.[1]

IV. CLINICAL STUDIES WITH HT ANTAGONISTS

Most of these studies were performed on patients with carcinoid tumor, where HT is known as a pathologic factor, or with hypertension, allergic skin diseases, or mental diseases.

In carcinoid tumor patients the compounds were tried with the aim of counter-

[1] A similar but more complete list entitled "Pharmacological Data on Antagonists of 5-Hydroxytryptamine" has been deposited as Document number 6824 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting $6.25 for photoprints, or $2.50 for 35 mm. microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.

TABLE 2

Potencies of various antiHT agents

Compound	Rat		Guinea Pig		Rabbit Ear	Other Tests
	Uterus	Paw Edema	Ileum	Bronchospasm		
ERGOT DERIVATIVES						
ergotamine	4% LSD (21)	very weak relative to LSD (33)			40 μg/l	Rabbit leg vessels EC50: 10^{-7} (102)
dihydroergotamine	11% LSD (21) 4–5* pA_2, 10 min = 6.9 (55) 0.2–0.3 mg/l (38)	very weak relative to LSD (33)	2.5 mg/l (59)	4 mg/kg (82) 25 μg†	20 μg/l	0.2–1.0 mg/kg is effective against the antidiuretic effect of HT (38) in rats. Rabbit leg vessels EC50: 3×10^{-8} (102)
methylergonovine	61% LSD (21)					
dihydroergonovine	58% LSD (21)					

* Drug ratio: ratio of the concentrations of the agonist and antagonist when the response is 50% of the original response previously elicited in the absence of antagonist; based on a single dose of the antagonist (see pp. 403–404). † Isolated lung.

LYSERGIC ACID DERIVATIVES						
d-lysergic acid amide	4% LSD (21)					
d-lysergic acid ethylamide	12% (21, 22)	22% LSD (21)				
d-lysergic acid amylamide	75% (21)					
1-methyl-*d*-lysergic acid propanolamide		259% LSD (21)				
1-methyl-*d*-lysergic acid butanolamide (UML 491)	400% LSD (40)	440% LSD (33)				2 mg/kg protects mice from the 48/80 potentiated toxicity of HT (165)
d-lysergic acid diethylamide (LSD)	10–150 (55)* pA_2 8.5–8.7 0.3–3 μg/l (54) 0.05–1 μg/l (28) 10–20 μg/l (156)	0.1 mg (106) 0.056 mg (33)	5×10^{-8} (102) 0.01 mg/l (59) 10–20 mg/l (156)	0.05 mg/kg (102) 0.02–0.04 mg (82) 0.25–4 μg‡ (7) 1/3–2* (92)	10 μg/l (54) 1 μg/l (135) 0.1 μg/ml† (197)	0.1–0.5 mg/kg effective in rat HT ulcer (34, 185); 2×10^{-7} effective in rat colon; 2×10^{-9} effective in rabbit leg vessels (102)
l-lysergic acid diethylamide	<1/100 LSD (22)					
1-methyl LSD	368% LSD (21)	91% LSD (33)				
2-bromo LSD	1–10 μg/l (156) 150% LSD (22)	28% LSD (33) 4 mg/kg (115)	2 mg/l (156)	5–150 μg‡ (91)	10 μg/l 10% LSD (135)	Drug ratio: 50 on rat stomach (172), 0.5 on rat duodenum (156). 1–1.4 × LSD on rat kidney, cat vessels, bronchi (22)
1-methyl,2-bromo-LSD	533% LSD (21)	26% LSD (33)				

* Drug ratio. † Sheep carotid ring. ‡ Isolated lung.

Compound	Rat Uterus	Sheep Artery Rings	Other Tests
INDOLE DERIVATIVES			
5-methylaminoindole		1:7* (146)	
2-methyl,3-ethyl-5-methylaminoindole		3 (146)	
2-methyl,3-ethyl-5-dimethylaminoindole (medmain)	1/20* (146) 1/60-80* (39)	5* (146) 10 μg/ml	Stimulant on rat and guinea pig uterus
1,2-dimethyl,3-ethyl,5-dimethylaminoindole (methyl medmain)	1/30-50* (39)	5* (146)	
* Drug ratios.			

