Key Words: paroxetine, pharmacology, serotonin, serotonin transporter

Neuropharmacology of Paroxetine

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ABSTRACT *~ Paroxetine is a potent and selective serotonin reuptake inhibitor (SSRI) with some neuropharmacologic properties unique among this class of compounds. The findings of early in vitro studies demonstrated the potency of paroxetine at inhibiting 5-HT uptake in rat synaptosomes. Paroxetine also has been shown to be a potent and selective inhibitor of the human serotonin transporter (SERT) and has recently been demonstrated to have moderate affinity for the norepinephrine transporter (NET). Because of the affinity and in vitro selectivity of this SSRI, tritiated paroxetine is now widely used as a marker for SERT in laboratory settings, and its use has advanced our understanding of neurotransmitter function in the brain and periphery. The in vivo pharmacologic properties of paroxetine are well characterized, especially following acute administration. However, the pharmacologic effects of chronically administered paroxetine remain an active area of study. Paroxetine administration in laboratory animals has been shown to be associated with decreased SERT density and function, maintenance of normal firing rates and release of 5-HT, and increased activation of postsynaptic 5-HT receptors. Using a novel ex vivo assay, we have demonstrated that paroxetine exhibits dose-related inhibition of the NET in patients treated for depression. At usual clinical doses (ie, 20 mg/d), paroxetine is a potent and selective inhibitor of the SERT; however, at higher doses (ie, ≥40 mg/d), paroxetine can exhibit marked NET inhibition. The application of these findings of in vivo NET inhibition by paroxetine in the treatment of mood and anxiety disorders will be informed by further clinical studies.* Psychopharmacology Bulletin. *2003;37(Suppl 1):8–18.*

INTRODUCTION

Although the directors of drug discovery for many pharmaceutical companies in the 1970s were not fully convinced that drugs that solely block serotonin (5-HT) uptake would possess antidepressant efficacy, seminal work in the late 1960s by the Nobel Laureate, Arvid Carlsson, and others, provided evidence in support of this hypothesis. Consequently, a number of pharmaceutical companies synthesized compounds that were selective inhibitors of 5-HT uptake and lacked activity at receptors responsible for the adverse effects of tricyclic antidepressants (eg, α_1,

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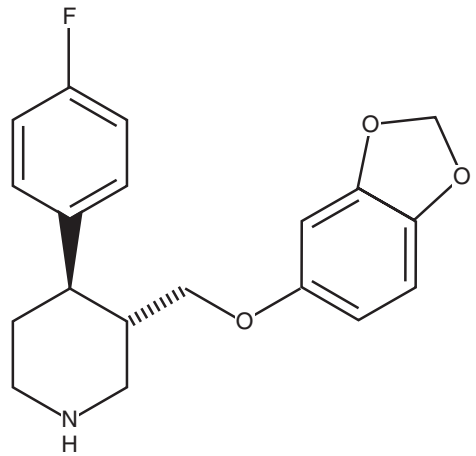
H_1, M_1). The first of these, fluoxetine, was reported by researchers at Eli Lilly and Company in 1974,[1,2] although advanced development as an antidepressant apparently did not begin in earnest until the benefits of zimelidine, the first marketed selective serotonin reuptake inhibitor (SSRI), were apparent.

In the course of screening a series of phenylpiperidine derivatives for pharmacological activity, investigators at the Danish pharmaceutical company Ferrosan identified several compounds that exhibited potent 5-HT uptake inhibition. The first compound of this series was femoxetine.[3] Shortly thereafter, the structural analogs paroxetine (Figure 1) and its dystomer (FG 7052) were also reported to inhibit 5-HT uptake in vitro and in vivo. Paroxetine was several-fold more potent than femoxetine.[4] Although referred to by its in-house designation FG 7051 at the time of the acceptance of the paper by Petersen and coworkers[4] in January of 1977, by June of 1977, the compound was known as paroxetine. Early clinical trials were already under way by the spring of 1978[5,6]; however, full-scale development of paroxetine as an antidepressant was also delayed. Paroxetine was approved for human use in the United Kingdom market in 1991 and in the United States in 1993. Although paroxetine was not the first in its class to reach the market in the United States, it was SmithKline Beecham who coined the term SSRI.

