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COMPARATIVE EFFECTS OF 5,6-DIHYDROXYTRYPTAMINE AND ITS BENZO[*b*]-THIOPHENE ANALOGUE ON BIOGENIC AMINES IN THE RAT*

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Abstract—The effects of 5,6-dihydroxytryptamine (5,6-DHT) and its benzo[*b*]thiophene analogue (5,6-DHT-S) have been compared with regard to their ability to influence tissue levels of serotonin (5-HT) and norepinephrine (NE) in rats. After i.p. administration, both compounds caused significant reduction in NE levels in heart and spleen, while only 5,6-DHT reduced spleen 5-HT, and neither compound had any effect on brain NE or 5-HT. When administered directly into the lateral ventricle, both compounds caused reduced NE levels; the duration of effect was less than 1 day. In contrast to the prolonged lowering of brain 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) observed after 5,6-DHT, the benzo[*b*]thiophene analogue was without effect.

The search for compounds to use as biochemical tools for examining the function of neurotransmitter systems has resulted in a significant volume of publications in the past decade. The initial discovery of the long-lasting depletion of heart norepinephrine (NE) following a single dose of 6-hydroxydopamine (6-HDA) [1] led to hundreds of studies of the latter compound, culminating in its characterization as an agent capable of producing a 'chemical denervation' of adrenergic neurons [2]. Because of the poor ability of 6-HDA to penetrate the blood–brain barrier, it was soon found that injections into the lateral ventricles or other area(s) of the brain were necessary to obtain effects on central norepinephrine systems [3]; once the blood–brain barrier was bypassed, the expected effects were obtained [4].

In 1971, Baumgarten *et al.* [5] published the first report of the actions of 5,6-dihydroxtryptamine (5,6-DHT), a compound apparently analogous to 6-HDA, but active only on neuronal fibers containing serotonin (5-HT). A number of papers have confirmed the fact that 5,6-DHT caused selective degeneration of indoleamine terminals in a manner similar to that caused by 6-HDA on adrenergic neurons [6–8]. As with 6-HDA, the poor ability of 5,6-DHT to cross the blood–brain barrier demands that the compound be administered by intraventricular injection in order to obtain an effect on brain 5-HT [5–9].

Additional efforts by Baumgarten *et al.* [10] demonstrated that peripheral administration of 5,6-DHT produced a marked decrease of NE levels in heart and spleen of rats and mice, although the NE levels returned to normal in 24 hr. In this regard, it is of interest that Heikkila and Cohen [11] found that 5,6-DHT was an inhibitor of 5-HT and dopamine uptake by brain slices; in contrast, 6-hydroxydopamine under similar conditions inhibited dopamine uptake but was without effect on 5-HT uptake. Decreased uptake of 5-HT by brain synaptosomes *in vitro* has been demonstrated by Baldessarini and Gerson [12] to occur after pretreatment of rats with 5,6-DHT; these authors found no reduction in NE uptake by spinal cord synaptosomes. Richardson *et al.* [13] found depletion of brain 5-HT, but not of brain NE, 14 days after a single dose of 5,6-DHT. Against this background, one unusual report is that of Costa *et al.* [14] who found that samples of 5,6-DHT differed in potency as measured by their effects on 5-HT.

In the application of principles of selective molecular modification, as a means of studying biological structure–activity relationships of indolic compounds, efforts have centred on the pharmacological effects of the benzo[*b*]thiophene and 1-methylindole analogues of indolealkylamines [15–17], on the intestinal absorption of similar analogues of tryptophan [18,19], and on the substrate specificity of aromatic-L-amino acid decarboxylase with regard to tryptophan analogues [20]. Recently, the synthesis of 5,6-DHT-S [21] made sufficient material available to permit a detailed study of the role of the indolic nitrogen in the action of 5,6-DHT on monoaminergic systems.

MATERIALS AND METHODS

Adult, male Sprague-Dawley rats (275–300 g) were obtained from the Murphy Breeding Laboratories, Plainfield, IN, and maintained for at least 5 days prior

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Table 1. Effects of parenteral administration of 5,6-DHT and 5,6-DHT-S*

