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Evolutionary conservation of the 5-HT_{2B} receptors

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We recently characterised the 5-HT_{2B} subfamily of serotonin receptors from human, mouse, and *Drosophila* species. The protein sequences and the pharmacology of these receptors are related, indicating a possible evolutionary conservation.

The 5-HT₂ family of serotonin (5-hydroxytryptamine, 5-HT) receptors mediates many central and peripheral physiological functions of serotonin in vertebrates. Central nervous system effects include neuronal sensitisation to tactile stimuli and mediation of the hallucinogenic effects of lysergic acid diethylamide and related phenylisopropylamine hallucinogens; Cardiovascular effects include contraction of blood vessels and alteration of platelet shape. The 5-HT₂ receptor (5-HT_{2R}) family comprises (i) the ubiquitous 5-HT_{2A}R (formerly 5-HT_{2R}), (ii) the 5-HT_{2C}R (formerly 5-HT_{1C}R), mainly expressed in the choroid plexus and (iii) the rat fundic 5-HT_{2F}R and the mouse 5-HT_{2C}R which have recently been assigned as to the new 5-HT_{2B}R subclass [1]. In addition, we recently cloned a 5-HT₂-like R in *Drosophila*.

Alignment of the mouse 5-HT_{2B} sequence [2] with that of various aminergic receptors, shows less than 30% homology with rat 5-HT_{1A}R and mouse 5-HT_{1B}R. This places this mouse cDNA within the 5-HT_{2R} family [3]. However, the levels of sequence identity with both the mouse 5-HT_{2A}R (60%) and 5-HT_{2C}R (57%) are low. By comparison, homologies between 5-HT_{2A}R and 5-HT_{2C}R of the same species are around 70%, and those between the 5-HT_{2A}R or the 5-HT_{2C}R from different species are over 95% and 85% respectively. The poor similarity of the rat 5-HT_{2B}R with the rat 5-HT_{2A}R and 5-HT_{2C}R (68%, and 70%, respectively) compared to its 88% homology with the mouse 5-HT_{2B}R protein over the transmembrane (TM) region, supports the classification of this rat receptor within the 5-HT_{2B}R subfamily. The human 5-HT_{2B}R [4-6], displays only 79% and 82% identity to the rat and mouse 5-HT_{2B} protein, respectively. The lower homologies observed with human 5-HT_{2A}R (71%) and 5-HT_{2C}R (73%) justify its classification as the third member of the 5-HT_{2B}R subfamily. Interestingly, we have cloned a distantly related *Drosophila* receptor cDNA that codes for a larger protein of 869 amino acids [7], which is more similar (40% homology over the TM region) to the mammalian 5-HT_{2A}R, 5-HT_{2B}R, or 5-HT_{2C}R than to any other receptor so far known including *Drosophila* 7TMRs. However, original characteristics distinguish this receptor, such as the presence of a long amino-terminus also described in the *Drosophila* muscarinic acetylcholine, serotonin 5-HTDro1, and octopamine receptors [8].

Confirming the sequence comparisons, the pharmacology of the 5-HT_{2B}Rs differs from that of other 5-HTRs. After transfection of the cDNAs into the monkey kidney COS-1 cells, the pharmacological profile of the 5-HT_{2B}Rs were analysed. The pharmacological values of the mouse 5-HT_{2B}R correlate with those of 5-HT_{2A}R (rs=0.64, p<0.001) or 5-HT_{2C}R (rs=0.42, p<0.05), but not with other 5-HT_{2R} subtypes. Furthermore, like 5-HT_{2A}R and 5-HT_{2C}R, the mouse 5-HT_{2B}R transfected into fibroblast cell line is coupled to the PLC second messenger system as well as in the serotonergic cell line 1C11* [9]. The pharmacological profile of the human 5-HT_{2B}R

