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Binding Potency of Paroxetine Analogues for the 5-Hydroxytryptamine Uptake Complex*

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Abstract—The in-vitro inhibition constants (K_i) of 14 structural analogues of the potent 5-hydroxytryptamine (5-HT)-uptake inhibitor paroxetine were determined to assess the structure-affinity relationship of these derivatives. A goal of these studies was to determine those positions on paroxetine which could be derivatized without significantly decreasing the affinity of the drug for the binding site, so that radiolabels such as [^{18}F]fluoroalkyl groups might be appended for future in-vivo imaging studies of the 5-HT uptake system. Using the methyl moiety as a steric probe for these studies, it was found that the rank order of potency of various methyl-substituted paroxetine analogues for inhibiting the binding of [^{3}H]paroxetine to the 5-HT re-uptake site was: 4′-≅ 3′-≅ 2″- > 2′-≅ 1- > 5″- > 6″-methyl. The in-vitro equipotent molar ratios (EPMR, K_i(analogue)/K_i(paroxetine)) of the analogues were determined, and the EPMRs of the 4′-, 3′-, and 2″-methyl derivatives were 1·9, 2·2 and 2·2, respectively. The 4′- and 2″-fluoromethyl and -fluoroethyl analogues were synthesized, and the EPMRs of the 4′- and 2″-fluoromethyl derivatives were determined to be 2·0 and 3·5, and those of the 4′- and 2″- fluoroethyl analogues were 5·2 and 6·2, respectively. The 2″-fluoromethyl analogue was unstable in aqueous solutions, and it is not a promising ligand for in-vivo studies. The 4′-fluoromethyl derivative was stable in aqueous solutions and, based upon its relatively high affinity, is a candidate for radiolabelling with ^{18}F for in-vivo positron emission tomography studies of the 5-HT re-uptake site.

Interest in the development of radioligands for in-vivo neuroreceptor studies using positron emission tomography (PET) has increased in recent years. PET studies of the 5-hydroxytryptamine (5-HT) system have focused on the postsynaptic 5-HT_2-receptor system (Wong et al 1984, 1987; Mayberg et al 1988; Blin et al 1990; Sadzot et al 1991). Successful PET studies of the presynaptic 5-HT uptake system have not been reported to date, since suitable positron-labelled radioligands have yet to be developed. In-vitro investigations have indicated that the regional cerebral concentration of 5-HT uptake sites is proportional to regional 5-HT-ergic innervation (De Souza & Kuyatt 1987; Cortes et al 1988). In-vivo studies of the presynaptic 5-HT re-uptake complex are of interest to determine changes in this system with depression (Perry et al 1983; Gross-Isseroff et al 1989), drug abuse (Battaglia et al 1987), and Parkinson's and Alzheimer's diseases (Raisman et al 1986; D'Amato et al 1987). In an effort to develop a useful radioligand for PET studies of the 5-HT re-uptake complex, analogues of the selective and potent 5-HT uptake inhibitor (−)-*trans*-paroxetine ((−)-*trans*-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)piperidine; (Fig. 1)) were synthesized, and their in-vitro inhibition constants (K_i) were determined against (−)-*trans*-[^{3}H]paroxetine[1].

Paroxetine

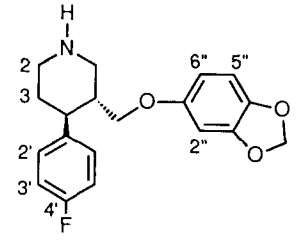

FIG. 1. Structure of paroxetine showing the three ring systems and position numbering schemes.