Time (hr)	Compound	Heart NE (μg/g)	Spleen NE (μg/g)	Spleen 5-HT (μg/g)	Brain NE (μg/g)	Brain 5-HT (μg/g)
0		0.29 ± 0.02	0.42 ± 0.07	1.40 ± 0.09	0.49 ± 0.04	0.61 ± 0.04
1	5,6-DHT	0.19 ± 0.02†	0.33 ± 0.02	1.35 ± 0.16	0.47 ± 0.03	0.61 ± 0.03
	5,6-DHT-S	0.24 ± 0.02	0.28 ± 0.02†	1.92 ± 0.18	0.49 ± 0.05	0.64 ± 0.07
2	5,6-DHT	0.14 ± 0.01†	0.25 ± 0.02†	1.14 ± 0.08†	0.48 ± 0.02	0.58 ± 0.07
	5,6-DHT-S	0.15 ± 0.01†	0.28 ± 0.03†	2.21 ± 0.28†	0.51 ± 0.05	0.59 ± 0.04
4	5,6-DHT	0.17 ± 0.01†	0.21 ± 0.01†	1.16 ± 0.13†	0.50 ± 0.03	0.60 ± 0.06
	5,6-DHT-S	0.18 ± 0.03†	0.21 ± 0.04†	1.56 ± 0.10	0.48 ± 0.03	0.58 ± 0.05
8	5,6-DHT	0.25 ± 0.02	0.20 ± 0.01†	0.97 ± 0.07†	0.51 ± 0.06	0.57 ± 0.03
	5,6-DHT-S	0.23 ± 0.01	0.25 ± 0.04†	1.42 ± 0.25	0.46 ± 0.02	0.62 ± 0.02
16	5,6-DHT	0.33 ± 0.02	0.25 ± 0.04†	0.72 ± 0.05†	0.47 ± 0.03	0.65 ± 0.07
	5,6-DHT-S	0.30 ± 0.02	0.37 ± 0.02	1.64 ± 0.21	0.50 ± 0.05	0.58 ± 0.03
24	5,6-DHT	0.31 ± 0.01	0.30 ± 0.03	0.85 ± 0.06†	0.48 ± 0.02	0.61 ± 0.02
	5,6-DHT-S	0.27 ± 0.03	0.39 ± 0.04	1.53 ± 0.04	0.45 ± 0.05	0.59 ± 0.05

* Each value is the mean ± S.E.M. of values obtained from four rats, except that control values are obtained from sixteen rats.

Single i.p. doses of 30μg/kg here given in each case.

† Values differ significantly from control ($P < 0.05$).

to use on a diet of Purina Laboratory Chow and tap water *ad lib.* All chemicals and reagents were purchased from commercial sources.

Drugs given intraperitoneally were made up as solutions in distilled water such that the specified dosage in mg/kg was contained in a volume of 1 ml/kg body wt. Drugs injected intraventricularly were dissolved in diluted mammalian Ringer's solution ($\frac{1}{3}$ distilled water, $\frac{2}{3}$ Ringer's solution) containing 0.1 mg ascorbic acid/ml [14]; the concentrations were such that the desired dose was contained in a volume of 10μl.

Intraventricular injections of drugs were accomplished according to the methods of Noble *et al.* [22] with the following modifications. Injection volumes were delivered by Hamilton 50-μl syringes and limited to 10 μl maxima. The syringes were equipped with $\frac{3}{8}$ in. 27-gauge needles and were stereotactically placed to a depth of 3.75 ± 0.05 mm in the lateral ventricle. Following injection, the hole in the skull was closed with bone wax, and the wound was dusted with sulfathiazole and closed with wound clips.

Rats were decapitated, and tissues were removed, washed in cold 0.9% saline, blotted dry and stored at −20° until assay. Brains were dissected, just prior to assay, into three sections: cerebral hemispheres, cerebellum and the remainder. Tissue levels of 5-HT, NE and 5-hydroxyindoleacetic acid (5-HIAA) were determined as reported by Miller *et al.* [23]. Statistical analyses were performed by a combination of analysis of variance for drug effects and two-tailed 't'-tests for individual comparisons.

RESULTS

Effects of parenteral administration of 5,6-DHT and 5,6-DHT-S. The results obtained after administration of single i.p. doses of 5,6-DHT and 5,6-DHT-S (30 mg/kg) to rats are presented in Table 1. The results for heart NE show that the compounds have virtually identical effects; an initial decrease to minimal values which are approximately 50 per cent of control at 2 hr is followed by a return to normal levels by 16 hr. The actions of the two analogues on spleen NE were also similar. 5,6-DHT reduced spleen NE levels to a minimal value which was less than 50 per cent of control at 8 hr after injection; at 24 hr values were still only 71 per cent of control. 5,6-DHT-S produced a 50 per cent level of depletion of NE at 4 hr, which returned to normal levels by 24 hr.

