Effect of *O*-methylation on the acceleration of efflux of noradrenaline produced by phenethylamine derivatives

The efflux of [^{3}H](−)-noradrenaline from reserpine- and pargyline-pretreated rabbit atria was accelerated by *p*-tyramine, (±)-metaraminol and (±)-noradrenaline, possibly as a result of accelerative exchange diffusion (Paton, 1973a, b). These and other results suggested that the efflux of [^{3}H](−)-noradrenaline from the cytosol of adrenergic nerves occurs by a cocaine-sensitive, carrier-mediated process.

We now report the effect of *O*-methylation on the ability of β-phenethylamine, *p*-tyramine, dopamine, (±)-noradrenaline and (−)-adrenaline to accelerate efflux of [^{3}H](−)-noradrenaline was examined and compared with the effects of *O*-methylation on inhibition of uptake of noradrenaline into adrenergic neurons (Burgen & Iversen, 1965).

As described previously (Paton, 1973a, b), atria, from reserpine-pretreated rabbits, were exposed to pargyline (5×10^{-4}M for 30 min) and tropolone (1×10^{-4}M throughout), and thereafter to $5{\cdot}8 \times 10^{-7}$M [^{3}H](−)-noradrenaline for 60 min. Tissues were then blotted, placed on fine metal hooks and transferred every 5 min to fresh media at 37°. Substituted phenethylamines were added between 60–90 min of efflux because, during this period, efflux occurs predominantly from adrenergic nerves (Paton, 1973b).

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:

$$f = \Delta A/(\Delta t.At)$$

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

The effects of all compounds were examined at a concentration of 5×10^{-5}M (Table 1). It is readily apparent that *O*-methylation always significantly reduced the ability of compounds to accelerate the efflux of [^{3}H]noradrenaline. It is noteworthy, however, that the degree of inhibition produced depended on the structural nature of the reference compound and, in particular, on the number of hydroxyl groups present. This is most evident when the effects of *O*-methylation at a single position are considered. For example, 4-methoxyphenethylamine possessed considerable activity whereas 3-methoxytyramine was much less active. By contrast, (±)-normetanephrine and (±)-metanephrine were essentially inactive. The addition of a second methoxy group (e.g., 2,4-, 2,5-, and 3,4-dimethoxyphenethylamine and 3,5-dimethoxy-4-hydroxyphenethylamine) resulted in a further reduction in activity. *O*-methylation at the 2 position appeared to be particularly inhibitory.

The results also illustrate the generally inhibitory effect of *N*-substitution (e.g., (±)-noradrenaline > (−)-adrenaline, and 3-methoxytyramine > *N*-acetyl-3-methoxytyramine) and of possession of phenyl and β-hydroxy groups (e.g., *p*-tyramine > dopamine and (±)-noradrenaline) (see also Paton, 1973c). The ability of tryptamine derivatives to accelerate (±)-noradrenaline efflux was similarly affected by *O*-methylation, *N*-substitution and the addition of hydroxyl groups (Paton, 1973d).

O-Methylation also very significantly reduced the ability of sympathomimetic amines to inhibit the uptake of [^{3}H]noradrenaline into peripheral and central adrenergic neurons (Burgen & Iversen, 1965; Horn, 1973) but in some cases, e.g., normetanephrine and metanephrine, markedly increased their ability to inhibit extraneuronal uptake in rat heart (Burgen & Iversen, 1965).

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Table 1. *Effect of* O*-methylation on the acceleration of* [^3H](−)*-noradrenaline efflux by phenethylamine derivatives.* All drugs were present from 60-90 min at 5×10^{-5}M. Mean ± s.e. of 6–25 observations.

Compound	Substitutions at: 2	3	4	5	β	R	Rate coefficient $\times 10^{-4}$ (min^{-1}) Basal rate	Mean increase at 62·5 min	(%) Increase
β-Phenethylamine	H	H	H	H	H	H	46 ± 5	447 ± 48	972
4-Methoxyphenethylamine	H	H	OCH_3	H	H	H	37 ± 5	138 ± 48	373
3,4-Dimethoxyphenethylamine	H	OCH_3	OCH_3	H	H	H	45 ± 8	45 ± 10	100
2,4-Dimethoxyphenethylamine	OCH_3	H	OCH_3	H	H	H	47 ± 8	−9 ± 11	−19
2,5-Dimethoxyphenethylamine	OCH_3	H	H	OCH_3	H	H	44 ± 9	11 ± 14	25
p-Tyramine	H	H	OH	H	H	H	62 ± 7	349 ± 31	563
Dopamine	H	OH	OH	H	H	H	53 ± 6	168 ± 21	316
3-Methoxytyramine	H	OCH_3	OH	H	H	H	47 ± 7	59 ± 10	126
N-Acetyl-3-methoxytyramine	H	OCH_3	OH	H	H	$COCH_3$	50 ± 6	−5 ± 5	−10
5-Methoxy dopamine	H	OH	OH	OCH_3	H	H	39 ± 7	47 ± 17	121
3,5-Dimethoxy-4-Hydroxy-phenethylamine	H	OCH_3	OH	OCH_3	H	H	38 ± 6	3 ± 7	8
(±)-Noradrenaline	H	OH	OH	H	OH	H	72 ± 16	277 ± 36	385
(−)-Adrenaline	H	OH	OH	H	OH	CH_3	71 ± 14	154 ± 15	217
(±)-Normetanephrine	H	OCH_3	OH	H	OH	CH_3	45 ± 9	7 ± 3	16
(±)-Metanephrine	H	OCH_3	OH	H	OH	CH_3	54 ± 9	−3 ± 5	−6

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