Compound	Rat Uterus	Guinea Pig		Rabbit Perfused Ear	Other Tests
		Ileum	Colon		
GRAMINE DERIVATIVES					
gramine	1/30-60† (39) 5 μg/l† (55) 10 μg/l† (54)	0.5 μg/l (55)	1/50†(119)	10 mg/l (54)	Weak and reversible antiHT action *in vitro* and *in vivo* in rats (37)
5-benzyloxygramine	1/15† (2) 1/2.4* (55) pA_2 10 min 6.79	0.1 μg/ml (59)			On certain molluscan hearts effective in 1-10 μg/ml (57)
2-methyl,5-chloro gramine	1/3-4†		1/5-1/10† (119)		Slight blocking effect on dog BP and urinary bladder (39)
2-methyl,5-bromo gramine	1/2-4† (39)		1/10-15† (119)		
* Specific. † Drug ratio.					

Compound	Rat Uterus	Guinea Pig Lung	Rat Paw Edema	Other Tests
TRYPTAMINE DERIVATIVES				
N,N-dimethyltryptamine	1/40* (55) 1/500 LSD (2)			Weak, reversible antiHT action in rat diuresis test and in isolated rat uterus (37); antiHT and antihistamine action on guinea pig ileum (2a).
N,N-dimethyl,5-hydroxytryptamine (bufotenine)	10 mg/l†			
1-benzyl,2-methyl-5-methoxytryptamine (BAS)	* 1/30‡ (147) 1/12,000 LSD (160)	slight antagonism in 500 μg *vs.* 35 μg HT (161)		4-8 mg/kg i.v. effective in cat BP; on rabbit less potent and toxic (87)
1-benzyl,2,5-dimethyl bufotenine (BAB)	1/10* (145)	slight antagonism in 500 μg *vs.* 35 μg HT (161)		Highly effective on dog BP (145, 147)
1-benzyl,2-methyl-5-hydroxytryptamine (BAS phenol)				Effective against HT on dog BP in 0.12-0.35 mg/kg i.v. (150) but also produces BP rise
1-(*p*-methoxybenzyl)-2-methyl-5-hydroxytryptamine HCl (hydroxindasol)	1/30 LSD* (160)		ED50: 2.8 mg/kg (160)	Effective against HT on dog BP in 0.25 mg/kg (160)
* Drug ratio. † Specific blockade after stimulation (55). ‡ Irreversible.				

TABLE 2—*Continued*

Compound	Rat Uterus	Sheep Artery Rings
CARBAZOL DERIVATIVES		
5-nitro,1,2,3,4-tetrahydrocarbazole	1/10*†	
6-N,N-dimethylaminomethyl,1,2,3,4-tetrahydrocarbazole	1/10† (144)	1/2† (144)
* Non-specific (55). † Drug ratio.		
CARBOLINE DERIVATIVES		
harmane	Ineffective in 10–20 mg/l (37) 0.4* 10 min† (73)	1 mg/l (143)
harmine	Ineffective in 10–20 mg/l (37) >2* 10 min† (73)	30 mg/l (197)
tetrahydroharmane	10 mg/l‡ (55)	
* Drug ratio. † Time of exposure. ‡ Stimulation followed by blockade.		

Compound	Rat		Guinea Pig		Rabbit	Other Tests
	Uterus	Paw Edema	Ileum	Bronchospasm	Leg Vessels	
ANTIHISTAMINES						
antazoline	0.9% LSD (32)	10 mg (33)		14 mg/kg (137)		
diphenhydramine	1/80* 2.8% LSD (32) 25–1000 μg/l (35, 170)		70–280 μg/l (120)			
phenindamine	3.7% LSD (32)	10 mg (33)		14 mg/kg (137)		
pyrilamine	1/40* 1.2% LSD (32) 0.1–1 mg/l (54)			1 mg/kg† (82) 0.05–2 mg (7)		
thenylpiperidine	26% LSD (32)			7 mg/kg (137) 0.2 mg‡ (91)		
tripelennamine	1.9% LSD (32)	10 mg (33)	5×10^{-7} (102) 6 mg/l (120)	10 mg/kg (102) 2 mg/kg (137)	10^{-6} (102)	10^{-6} is effective on rat colon (102)

* Drug ratio (55). † Isolated lung; 0.5 μg effective on the perfused pig's ear (68). ‡ Perfused lung; 0.1 mg is effective against the HT-bronchospasm in cats (92).