The results of the two compounds for 5-HT in spleen were quite different. 5,6-DHT caused a significant and persistent decrease, reaching a minimal level of about 50 per cent of control at 16 hr and lasting more than 24 hr. In contrast, 5,6-DHT-S produced an initial increase in spleen 5-HT, which peaked at 2 hr, and returned to normal levels by 4 hr. No effects on brain 5-HT or NE were seen with either compound.

Time course of effect of intraventricular administration of 5,6-DHT on 5,6-DHT-S. Since the blood–brain barrier prevents the 5,6-dihydroxy compounds, given parentally, from having any effects on brain biogenic amines, a series of studies was performed in which the compounds were injected directly into the lateral ventricles of the rat brain. Because of the well-known differences in amine biochemistry in various brain areas, brains were divided into three parts prior to the assay. The results are presented in Table 2, for the highest dose (80 mg) of each compound.

The NE levels indicate that both the indole and benzo[*b*]thiophene compounds have an effect only on the day of injection. The effects of both compounds, in all three brain areas, are manifested in a decreased level of NE. In cerebellum, there is, at most, a 25 per cent reduction of NE levels, which is seen at 1 hr, and is over by 4 hr. In the cerebral hemispheres, both compounds cause a maximal reduction of 30–40 per cent with an effect beginning at 2 hr post-injection and extending for 24 hr. In the remainder of the brain, a 25–30 per cent decrease in NE is seen at 1 hr and recovery is complete in 24 hr. With a dose of 40 μg/rat, the benzo[*b*]-thiophene compound was active at 4 hr only in the cerebral hemispheres, while the indole compound reduced NE in all three brain areas to an extent (in magnitude and duration) only slightly less than the higher dose. At a dose of 20 μg/rat, both compounds were devoid of significant effects on NE.

Table 2. Effects of intraventricular injection of 5,6-DHT and 5,6-DHT-S on regional brain NE, 5-HT and 5-HIAA*