Paroxetine selectively binds to the 5-HT transporter complex located on platelets and presynaptic 5-HT CNS neurons (Habert et al 1985). Paroxetine has one of the highest affinities for the 5-HT uptake site of any antidepressant reported to date (Hytell 1982; Magnussen et al 1982; Plenge & Mellerup 1985; Habert et al 1985; Mellerup & Plenge 1986; Thomas et al 1987; Plenge et al 1987; Marcusson et al 1988). In addition, paroxetine has low affinity for non-5-HT-ergic transporter systems and other pre- and postsynaptic receptor sites (Habert et al 1985; Marcusson et al 1988). In-vitro studies of [^{3}H]paroxetine binding to cerebral tissue indicated that this ligand bound selectively to regions of rat and human brain known to contain high densities of the 5-HT re-uptake complex (Marcusson & Eriksson 1988; Laurelle et al 1988; Backstrom et al 1989; Gobbi et al 1990; Plenge et al 1990; Hrdina et al 1990). In-vivo studies of [^{3}H]paroxetine in mice and rats have demonstrated that the distribution of specific binding paralleled the distribution of 5-HT uptake sites in rodent brain (Scheffel &

[1] Unless otherwise noted, paroxetine and [^{3}H]paroxetine refer to the (−)-*trans*-enantiomer and (±)-*trans*-racemic mixtures are referred to as (±)-X.

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Hartig 1989; Hashimoto & Goromaru 1990a,b; Scheffel & Ricaurte 1990). The specific in-vivo binding of [^{3}H]paroxetine was selectively blocked by pretreatment of the animals with 5-HT uptake inhibitors, and pretreatment of rats with the 5-HT-ergic neurotoxin MDMA led to a reduction in specific [^{3}H]paroxetine binding in-vivo (Scheffel & Ricaurte 1990). These in-vitro and in-vivo data indicate that positron-labelled paroxetine would be valuable as a PET radioligand for studying 5-HT neurons in living human brain. Attempts to employ 1-([^{11}C]methyl)paroxetine for PET studies of the 5-HT transporter system were only partially successful as the 20·3 min half-life of ^{11}C was not sufficiently long to allow for the clearance of the non-specifically bound radioactivity for cerebral tissues (Villegmagne et al 1989; Scheffel & Ricaurte 1990). PET studies of positron-labelled paroxetine may require a longer-lived radionuclide such as ^{18}F (109·8 min half-life) so that relatively slow in-vivo non-specific binding clearance can be effected.

While paroxetine contains a fluorine atom at the 4-position of the prime aromatic ring (Fig. 1), an efficient radiosynthesis of high specific activity ^{18}F-labelled paroxetine is complicated by the nonreactive nature of this phenyl ring to nucleophilic substitution with [^{18}F]fluoride ion (Kilbourn 1990). Determination of the effects of chemical modification on binding potency was necessary to identify those positions on paroxetine which could be derivatized without significantly decreasing the binding affinity of the analogue for the 5-HT re-uptake site. Placement of a ^{18}F-labelled fluoroalkyl group (Gerdes et al 1988; Bishop et al 1991) at one of these sterically forgiving sites could lead to a fluorinated paroxetine analogue of value for PET studies of the presynaptic 5-HT uptake system. The effects of derivatization at seven different positions in paroxetine upon the binding potency of the analogues to the 5-HT transport complex are reported here.

Materials and Methods

In-vitro binding studies

Receptor binding assays were performed according to the methods of Habert et al (1985). Briefly, cerebral cortex from adult rat brains (Pel-Freeze Biologicals Inc., Rogers, AK, USA) was dissected and homogenized in 20 vol of 50 mM Tris-HCl buffer (pH 7·4 at 25°C) using a Brinkmann Polytron tissue homogenizer and then centrifuged (49 000 *g*) for 10 min. The supernatant was discarded and the pellet resuspended in the same volume of Tris-HCl buffer and incubated at 37°C for 10 min before a second centrifugation at 49 000 *g* for 10 min. The final pellet was resuspended at a concentration of approximately 1 mg wet wt mL^{-1} in 50 mM Tris-HCl buffer (pH 7·4) containing 120 mM NaCl and 5 mM KCl. The tissue suspension was immediately used in the binding assays.