correlates with that of the mouse 5-HT_{2B}R (rs=0.60, p<0.001) and pig 5-HT_{2C}R (rs=0.44, p<0.01) but not rat 5-HT_{2A}R. Moreover, the pharmacology published for the rat 5-HT_{2B}R either transiently expressed in COS cells [10] or stably expressed [11], do not correlates with that of the mouse, however strong correlation is obtained with the human 5-HT_{2B}R (not shown). Thus, despite their structural differences, the pharmacology of the rat 5-HT_{2B}R is closer to the that of the human than to that of the mouse. The comparison of *Drosophila* 5-HT₂R pharmacological properties (Figure 1- Table I) with those of other 5-HTR shows a good correlation with those of mouse 5-HT_{2B}R (rs=0.87, p<0.001), pig 5-HT_{2C}R (rs=0.64, p<0.001), rat 5-HT_{2A}R (rs=0.60, p<0.001), or human 5-HT_{2B}R (rs=0.55, p<0.01) [1, 9], but no significant correlation is seen for any other serotonin receptor (not shown). Therefore, it appears closer to the mammalian 5-HT₂Rs than to the *Drosophila* 5-HT₁DroR, 5-HTDro_{2A}R, and 5-HTDro_{2B}R [8]. In accordance with the new mammalian nomenclature [1], we propose this receptor be called 5-HT₂Dro and that 5-HTDro_{2A}, 5-HTDro_{2B}, and 5-HT₁Dro, be renamed 5-HT_{1A}Dro, 5-HT_{1B}Dro, and 5-HT₇Dro respectively.

The original long amino-terminus of the 5-HT₂DroR, when deleted affects only poorly the pharmacology (Table I): The most important effects are seen for the 5-HT, 5-CT, and ketanserin which change the affinity about 10 times. This indicates that the external N-terminus affects the conformation of the receptor TM regions involved in interactions with these compounds, information which may be of importance for receptor modelling which usually use deleted N-terminus receptor sequence.

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TABLE I - Competition experiment for [125I] DOI labeled membrane from 5-HT_{2Dro} and 5-HT_{2Dro} N-terminus deleted (N) COS-1 transfected cells. Comparison with the rat 5-HT_{2A}, mouse (M) and human (H) 5-HT_{2B} and pig 5-HT_{2C} receptors. Each value is the mean of at least 3 independent trial run in triplicate. 5-CT, 5-carboxamidotryptamine; 8-OH-DPAT, (±)-8-hydroxy-2-(di-n-dipropylamino) tetralin; TFMPP, N-(3-trifluoromethylphenyl) piperazine.

Drug	5-HT _{2A} R	5-HT _{2B} M	pKi 5-HT _{2B} H	5-HT _{2C} P	5-HT _{2Dro} N	5-HT _{2Dro}
Agonists						
1 N-Acetyl-5-HT	5.5	8.1	8.1	6.1	7.2	7.3
2 Tryptamine	6.0	6.9	6.8	7.2	5.8	5.9
3 5-CT	3.5	6.7	7.5	5.7	4.4	5.5
4 (±)a-Me-5-HT	7.3	6.5	6.8	7.3	6.8	6.7
5 5-HT	5.5	5.8	7.9	7.5	7.8	6.7
6 1-Me-5-HT	6.3	5.6	5.7	8.4	5.5	5.6
7 5-MeOH-Tryptamine	5.5	5.6	7.6	7.6	5.3	5.4
8 8-OH-DPAT	5.0	5.3	5.5	5.2	4.9	5.0
9 Quipazine	6.2	5.2	6.6	6.7	5.2	5.1
10 2-Me-5-HT	5.2	5.1	7.0	5.8	5.8	5.7
11 5-Me-Tryptamine	5.2	5.0	4.7	8.1	4.9	5.0
12 NNdiMe-5-MeOHTrypt.	6.2	4.9	5.2	7.0	4.2	4.3
28 RU 24969	6.0	4.9	7.2	6.5	4.3	4.4
Antagonists						
13 Ritanserin	9.3	8.4	7.6	8.6	8.3	8.4
14 Pizotifen	7.8	8.3	8.1	8.1	8.1	8.2
15 Methysergide	8.6	7.9	7.2	8.6	7.1	7.2
16 Mesulergine	8.4	7.7	7.4	8.8	7.2	7.3
17 Methiothepine	8.8	7.5	7.5	7.6	7.1	7.2
18 Cyproheptadine	8.5	7.6	7.3	7.9	7.2	7.4
19 Ketanserin	8.9	7.2	6.4	7.0	8.2	7.2
20 Spiperone	8.8	7.2	4.9	5.9	7.2	7.3
21 Setoperone	8.6	7.2	6.9	7.3	7.7	7.6
22 TFMPP	6.6	7.1	7.2	7.2	7.2	7.3
23 Rauwolscine	6.1	6.7	7.0	5.8	6.7	6.8
24 Buspirone	6.1	6.6	5.8	5.1	6.5	6.6
25 Yohimbine	6.0	6.4	7.4	4.4	6.4	6.4
26 Bufotenine	6.4	5.8	6.2	7.2	6.0	6.8
27 ICS 205-930	5.3	5.0	4.8	4.6	4.9	5.0
29 Iodocyanopindolol	4.9	4.7	4.3	5.0	4.8	4.6
30 MDL 72 222	6.8	4.7	<4	6.3	4.7	4.5
31 Mianserin	8.0	6.4	7.1	8.1	5.7	5.8
32 Cis-flupenthixol	7.6	6.6	6.8	6.1	5.4	5.5
33 Haloperidol	6.6	6.5	4.8	4.8	5.3	5.5
34 Clozapine	7.2	6.4	6.3	5.9	5.5	5.6
35 Sulpiride	4.5	4.9	4.3	4.1	6.0	5.9