Time	Compound	Cerebral hemispheres NE (μg/g)	Cerebral hemispheres 5-HT (μg/g)	Cerebral hemispheres 5-HIAA (μg/g)	Cerebellum NE (μg/g)	Cerebellum 5-HT (μg/g)	Cerebellum 5-HIAA (μg/g)	Remainder NE (μg/g)	Remainder 5-HT (μg/g)	Remainder 5-HIAA (μg/g)
0 hr		0.40 ± 0.05	0.33 ± 0.02	0.56 ± 0.06	0.17 ± 0.02	0.19 ± 0.02	0.25 ± 0.02	1.01 ± 0.11	1.17 ± 0.13	0.77 ± 0.08
1 hr	5,6-DHT	0.36 ± 0.04	0.32 ± 0.04	0.62 ± 0.06	0.13 ± 0.02†	0.16 ± 0.02	0.26 ± 0.02	0.85 ± 0.10†	0.85 ± 0.13†	0.86 ± 0.12
1 hr	5,6-DHT-S	0.39 ± 0.07	0.33 ± 0.05	0.50 ± 0.09	0.13 ± 0.02†	0.96 ± 0.17	0.24 ± 0.05	0.70 ± 0.13†	1.18 ± 0.18	0.80 ± 0.12
2 hr	5,6-DHT	0.28 ± 0.07†	0.29 ± 0.03	0.52 ± 0.11	0.13 ± 0.02†	0.18 ± 0.02	0.20 ± 0.06	0.74 ± 0.14†	0.89 ± 0.06†	0.97 ± 0.16†
2 hr	5,6-DHT-S	0.37 ± 0.04	0.31 ± 0.04	0.48 ± 0.12	0.15 ± 0.03	0.19 ± 0.03	0.27 ± 0.05	0.72 ± 0.14†	1.11 ± 0.11	1.00 ± 0.09†
4 hr	5,6-DHT	0.29 ± 0.03†	0.26 ± 0.03†	0.43 ± 0.09†	0.16 ± 0.02	0.17 ± 0.02	0.18 ± 0.03†	0.77 ± 0.06†	0.84 ± 0.16†	0.87 ± 0.17
4 hr	5,6-DHT-S	0.34 ± 0.04†	0.31 ± 0.04	0.56 ± 0.06	0.16 ± 0.02	0.22 ± 0.04	0.28 ± 0.05	0.79 ± 0.10†	1.05 ± 0.11	0.98 ± 0.18
8 hr	5,6-DHT	0.30 ± 0.05†	0.28 ± 0.03†	0.45 ± 0.05†	0.16 ± 0.02	0.19 ± 0.01	0.20 ± 0.04†	0.91 ± 0.13	0.83 ± 0.12†	0.57 ± 0.08†
8 hr	5,6-DHT-S	0.27 ± 0.08†	0.30 ± 0.03	0.55 ± 0.10	0.16 ± 0.03	0.20 ± 0.03	0.27 ± 0.03	0.93 ± 0.16	1.13 ± 0.15	0.73 ± 0.11
16 hr	5,6-DHT	0.27 ± 0.03†	0.22 ± 0.06†	0.45 ± 0.05†	0.15 ± 0.03	0.14 ± 0.03†	0.20 ± 0.05	0.93 ± 0.11	0.91 ± 0.07†	0.59 ± 0.06†
16 hr	5,6-DHT-S	0.32 ± 0.04†	0.37 ± 0.03	0.63 ± 0.08	0.15 ± 0.02	0.20 ± 0.03	0.23 ± 0.03	1.04 ± 0.11	1.17 ± 0.06	0.67 ± 0.09
1 day	5,6-DHT	0.34 ± 0.09	0.26 ± 0.02†	0.38 ± 0.04†	0.14 ± 0.03	0.14 ± 0.02†	0.20 ± 0.04†	0.94 ± 0.10	0.97 ± 0.10†	0.62 ± 0.07†
1 day	5,6-DHT-S	0.33 ± 0.09	0.30 ± 0.06	0.50 ± 0.07	0.17 ± 0.01	0.19 ± 0.03	0.28 ± 0.03	0.93 ± 0.11	1.18 ± 0.11	0.85 ± 0.08
2 days	5,6-DHT	0.43 ± 0.05	0.28 ± 0.01	0.44 ± 0.07†	0.15 ± 0.03	0.16 ± 0.02	0.18 ± 0.03†	0.93 ± 0.11	0.95 ± 0.11	0.55 ± 0.10†
2 days	5,6-DHT-S	0.37 ± 0.02	0.32 ± 0.03	0.57 ± 0.08	0.16 ± 0.02	0.28 ± 0.06	0.28 ± 0.06	0.98 ± 0.17	1.05 ± 0.12	0.89 ± 0.07
4 days	5,6-DHT	0.41 ± 0.11	0.26 ± 0.03†	0.39 ± 0.02†	0.17 ± 0.01	0.16 ± 0.01†	0.23 ± 0.04	0.93 ± 0.13	0.97 ± 0.14†	0.59 ± 0.11†
4 days	5,6-DHT-S	0.43 ± 0.09	0.32 ± 0.03	0.57 ± 0.06	0.17 ± 0.02	0.18 ± 0.02	0.23 ± 0.03	0.99 ± 0.14	1.19 ± 0.13	0.79 ± 0.15
8 days	5,6-DHT	0.37 ± 0.05	0.27 ± 0.03†	0.34 ± 0.11†	0.15 ± 0.01	0.21 ± 0.02	0.28 ± 0.03	0.92 ± 0.09	0.74 ± 0.20†	0.60 ± 0.05†
8 days	5,6-DHT-S	0.43 ± 0.04	0.33 ± 0.03	0.61 ± 0.11	0.16 ± 0.02	0.18 ± 0.03	0.21 ± 0.06	1.05 ± 0.11	1.19 ± 0.13	0.88 ± 0.09
16 days	5,6-DHT	0.35 ± 0.12	0.23 ± 0.03†	0.46 ± 0.04†	0.16 ± 0.02	0.18 ± 0.02	0.21 ± 0.04	0.98 ± 0.07	0.91 ± 0.08†	0.52 ± 0.13†
16 days	5,6-DHT-S	0.35 ± 0.08	0.33 ± 0.02	0.58 ± 0.12	0.15 ± 0.03	0.18 ± 0.03	0.25 ± 0.03	0.99 ± 0.05	1.09 ± 0.10	0.90 ± 0.13

* Each value is the mean ± S.E.M. of values obtained from four rats, except that control values are obtained from sixteen rats. The values are the results of the highest dose (80 mg) given of each compound.

† Values differ significantly from control ($P < 0.05$).