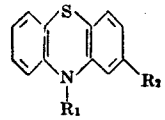
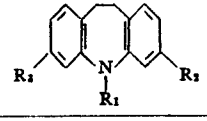
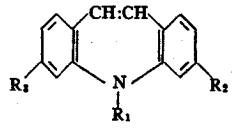
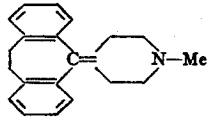
Compound		Rat			Guinea Pig		Other Tests
		Colon	Uterus	Paw Edema	Ileum	Bronchospasm	
PHENOTHIAZINES AND RELATED COMPOUNDS							
							
R_1	R_2						
$-(CH_2)_3-N(Me)_2$ chlorpromazine	Cl	10^{-7} (102)	10^{-7} (25)	5–10 mg (32)	10^{-7} (102)	10 mg/kg (102)	2 × 15 mg effective against rat ulcers (34, 185)
(CPZ)		10^{-8} (4)	48% LSD (32)	1–5 mg (106)		0.95 mg (137)	Rabbit leg vessels (102)
$-CH_2-CH(CH_3)-N(Me)_2$	H	5×10^{-7} (6)	1.8×10^{-12} (74)	0.5–3 mg (5)		50 μg isolated lung (91)	
			94% LSD (32)	5–10 mg (32)	13 × CPZ (34)	1–3 mg (82) 12 mg (137)	Ineffective in rat ulcers (185)
promethazine			6×10^{-11} (74)	0.5 × CPZ (115)		50 μg–2 mg isolated lung (7)	Ineffective in rat paw edema (115) 10^{-8} rabbit leg vessels (102)
$-CH_2-CH(CH_3)-CH_2N(Me)_2$ RP-7044	CH_3O			6 × CPZ (116)			Potent also against the histamine-induced rat paw edema (116)
Iminodibenzyl and iminostilbene derivatives							
							
R_1	R_2 / R_3						
$-CH_2-CH_2-CH_2-N(Me)_2$ imipramine	H / H			50 mg/kg	2.5 × CPZ (34)		2 × 30 mg/kg effective against the HT stomach ulcers in the rat (34, 185)
$-CH_2-CH(CH_3)-N(Me)_2$	H / H				9 × CPZ (34)		

TABLE 2—*Continued*

Compound	Rat			Guinea Pig		Other Tests
	Colon	Uterus	Paw edema	Ileum	Bronchospasm	
						
R_1 / R_2 / R_3						
$-CH_2-CH_2-CH_2-N(Me)_2$ / H / H				5 × CPZ		
$-CH_2-CH(CH_3)-N(Me)_2$ / H / H				16 × CPZ (34)		
 cyproheptadine		EC50: 0.34 μg/l 6 × LSD (160)	30 μg/kg (160)			ED50 on dog BP: 50 μg/kg (160)

Compound	Rat		Guinea Pig		Rabbit		Other Tests
	Colon	Uterus	Ileum	Bronchospasm	Ear	Leg vessels	
ADRENOLYTIC AND HYPOTENSIVE DRUGS							
dibenamine	3×10^{-7} (102)	0.5–10 μg/l drug ratio: 24–50 (55) 5 μg/l (54) pA_2 10 min 7.72 (55)		10 mg/kg (102) 125 μg: feeble action on isolated guinea pig lung (7)	0.1 mg/l		10 mg/kg effective in rats against the antidiuretic effect of HT (38)
phentolamine	10^{-6} (102)		5×10^{-7} (102)	10 mg/kg (102) 0.5 mg isolated guinea pig lung (7)		2×10^{-6} (102)	
yohimbine	5×10^{-6} (102)		2×10^{-6} (102)	10 mg/kg (102) 1 mg/kg (82)		10^{-6} (102)	0.1–0.2 mg/l sheep artery ring (194, 197)

ATROPINE AND ATROPINE-LIKE DRUGS, SPASMOLYTICS

atropine	10^{-5} (102)	0.1-1 mg/l (54) pA_2-5.84 at 4 min (55) 1/200*	10^{-7} (124, 151) 5×10^{-6} (102) pA_{10}-6.31 (62a) 14 μg/l (120) † 10-100 μg/l (18)	10 mg/kg (102) 0.3-1.3 mg (81, 82) 1 mg isolated lung (7) 100 μg/l isolated lung (54)		$>10^{-5}$ (102)	10^{-6} rabbit ileum (124); ineffective against the HT stomach ulcers in rats (185)
papaverine	3×10^{-6} (102)			>10 mg/kg (102)		10^{-6} (102)	Ineffective against the HT stomach ulcer in rats (185)
2-diethylaminoethyl diphenylacetate (adiphenine (R))	3×10^{-7} (102)			>10 mg/kg		10^{-6}‡ (102)	
1-(diethylamino),3-diphenyl, 3-oxypropane methoiodide			pA_{10}-7.43 (62a)				

* Drug ratio. † Superfusion technique. ‡ Hexahydroadiphenine.