Binding to the 5-HT uptake complex was determined using 0·1 mL of pH 7·4 Tris-HCl buffered [^{3}H]paroxetine (sp. act. 20·5 Ci mmol^{-1}, final binding assay concentrations 0·2–0·3 nM) as the radioligand, 0·1 mL buffered competing paroxetine analogue (added in increasing concentrations from 10^{-10} to 10^{-5} M), and 0·8 mL tissue suspension. Non-specific binding was determined by adding 0·1 mL of buffered 10 μM fluoxetine to 0·1 mL of the [^{3}H]paroxetine stock solution and 0·8 mL of the tissue suspension. Total binding was assessed by adding 0·1 mL of the [^{3}H]paroxetine stock solution to 0·1 mL of Tris-HCl buffer solution and 0·8 mL of the tissue suspension. Each assay group also included at least one competition curve for (−)-*trans*- or (±)-*trans*-paroxetine as the reference compound. Competition incubations were performed at 25°C for 60 min, and 5 mL of 50 mM Tris-HCl buffer (pH 7·7 at 4°C) were then added. The solutions were rapidly filtered under vacuum through Schleicher and Schuell (Keene, NH, USA) #32 glass fibre filters using a Brandell cell harvestor. The filters were washed twice with 5 mL of 50 mM Tris-HCl buffer (at 4°C) and air dried. The filters were transferred to scintillation vials, and 5 mL of Biosafe scintillation fluid (Research Products, Inc.) was added. The vials were shaken for 60 min at room temperature (23°C), and the radioactivity concentrations were determined by a Packard Model 2500TR liquid scintillation counter at approximately 41% efficiency. Data from the competition assays were plotted as percent of total specific binding vs log molar concentrations of unlabelled (competing) drug. The IC50 (inhibitor concentration of 50% [^{3}H]paroxetine binding inhibition) was determined from a Hill plot of seven or more data points. The inhibition binding constant (K_i) was calculated according to the relationship $K_i = IC50/(1 + [L]/K_D)$, where [L] = the concentration of free (unbound) [^{3}H]paroxetine and $K_D = 0{\cdot}15$ nM (Habert et al 1985). All determinations were performed in triplicate, and the mean ± standard error of the mean (s.e.m.) are reported.

Drugs

[^{3}H]Paroxetine was purchased from New England Nuclear (Boston, MA, USA). Paroxetine hydrochloride and fluoxetine hydrochloride were gifts from Beecham Pharmaceuticals (Betchworth, Surrey, UK), and Eli Lilly Co. (Indianapolis, IN, USA), respectively. The structural analogues of paroxetine (compounds (±)-1, (−)-2–(−)-4 or (±)-5–(±)-15; Table 1) were synthesized at Lawrence Berkeley Laboratory, and the spectroscopic properties (^{1}H NMR, ^{19}F NMR and IR) and elemental analyses were consistent with the assigned structures. Several of the paroxetine analogues (compounds (−)-2–(−)-4) were prepared from enantiomerically pure (−)-*trans*-paroxetine ((−)-1) such that the (−)-*trans* configuration of the parent molecule was retained. It is known (Plenge et al 1987) that (−)-*trans*-paroxetine possesses a higher binding affinity for the 5-HT transporter system than the (+)-*trans*-, (−)-*cis*-, and (+)-*cis*-enantiomers. For synthetic expediency, the more readily prepared (±)-*trans* racemic mixtures of compounds 5–15 were utilized for the exploratory structure-affinity studies described here. Racemic (±)-*trans*-paroxetine ((±)-1) was synthesized to compare the potency of the (±)-*trans* derivatives (compounds (±)-5–(±)-15) to an enantiomerically similar reference standard. The equipotent molar ratios (EPMR) of the analogues (i.e. the ratio of the K_i of the (−)-*trans* or (±)-*trans* analogue of paroxetine to the K_i of (−)-1 or (±)-1) indicate how many times less potent the analogues were in competing for the 5-HT re-uptake site as compared with their enantiomerically similar paroxetine standard.