The effects of the two compounds on 5-HT levels were distinctly different. 5,6-DHT-S was completely ineffective; no significant alterations in 5-HT levels were seen in any brain area, at any dose or time point. In contrast, the effects of 5,6-DHT were unique in each brain area. In the cerebral hemispheres, the dose of 80 μg/rat was effective for at least 16 days; the maximum reduction was 65–70 per cent of the control levels. An action on cerebellar 5-HT was seen only over the period from 16 hr to 4 days post-injection; the maximum depletion was to about 75 per cent of control. In the remainder of the brain, a lowering of 5-HT to 65–80 per cent of control was observed from 1 hr to 16 days post-injection. In the cerebral hemispheres, 40 μg/rat of 5,6-DHT had an effect similar to that of the higher dose but of somewhat lessened magnitude and shorter duration, while 20 μg/rat was ineffective. The cerebellar 5-HT levels were not altered at all by doses of 20 or 40 μg/rat, while in the remainder of the brain the 40 μg/rat dose of 5,6-DHT had an effect virtually identical to that of the higher dose in both magnitude and duration. With the 20 μg/rat dose, a significant decrease in 5-HT levels in the remainder of the brain was seen only at 4 hr and 24 hr; although there was a modest lowering during the period from 1 hr to 4 days, analysis of variance did not indicate a significant drug effect.

The effects of 5,6-DHT on 5-HIAA levels in all three brain areas reflected the lowering of 5-HT values (or lack thereof) at all doses and times. A transient increase in 5-HIAA in the remainder area was seen at 2 and 4 hr after 5,6-DHT-S, and the cerebellum was, in general, the area least affected.

DISCUSSION

Since the first report by Baumgarten *et al.* [5] on the selective neurotoxicity of 5,6-DHT, this compound has been of wide interest to investigators dealing with various aspects of serotonergic function in animals. Of particular interest has been the selectivity of the compound. Its ability to cause damage to serotonergic stores without affecting catecholaminergic stores is unique, as is its exceptionally long duration of action [5–13]. Although some questions have been raised of its relative potency (perhaps due to an impurity in some preparations), 5,6-DHT has, in general, been shown to be an effective and selective serotonin neurotoxin [14].

Beginnning with the comparative effects of serotonin and its benzo[*b*]thiophene analogue [15], and continuing through the pressor effects of tryptamine and its benzo[*b*]thiophene and 1-methylindole analogues [16], studies have shown that certain similarities and differences in pharmacologic potency exist with regard to the atom located at the 1-position of the heterocycle. For example, the substitution of a sulfur atom for the ring nitrogen in tryptophan has little effect on the active transport of the molecule across the intestine [19]; however, the slightly greater lipid solubility of the benzo[*b*]thiophene analogue of tryptophan does lead to a slightly more rapid passive diffusion component in the *in vivo* perfused intestine [18]. When the analogues of tryptophan were tested as substrates for aromatic-L-amino acid decarboxylase, however, replacement of the indolic nitrogen by a sulfur atom led to a complete loss of substrate activity [20].

The possibility of examining the neurotoxic action of 5,6-DHT by use of its benzo[*b*]thiophene analogue led to its synthesis [21] and to the comparative studies reported in the present paper. When administered parenterally to rats, 5,6-DHT-S had an effect on NE in heart and spleen basically similar to that of 5,6-DHT, that is, a modest elevation at 2 hr (Table 1).

When administered by direct injection into the lateral ventricle of the rat brain, 5,6-DHT-S had, in general, effects on NE similar to those of the indolic 5,6-DHT (Table 2). In sharp contrast, however, the 5,6-DHT-S had no effects on brain 5-HT. The actions of 5,6-DHT, as reported in the present paper, are basically in agreement with previous reports, especially that of Costa *et al.* [14]. Thus, the cerebellum was most resistant to the 5-HT-depleting actions; no significant effects were seen until a dose of 80 μg was reached. Another similarity is the extent of 5-HT depletion seen with 5,6-DHT. The material used in this study was obtained from the Regis Chemical Co, Chicago, IL, is presumably similar to that described as 5,6-DHT-II by Costa *et al.* [14], and therefore, is slightly less potent than the material originally used by Baumgarten *et al.* [5].

Perhaps the most significant aspect of the present report lies in the inability of the benzo[*b*]thiophene analogue of 5,6-DHT to exert any significant effects on levels of 5-HT. One explanation for this striking difference may lie in the possiblity that the action of 5,6-DHT on 5-HT stores requires an intermediate quinone-type structure, as has been proposed for 6-hydroxydopamine [24]. If one considers the structures of 5,6-DHT and its benzo[*b*]thiophene analogue, it is reasonable to assume that a quinone structure can be proposed for the indolic compound that would not be chemically feasible for the benzo[*b*]thiophene. Such a structure may be active in causing 5-HT depletion and degeneration of serotonergic fibers. In this sense, both compounds might be expected to have a short-acting effect on NE stores, merely because they both contain a catechol function that could act as a nonspecific substitute for catecholamines in their storage processes.

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