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Functional selectivity and erratic agonist behaviour of hallucinogenic 5-HT_{2A} agonists in the rat aorta

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So-called "legal highs" are novel psychoactive substances (NPS) which are sold legitimately until regulators restrict their sale through legislative measures. These drugs are sold for their varied pharmacological similarities to cocaine, MDMA ("Ecstasy") and hallucinogens. Sold without any pharmacodynamic testing (unless the structures have been sourced from published research), these compounds are likely to have unpredictable pharmacological actions in the periphery, including direct and indirect vasoconstriction via several mechanisms. We recently started screening these compounds for likely cardiovascular effects.

Test compounds were applied cumulatively to isolated rings of Wistar rat (male, 200-300 g) aorta (with endothelium intact) mounted in conventional organ baths for isometric tension recording. Contractions are expressed as a percentage of a reference contraction elicited by raising extracellular K^+ to 68 mM. Of the compounds tested (all dissolved in distilled water), three caused concentration-dependent contractions that were completely abrogated by the 5-HT_{2A} receptor antagonist ketanserin (0.1 µM): 5-(2-aminopropyl)benzofuran (5-APB; "Benzofury"), 6-(2-aminopropyl)benzofuran (6-APB; also known as "Benzofury") and 2-(4-chloro-2,5,-dimethoxyphenyl)-*N*-[2-methoxyphenyl)methyl]ethanamine (2C-C-NBOMe). In comparison with 5-HT itself, all of these compounds had erratic maximal responses (S.E. of the mean >10% of the maximal response; Table 1) in our hands. Therefore, we decided to determine whether these compounds, 5-HT itself and two 5-HT_{2A} agonists (α-5-Methyl-5-HT and (2-bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine (TCB-2)) caused contractions via different signalling mechanisms. Separate preparations were treated with nifedipine (1 µM) to block voltage-gated calcium channels (VGCC) and cumulative concentration effect curves were again constructed. The results are summarised in Table 1.

Table 1

	Control		Nifedipine	
Drug	pEC_{50} (n)	KCl Max %	pEC_{50} (n)	KCl Max %
5-HT	5.37 ± 0.1 (4)	214 ± 12	5.38 ± 0.1 (4)	158 ± 9*
α-Methyl-5-HT	5.99 ± 0.1 (4)	150 ± 14	5.73 ± 0.1 (4)	79.0 ± 4*
TCB-2	6.66 ± 0.2 (8)	166 ± 17	6.66 ± 0.3 (4)	26.4 ± 4*
5-APB	5.47 ± 0.4 (5)	55 ± 11	5.11 + 0.1 (4)	18 ± 1
6-APB	5.65 ± 0.3	138 ± 17	5.10 ± 0.3 (6)	90 ± 18

	(4)			
2C-C-NBOMe	8.94 ± 0.7 (6)	140 ± 98	8.29 ± 0.4 (5)	16.7 ± 2

* P<0.05 compared to controls (Mann-Whitney test)

Nifedipine had no effect on the potency of any of the compounds examined, but significantly reduced the maximal effects of 5-HT, α-methyl-5-HT and TCB-2. By contrast, while there was a trend for a reduction in the maximal response to 5-APB, 6-APB and 2C-C-NBOMe, this did not reach statistical significance. However, the maximal responses to these compounds were far less erratic in the presence of nifedipine.

Our data suggest that these three NPS are potential vasoconstrictors via activation of 5-HT_{2A} receptors. In contrast to conventional agonists of these receptors, 5-APB, 6-APB and 2C-C-NBOMe produce responses with erratic maxima, which may be due, in part, to differential coupling to the opening of VGCC. In conclusion, our results suggest that these compounds may have unpredictable cardiovascular effects in man.