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LETTERS TO THE EDITOR

Effect of substituted tryptamines on the efflux of noradrenaline from adrenergic nerves in rabbit atria

Previous studies have suggested that the efflux of [^{3}H] (−)-noradrenaline (^{3}H-NA) from the cytosol of adrenergic nerves occurs by a cocaine-sensitive, carrier-mediated process (Paton, 1973a, b, c). The efflux of ^{3}H-NA from reserpine- and pargyline-pretreated rabbit atria was temperature-sensitive and was accelerated by ouabain, omission of K^+ and metabolic inhibition, these effects being inhibited by cocaine and desipramine. A number of phenethylamine derivatives also increased efflux, the most potent compounds studied being β-phenethylamine and amphetamine.

5-Hydroxytryptamine (5-HT) has been shown to be transported into peripheral adrenergic nerves by the cocaine-sensitive membrane carrier, to be incorporated into the intraneuronal storage vesicles and to cause the release of noradrenaline from such vesicles (Snipes, Thoenen & Tranzer, 1968; Thoa, Eccleston & Axelrod, 1969; Pluchino, 1972). In the present study, the effects of 5-HT and of related substituted tryptamines on the efflux of ^{3}H-NA from the cytosol of adrenergic nerves in rabbit atria have been examined.

As described previously (Paton, 1973a, b), atria, from reserpine-pretreated rabbits, were exposed to pargyline and tropolone, and thereafter to $5{\cdot}8 \times 10^{-7}$M ^{3}H-NA for 60 min. Tissues were then blotted, placed on fine metal hooks and transferred every 5 min to fresh media at 37°. Substituted tryptamines were added between 60–90 min of efflux because, during this period, efflux occurs predominantly from adrenergic nerves.

Changes in the rate of efflux produced by these compounds were expressed as mean increases in rate coefficient determined by subtracting the mean rate coefficient during the 20 min period before the addition of compounds (referred to as basal rate in the Tables). The rate coefficient (f) was determined as follows:

$$f = \frac{\Delta A}{\Delta t.At}$$

Table 1. *Effect of hydroxytryptamines (HT) on the efflux of [^{3}H] (−)-noradrenaline in rabbit atria.* All drugs were present from 60–90 min. Values are the mean ± s.e. of 6 observations.

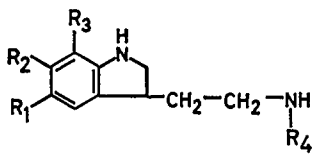
Compound	Concentration (M)	Rate Coefficient (min^{-1}) Basal rate	Mean increase at 62·5 min	% Increase
4-HT	5×10^{-6}	0·0063 ± 0·0017	0·0008 ± 0·0004	12
	5×10^{-5}	0·0062 ± 0·0019	0·0029 ± 0·0006	47
5-HT	5×10^{-6}	0·0042 ± 0·0013	0·0022 ± 0·0008	52
	5×10^{-5}	0·0051 ± 0·0017	0·0066 ± 0·0014	129
6-HT	5×10^{-6}	0·0076 ± 0·0014	0·0042 ± 0·0010	55
	5×10^{-5}	0·0063 ± 0·0009	0·0127 ± 0·0022	201
7-HT	5×10^{-6}	0·0051 ± 0·0010	0·0024 ± 0·0009	47
	5×10^{-5}	0·0083 ± 0·0016	0·0091 ± 0·0016	109

where ΔA represents the disintegrations lost in the time interval Δt, and At is the amount of [^{3}H]noradrenaline in the tissue at the midpoint of the interval Δt.

Preliminary studies (Table 1) showed that these compounds were considerably less active than the phenethylamines previously examined (Paton, 1973c). At 5×10^{-6} and 5×10^{-5}M, 4-, 5-, 6- or 7-hydroxytryptamine all produced relatively small increases in efflux. By contrast, *p*-tyramine produced mean increases of $0{\cdot}0221 \pm 0{\cdot}0028$ and $0{\cdot}03491 \pm 0{\cdot}0031$ (min^{-1}) at 5×10^{-6} and 5×10^{-5}M respectively.