LOCAL ANESTHETICS

					Ileum	Auricle	
cocaine	10^{-4} (102)	4.4 × Proc.* (151)	2.5 × Proc. (151) 1-10 mg/l (125)	>10 mg/kg (102)	2.5 × Proc. (151)	2 × Proc. (151)	On cat trachea 4.1 × Proc. (151) On cat sup. cerv. gang. 0.1-0.5 mg i.a. effective (167)
dibucaine	2×10^{-6} (88, 102)	25 × Proc. (151)	9.8 × Proc. (151)	>5 mg/kg (102)	10 × Proc. (151)	10 × Proc. (151)	On cat trachea 7.5 × Proc. (151)
procaine	3×10^{-5} (88, 102)	5×10^{-4} (151)	5×10^{-6} (151) 10 mg/l (59)	>10 mg/kg	10^{-5} (151)	5×10^{-7} (151)	On cat trachea 2×10^{-4} (151)

* Proc. = procaine.

MORPHINE TYPE ANALGETICS

					Ear		
morphine			pA_2-8.58 (101) 1 mg/l (59)		>1 mg/l		On cat sup. cerv. gang. 20-30 μg effective (166). On cat inf. mes. gang. specific blockade (7a)

TABLE 2—*Continued*

Compound	Rat		Guinea Pig		Rabbit	Other Tests
	Colon	Stomach	Ileum	Bronchospasm	Hind leg vessels	
SYMPATHOMIMETIC AMINES						
epinephrine	2×10^{-8} (88)	25 μg/l	2×10^{-8} (88)	1 mg/kg (88) 5 μg* (7)		
isoproterenol	8×10^{-10} (88)	4 μg/l (172)	2×10^{-10} (88)	0.2–1% aerosol† (44) 1 mg/kg (88) 5 μg* (7)	10^{-8} (88)	

* Isolated guinea pig lung. † Effective also against histamine.

acting the symptoms produced by the over-secretion of HT, as manifested by flushing attacks. Ergotamine, LSD, BOL, and antihistaminic agents were found to be ineffective (152, 155). 1-Methyl-*d*-lysergic acid butanolamide (methysergid) had no influence on the flushing attacks or on the excretion of the increased amount of 5-hydroxyindoleacetic acid (5-HIAA) in the urine, but inhibited the diarrhea which regularly occurs in those patients (94). Chlorpromazine was the only compound found to be effective in suppressing most of the symptoms and also in decreasing the 5-HIAA excretion in the urine (26, 152).

Patients with hypertension responded with a decrease in the arterial pressure and with a reserpine-like sedation after receiving 80 to 100 mg BAS orally each day (187, 188). 2,3-Dimethyl-5-aminoindole was ineffective in producing a hypotensive effect (86). A few other antiHT agents were tested on hypertensive patients, including 1-ethyl-3(-2-dimethylamino-1-hydroxyethyl) indole and 1-N′(diphenyl-acetyl-) 1-phenyl-N′ N^2N^2 trimethyl 1-2-propane diamine HCl. Both compounds showed marked side effects, including intestinal symptoms, urticaria, and psychic manifestations. Further studies with these substances were therefore discontinued (188).

Few antiHT agents were investigated on human beings against the vascular reactions elicited by HT; of the compounds studied, 2-methyl,3-ethyl,5-aminoindole and 2-methyl,3-ethyl,5-nitroindole were ineffective against the HT-induced BP rise (158). Tolazoline, when given i.v., blocked the pressor response elicited by HT, but it was also potent against the pressor effects of epinephrine and norepinephrine. On the other hand, it was proved to be ineffective against the vasoconstrictor effect of all these amines on the vessels of the skin and muscles (8). Certain cardiovascular effects of HT were inhibited by BAS given chronically, but antihistaminic agents such as pyrilamine and diphenhydramine were potent in smaller doses than BAS (85). The exaggerated cyanotic vascular reaction induced by HT in patients with rheumatoid arthritis was effectively antagonized by BOL (135a).

A recently developed antiHT drug, cyproheptadine, which also has antihistaminic properties, proved to be superior to antihistaminic agents in antagonizing allergic skin reactions (89a) and pruritic conditions (89b, 99).

As discussed before, the role of HT and antiHT drugs in mental diseases is questionable. Since HT does not produce marked psychological alterations, clinical investigations utilizing a direct HT-antiHT relationship are not possible. Many potent antiHT drugs do not produce behavioral effects in animals or in human beings. However, it should not be forgotten that two drugs, LSD and chlorpromazine, which gained their greatest popularity in pharmacology and clinical psychiatry in the last few years, are outstandingly potent inhibitors of the actions of HT. These two drugs not only antagonize the action of HT but probably also interfere with its metabolism. Lysergic acid diethylamide and chlorpromazine were both shown to decrease the urinary excretion of HT or its metabolite, 5-HIAA (26, 126, 134). It is unfortunate that relatively few clinical studies have been performed on mental patients with antiHT drugs. Only BAS was reported to have some influence, a mild tranquillizing action (3a, 130).