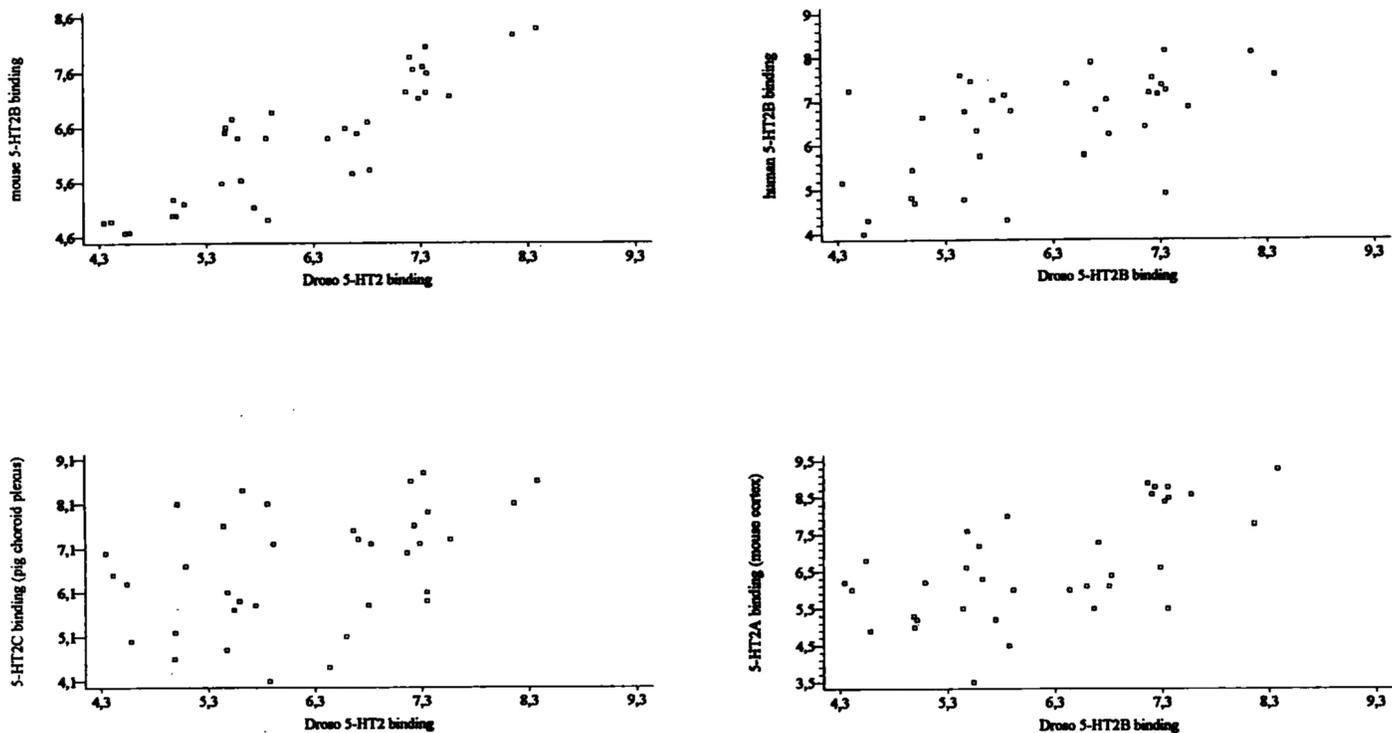


FIGURE 1 Comparison of pKi values of *Drosophila* 5-HT₂R with other 5-HTR