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INTERACTION OF 5-HT AGONISTS WITH GUINEA-PIG BRAIN STEM 5-HT RECEPTORS AND THE INDUCTION OF MYOCLONUS

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5-Hydroxytryptamine (5HT) precursors and indole-containing 5HT agonists induce dose-related myoclonus in guinea pigs which originates from brain stem (Chadwick et al,1978; Luscombe et al,1982). In contrast, 5HT agonists containing a piperazine moiety do not induce myoclonus in pharmacologically effective doses (Luscombe et al,1982). We now report the relationship between the ability of a range of 5HT agonists to induce myoclonus and their ability to displace ^{3}H-5HT and ^{3}H-spiperone from 5HT-1 and 5HT-2 receptors in guinea-pig brain stem preparations.

Brainstem (minus cerebellum) preparations from female guinea pigs (250-500 g) were used for ligand binding assays. ^{3}H-5HT (16.6 Ci/mmole; 0.5-64 nM) or ^{3}H-spiperone (21 Ci/mmole; 0.25-32 nM) were incorporated into 10 tissue incubates (1.0 ml; 10mg tissue) and specific binding defined by the incorporation of 5HT (10^{-5} M or d-lysergic acid diethylamide (d-LSD) (10^{-6} M). Saturation analysis of ^{3}H-5HT binding revealed two sites: a high affinity site (Bmax 1.97 $\pm$ 0.01 pmoles/g wet weight of tissue; K_D 3.7 $\pm$ 1.0 nM) and a low affinity site (Bmax 9.2 $\pm$ 2.2 pmoles/g wet weight of tissue; K_D 29.1 $\pm$ 4.0 nM). Specific binding of ^{3}H-spiperone to guinea pig brain stem preparation was very low and could not be reliably measured. This data would suggest that 5HT-1 receptors (Peroutka & Snyder, 1979) predominate in this region of guinea-pig brain.

The specific binding of ^{3}H-5HT (4 nM) to guinea pig brain stem preparations was potently displaced by indole-containing 5HT agonists (Table 1; range IC_{50}: 3.4-519 nM) but only weakly displaced by piperazine-containing 5HT agonists (Table 1; range IC_{50}; 408-42,551 nM).

Table 1 Displacement of specific ^{3}H-5HT binding by indole-containing and piperazine-containing 5HT agonists

Indole compounds	IC_{50} (nM)	Piperazine compounds	IC_{50} (nM)
d-LSD	3.4 $\pm$ 1.7	1-(m-trifluoromethyl-phenyl)piperazine	408 $\pm$ 124
Bufotenine	23 $\pm$ 12	m-Chlorophenylpiperazine	3261 $\pm$ 2738
RU 24969	30 $\pm$ 6	Quipazine	7241 $\pm$ 2714
5-Methoxy-N,N-dimethyltryptamine	158 $\pm$ 24	Phenylpiperazine	7476 $\pm$ 2725
Psilocin	241 $\pm$ 81	p-Chlorophenylpiperazine	8729 $\pm$ 4303
N,N-Dimethyltryptamine	280 $\pm$ 105	6-Chloro-2-(1-piperazinyl) pyrazine (MK 212)	17260 $\pm$ 9714
Psilocybin	519 $\pm$ 82	2-(1'-piperazinyl) quinoxaline	42551 $\pm$ 21,742

The ability of 5HT agonists to induce myoclonus in guinea pigs is related to the capacity to displace the specific binding of ^{3}H-5HT to 5HT-1 receptors in guinea pig brain stem.

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