At 1×10^{-4}M, several indolethylamines accelerated the efflux of ^{3}H-NA (Table 2). The most potent compound studied was tryptamine but even it was much less potent than most of the phenethylamines previously examined (Paton, 1973c). Addition of a hydroxyl group to the indole ring reduced activity, the relative potencies being 6-HT > 7-HT > 5-HT > 4-HT. Addition of a second hydroxyl to the indole ring reduced activity still further. It is interesting to note that 6,7-dihydroxytryptamine was only weakly active. Interpretation of results obtained using 5,6-dihydroxytryptamine are difficult because this compound is rapidly oxidized to toxic products and, as noted by Baumgarten & Lachenmeyer (1972), tissues turn brown after exposure to it.

Table 2. *Effect of substituted tryptamines on the efflux of* [^{3}*H*] *(−)-noradrenaline in rabbit atria.* All drugs were present from 60–90 min at 1×10^{-4}M ± s.e. of 6–10 observations.



R_1	R_2	R_3	R_4	Compound	Rate Coefficient (min^{-1}) Basal rate	Mean increase at 62·5 min	% Increase
H	H	H	H	tryptamine	0·0053 ± 0·0005	0·0201 ± 0·0023	320
OH	H	H	H	5-hydroxy-tryptamine	0·0042 ± 0·007	0·0068 ± 0·0014	161
CH_3	H	H	H	5-methyl-tryptamine	0·0042 ± 0·0007	—0·0008 ± 0·0004	—19
CH_3O	H	H	H	5-methoxy-tryptamine	0·0042 ± 0·0009	—0·0006 ± 0·0003	—15
OH	H	H	CH_3	*N*-methyl-5-hydroxytryptamine	0·0042 ± 0·0007	0·0055 ± 0·0021	129
OH	H	H	CH_3CO	*N*-acetyl-5-hydroxytryptamine	0·0051 ± 0·0009	0·0008 ± 0·0008	15
H	OH	H	H	6-hydroxy-tryptamine	0·0051 ± 0·0009	0·0178 ± 0·0039	350
H	H	OH	H	7-hydroxy-tryptamine	0·0039 ± 0·0011	0·0108 ± 0·0037	273
H	H	OH	CH_3CH_2	*N*-ethyl-7-hydroxy-tryptamine	0·0045 ±0·0007	0·0005 ± 0·0002	11
OH	OH	H	H	5,6-dihydroxy-tryptamine	0·0053 ± 0·0006	0·0075 ± 0·0007	141
OH	H	OH	H	5,7-dihydroxy-tryptamine	0·0054 ± 0·0008	0·0060 ± 0·0011	112
H	OH	OH	H	6,7-dihydroxy-tryptamine	0·0040 ± 0·007	0·0014 ± 0·0006	35

Substitution of the 5-hydroxyl group in 5-HT with either a methyl or a methoxy group abolished activity as did *N*-substitution with acetyl or ethyl groups.

The structural requirements for indolethylamines to accelerate the efflux of ^{3}H-NA are thus similar to those previously described for a series of phenethylamines (Paton, 1973c). Addition of phenolic hydroxyl or methoxy groups, or *N*-methylation all reduced the activity of phenethylamines. The mechanisms by which phenethylamines and indolethylamines accelerate ^{3}H-NA efflux have not been finally established but could involve accelerative exchange diffusion or possibly displacement of ^{3}H-NA from reserpine-resistant intraneuronal binding sites.

In addition to 5-HT, a number of other substituted tryptamines has been shown to be transported into adrenergic nerves. 7-HT caused noradrenaline release (Göthert, Tuchinda & Baumgarten, 1973) while both 5,6- and 5,7-dihydroxytryptamine produced degeneration of serotinergic and adrenergic neurons in the brain (Baumgarten, Björklund & others, 1971; Baumgarten & Lachenmeyer, 1972). The present study has thus added to the growing evidence that a number of substituted tryptamines may influence the uptake, release and efflux of noradrenaline from both central and peripheral adrenergic neurones.

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