Results and Discussion

A representative in-vitro competitive binding plot for the 4′-fluoromethyl derivative (±)-9 is shown in Fig. 2, and the binding results for paroxetine and 14 analogues are presented in Table 1. The two paroxetine standards (−)-1 and (±)-1 differed in binding affinity for the 5-HT re-uptake complex by a factor of 2·6, with (−)-1 displaying greater affinity than (±)-1 in agreement with the reported higher affinity of (−)-1 compared with (+)-1 (Plenge et al 1987). The EPMR of (−)-*trans*-*N*-methylparoxetine ((−)-2) was 5·3, which is about a factor of two lower than that reported by Plenge et al (1987). The (−)-*trans*-*N*-fluoroethyl and (−)-*trans*-*N*-fluoropropyl analogues ((−)-3 and (−)-4) were several orders of magnitude less potent than (−)-*trans*-paroxetine, indicating that *N*-[^{18}F]fluoroalkyl-containing compounds are not likely candidates for in-vivo studies of the 5-HT uptake complex. The EPMR of the desfluoro compound (±)-5 was slightly higher than that measured by Plenge et al (1987) (1·4 vs 0·91).

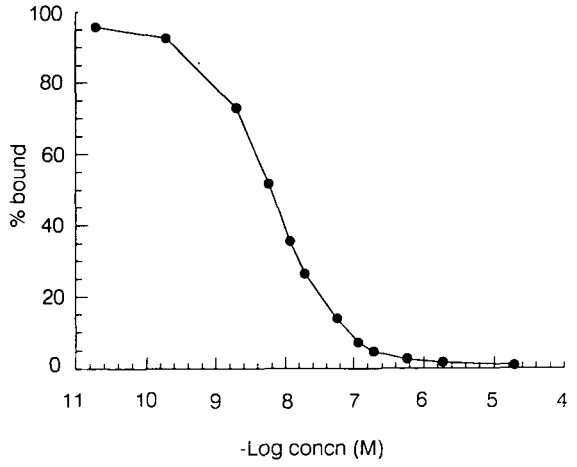
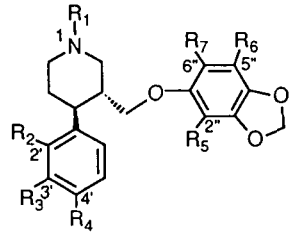


FIG. 2. In-vitro competition of (±)-*trans*-4′-fluoromethylparoxetine (compound (±)-9) with (−)-*trans*-[^{3}H]paroxetine binding to rat cortical membranes. Percent bound was calculated from the ratio of specific binding at each concentration of competitor to total specific binding. Specific binding at each concentration of competitor was defined as the difference between the activity bound and non-specific activity bound (with 10 μM fluoxetine added), and total specific binding was defined as the difference between the total binding (no competitor added and [^{3}H]paroxetine ≅ 0·2 nM) and non-specific binding.

Methylation of the prime ring at the 3′- and 4′-positions resulted in (±)-*trans*-derivatives ((±)-7 and (±)-8) which were only about a factor of two less potent than (±)-1. The 2′-methyl derivative ((±)-6) was less potent than the 3′- and 4′-methyl analogues and resulted in an EPMR of 5·2. Fluoroalkylation at the 4′-position yielded the 4′-fluoromethyl ((±)-9) and 4′-fluoroethyl ((±)-10) compounds. The 4′-fluoromethyl derivative (±)-9 was quite potent with an EPMR of 2·0, and the 4′-fluoroethyl derivative (±)-10 was less potent than the 4′-fluoromethyl analogue with an EPMR of 5·2. Exploratory fluoroalkylation at the 3′-position offered no apparent advantages over fluoroalkylation at the

Table 1. Sites of substitution, in-vitro inhibition binding constants (K_i)[a], and equipotent molar ratios (EPMR)[b] of paroxetine and paroxetine analogues.



Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	K_i (nM)	EPMR
(−)-1	H	H	H	F	H	H	H	0·81±0·15	1·0[c]
(−)-2	CH_3	H	H	F	H	H	H	4·3±0·2	5·3
(−)-3	$(CH_2)_2F$	H	H	F	H	H	H	360±90	440
(−)-4	$(CH_2)_3F$	H	H	F	H	H	H	150±10	190
(±)-1	H	H	H	F	H	H	H	2·1±0·2	1·0[c]
(±)-5	H	H	H	H	H	H	H	3·0±0·5	1·4
(±)-6	H	CH_3	H	H	H	H	H	11±2	5·2
(±)-7	H	H	CH_3	H	H	H	H	4·6±1·2	2·2
(±)-8	H	H	H	CH_3	H	H	H	4·0±0·5	1·9
(±)-9	H	H	H	CH_2F	H	H	H	4·1±0·7	2·0
(±)-10	H	H	H	$(CH_2)_2F$	H	H	H	11±3	5·2
(±)-11	H	H	H	F	CH_3	H	H	4·7±1·1	2·2
(±)-12	H	H	H	F	CH_2F	H	H	7·3±1·1	3·5
(±)-13	H	H	H	F	$(CH_2)_2F$	H	H	13±1	6·2
(±)-14	H	H	H	F	H	CH_3	H	160±30	76
(±)-15	H	H	H	F	H	H	CH_3	80±27	38

[a] Rat cortical membranes were labelled with [^{3}H]paroxetine. See Methods for details. The IC50, from which the K_i was calculated, was determined from a Hill plot of seven data points in triplicate. The K_i data represent the mean ±s.e.m. of three or more individual determinations performed on separate days. [b] The equipotent molar ratio (EPMR) of the analogues is the ratio of the K_i of the (−)-*trans* or (±)-*trans* analogue of paroxetine (compounds (−)-2–(−)-4 or (±)-5–(±)-15) to the K_i of (−)-1 or (±)-1, respectively. [c] The EPMRs of (−)-1 and (±)-1 are both 1·0, as each compound served as a reference either for compounds (−)-2–(−)-4 or (±)-5–(±)-15.

4′-position, as the 3′-methyl compound (±)-7 displayed a similar potency compared with the 4′-methyl compound (±)-8.

Methylation of the double prime ring (Fig. 1) resulted in the identification of only one favourable site for fluoroalkylation. The 2″-methyl analogue ((±)-11) had an EPMR of 2·2, while the 5″- and 6″-methyl derivatives ((±)-14 and (±)-15) were more than an order of magnitude less potent than (±)-11. The 2″-fluoromethyl analogue (±)-12 was found to be only slightly less potent than the 4′-fluoromethyl analogue (±)-9, but (±)-12 was found to be unstable in pH 7·4 aqueous solvent systems. In contrast, the 4′-fluoromethyl derivative (±)-9 was stable in aqueous solutions. The 2″-fluoroethyl analogue (±)-13 demonstrated a factor of about two decreased affinity for the 5-HT uptake site, compared with the 2″-fluoromethyl analogue (±)-12.

Conclusions

Studies of the effects of methyl group derivatization at seven different positions on (−)-*trans*- and (±)-*trans*-paroxetine identified several sites as candidates for fluoroalkylation. The rank order of potency of the various methyl-substituted paroxetine analogues for inhibiting the binding of [^{3}H]paroxetine to the 5-HT transporter system was determined to be: 4′-≅ 3′-≅ 2″->2′-≅ 1->5″->6″-methyl. The fluoromethyl and fluoroethyl derivatives at the 4′- and 2″-positions were synthesized, and the (±)-*trans*-4′-fluoromethylparoxetine analogue ((±)-9) displayed chemical stability in aqueous solutions and possessed 50% of the potency of (±)-*trans*-paroxetine for inhibiting [^{3}H]paroxetine binding to the 5-HT uptake site. Future efforts will be directed towards obtaining the (−)-*trans*-enantiomer of [^{18}F]-4′-fluoromethylparoxetine for evaluation in PET studies of the 5-HT re-uptake complex.

Acknowledgements

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