Cyproheptadine and methysergid, two new antiHT agents which were very potent in animal experiments, did not show appreciable mental effects (9, 40).

V. CONCLUSIONS

The demonstrations that many chemically different molecules are antagonistic to HT does not support the assumption that HT has well-characterized, uniform receptor sites. The possibility of the existence of variable types of HT receptors is represented by the discovery of M and D receptors in the gut (58) and it is very likely that still different types of receptors will be found. The existence of different HT receptors might be of great importance in the future applications of various HT blocking agents. The following explanation is offered to support this belief. Theoretically, blocking agents of competitive nature may not only prevent fixation of an agent like HT to a given receptor, but, depending upon their affinity to these receptors, they may also displace it from those sites. Thus, blocking agents may liberate HT from one receptor which, in turn, might be taken up by another receptor which remains unaffected by the antagonist. Accordingly, a possibility for a shift of HT from receptor A to B, or B to A, exists whenever a blocking agent, selective for a given receptor, acts on that receptor. This is but one example of the many possibilities where HT antagonists may act on a multiple receptor system, *i.e.*, in the whole organism. Besides typical receptors, which actively participate in the development of a pharmacological action, one must also consider surfaces of the inactivating enzymes (discussed in section II) as well as non-specific binding sites. Regardless of the differences in the receptors, two potent classes of antiHT agents, the lysergic acid derivatives and the phenothiazines, are indicative that systematic structure-activity studies in this field would be of great value and would help to characterize the type of receptors and drug-receptor interactions. With the group of lysergic acid compounds, the obvious common structural feature between the antagonist and HT is the indole nucleus and an attached ethylamine grouping which occurs as a free chain in HT and as a part of the ring system in lysergic acid derivatives. The high affinity to HT receptors of some phenothiazine and related compounds can be explained by the presence of a similar molecular fragment. The $=\overset{|}{C}-CH_2-CH_2-NH_2$ grouping of the HT molecule is mimicked by the $=N-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-N-$ fragment of certain phenothiazines and by the $=\overset{|}{C}-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-N-$ fragment of some highly potent related compounds. The analogy to the structural relationship between the "pharmacophore" group of histamine and antihistaminic agents of the substituted ethylenediamine type is apparent. Although the idea of developing antiHT agents on the basis of the structure of antihistaminic agents is fairly old (69, 120), little systematic work has been conducted in this direction.

The future role and significance of antiHT agents as experimental tools in pharmacology, and as possible therapeutic agents as well, will depend largely upon future discoveries concerning the physiologic and pathologic role of HT, or on the possibility of discovering new, physiologically occurring HT-like indole derivatives. Until recently, it has generally been considered that, regardless of its many-fold pharmacologic actions, HT has only a rather restricted physiologic role: regulation of the motility of the gut and modification of the tone of the bronchial muscle (40). Its participation in allergic and vascular diseases (135a) and in transmitting visceral sensory perception are subject to dispute. The role of HT in mental functions is still obscure (*cf.* 112, 113). Recent findings indicating an intensive action of HT on some nervous receptors of visceral organs (intestines (3, 63), bladder (72), blood vessels (104), and in autonomic ganglia (7a, 167)), open a new way of searching for antiHT agents by using nervous receptors as test objects rather than employing isolated smooth muscle. (Utilizing these nervous receptors has already led to the discovery of the first "neurotropic" HT antagonists which are considerably more potent and selective on these receptors than the "conventional" HT blocking agents (73)). The big discrepancy in the results between isolated organ systems and antiHT tests *in vivo* is another warning against the exclusive use of the former for testing antiHT action. As far as the CNS is concerned, it is less likely that there will be suitable test preparations available in the near future for studying interactions of HT with its antagonists in the CNS.

The use of suitable biological tests and a careful selection of those chemical structures which may yield HT antagonists of great potency or selectivity are only part of the problem. Further studies of the biochemistry of indole compounds seem to be equally important, since it is possible that new, still unknown, products of indole metabolism will emerge which may alter our present concepts concerning the role of HT and its antagonists. Even if this proves so, the availability of pharmacologically well-defined, potent, and selective antiHT agents will be of help in pharmacology in analyzing problems such as drug-receptor interactions, or in developing new therapeutic or diagnostic agents.

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