FIGURE 1

CHEMICAL STRUCTURE OF PAROXETINE



(3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluoropheny)-piperidine; (-)-paroxetine.

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IN VITRO PHARMACOLOGY

The findings of in vivo pharmacology studies of paroxetine, including reductions in whole blood serotonin, protection from PCA-induced decreases in serotonin, and changes in pressor responses to serotonergic challenges, were all consistent with 5-HT uptake blockade. However, the in vitro potency of paroxetine and other compounds to inhibit [^{3}H]-5-HT uptake into synaptosomes prepared from rodent brain represented the most direct evidence of the pharmacology of this emerging class of compounds.[7] Some of the initial affinity data for these compounds are presented in Table 1.

Paroxetine, which is the *trans*-(-)-(3*S*, 4*R*)-isomer of 4-(*p*-fluorophenyl)-3-((3,4 methylene dioxyphenoxy)-methyl)-piperidine (Figure 1), is 60 to 180 times more potent in inhibiting 5-HT uptake than the other 3 stereoisomers of this structure.[13] Metabolism of paroxetine via cleavage of the methylenedioxy bridge produces a catechol intermediate that quickly forms either of 2 metabolites: a 3-hydroxy-4-methoxy metabolite or a 3-methoxy-4-hydroxy metabolite. Both are approximately 60 to 80 times weaker at inhibiting 5-HT uptake than paroxetine. Moreover, these metabolites are rapidly conjugated to either glucuronide or sulfate, resulting in polar metabolites that are essentially inactive.[14]

More recently, detailed uptake and binding studies have been performed using rodent and the now cloned human monoamine transporters (Table 2). Paroxetine is a potent and selective inhibitor of the serotonin transporter (SERT) and 5-HT uptake in vitro (Tables 1 and 2). Although paroxetine has a very high affinity for the SERT, recent

TABLE 1

EARLY STUDIES' RANGE OF AFFINITIES OF INVESTIGATIONAL SSRIS FOR THE SERT AND NET TRANSPORTERS[7-12]

	5-HT UPTAKE	[^{3}H]-PAROXETINE BINDING	NE UPTAKE
Drug	IC_{50} *(nmol/L)*	K_i *(nmol/L)*	IC_{50} *(nmol/L)*
Paroxetine	0.29-3.2	0.11-0.15	81-350
Femoxetine	8-80	20	710
Citalopram	1.8-11	1	3900-6100
Fluoxetine	6.8-30	14	370-500
Fluvoxamine	3.8-6.2		620-1100
Zimelidine	170-300		8600
Sertraline	0.19		160
Imipramine	45-100	41	65

SERT=serotonin transporter; NET=norepinephrine transporter; 5-HT=serotonin; NE=norepinephrine; SSRI=selective serotonin reuptake inhibitor.

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studies using the human norepinephrine transporter (NET) show that paroxetine also possesses moderate affinity for the NET (Table 2). Whether this is relevant to the pharmacology of paroxetine at doses used clinically is discussed later in this review. Other than this moderate affinity for the NET, paroxetine possesses little affinity for any other transporter or receptor. The only exception is the muscarinic cholinergic receptor, where paroxetine also displays moderate affinity (ie, affinity values slightly less than 100 nmol/L).[11,12,15]

TABLE 2

RANGE OF AFFINITIES OF VARIOUS ANTIDEPRESSANTS FOR THE SERT, NET, AND DAT TRANSPORTERS

Inhibition of monoamine uptake (K_i; nmol/L)

	5-HT UPTAKE		NE UPTAKE		DA UPTAKE	
Drug	*Human*	*Rat*	*Human*	*Rat*	*Human*	*Rat*
Paroxetine	0.34-0.83	0.73	156-328	33	963	1700
Sertraline	2.8-3.3	3.4	925-1716	220	315	260
Citalopram	8.9-9.6		5000-30,000		>100,000	
Escitalopram	2.5		6500			
Fluoxetine	5.7-20	14	574-2186	143	5960	3050
Fluvoxamine	11-14		1100-4700		32,000	
Venlafaxine	102	39	1644	210		5300
Imipramine	20	41	142	14		11,000
Desipramine	163	180	3.5	0.61		11,000

Binding affinity (K_i; nmol/L) data from references 15, 16, 18. Selectivity is a unitless value with numbers >1 representing relatively greater affinity for the serotonin (SERT) vs the norepinephrine (NET) and dopamine (DAT) transporters, respectively.

	SERT	NET	DAT	SELECTIVITY	SELECTIVITY
Drug	*Human*	*Human*	*Human*	*SERT vs NET*	*SERT vs DAT*
Paroxetine	0.065-0.13	40-85	268-490	300-1310	2680-3700
Sertraline	0.15-0.29	420-817	22-25	1400-5450	85-86
Citalopram	1.2-1.6	4070-7865	16,540-28,100	3500-5243	2400-10,340
Escitalopram	1.1	7841	27,400	7130	25,000
Fluoxetine	0.81-1.1	240-777	3600-3760	300-863	3420-4300
Fluvoxamine	1.6-2.3	1300-2950	9200-16,800	580-1840	4100-7300
Venlafaxine	7.5-8.9	1060-2269	9300	120-300	1000
Imipramine	1.3-1.4	20-37	8500	15-27	6100
Desipramine	18-22	0.63-0.83	3190	0.03-0.05	180

Range of affinities of various antidepressants for the serotonin (SERT), norepinephrine (NET), and dopamine (DAT) transporters.

Human data from references 15, 16; rat data from reference 17.
5-HT=serotonin; DA=dopamine; NE=norepinephrine.

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The high in vitro affinity and selectivity of paroxetine led to the widespread use of commercially available [^{3}H]-paroxetine as a marker for SERTs. Thus, [^{3}H]-paroxetine has gained widespread laboratory use to visualize the SERT using autoradiography and for quantifying SERT density in brain and other tissues, such as platelets.[8,19,20]

IN VIVO PHARMACOLOGY

As noted earlier, the preclinical in vivo pharmacology of paroxetine was consistent with its primary action as an antagonist of the SERT. As reviewed elsewhere,[21,22] paroxetine alters sleep architecture in rats and humans as do other SSRIs.[23,24] Behavioral tests have shown that paroxetine possesses antianxiety activity in rodent behavioral models,[25,26] confirming the results of clinical studies. Recent data by Plotsky and colleagues[27] reveal that chronic paroxetine administration decreases endocrine and behavioral measures of anxiety in adult rats exposed to early-life stress. Chronic paroxetine administration also reduces the increased alcohol consumption in rats exposed to early-life stress. Of considerable interest, these neurochemical, endocrine, and behavioral alterations return to pretreatment baseline levels 2 weeks following cessation of paroxetine administration, which suggests that normalization of these early-life stress-induced changes in physiology and behavior requires maintenance of steady-state paroxetine concentrations.

Because clinical response is typically delayed 3 to 5 weeks or longer following initiation of antidepressant treatment in patients with major depression, investigators have long been interested in elucidating the neurochemical changes that occur following chronic, but not acute, antidepressant administration. The goals are elucidation of the target system(s) responsible for efficacy, as well as identifying novel targets for new antidepressant drug development. Various neurochemical changes have been scrutinized following paroxetine administration. Many, but not all, of these studies used once-daily dosing. Because of marked pharmacokinetic differences in metabolism between rodents and humans, we are not confident that once-daily administration in rodents appropriately mirrors the human situation. Nevertheless, we review some of the reported findings below.

Actions on the SERT

Early studies focused on the effects of antidepressant treatment on the SERT itself. Most of the early studies revealed that the number of SERTs was unaffected by chronic antidepressant treatment (eg, citalopram or chloroimipramine).[28] In contrast to these findings, chronic paroxetine administered via osmotic minipump (ie, continuous paroxetine exposure) resulted in 60% to 70% decreases in SERT density as determined from

binding studies.[29] These investigators also provided electrophysiological and ex vivo 5-HT uptake measures consistent with a decrease in SERT function. Very similar findings have been reported by Benmansour and colleagues.[30] Chronic paroxetine, delivered by minipump, reduced SERT density by 80% to 90%. These biochemical findings were further supported by electrochemical recordings showing that acute challenge with an SSRI did not modify 5-HT clearance from extracellular fluid in rats chronically treated with paroxetine. This would be consistent with a decrease in SERT density. However, consistent with other findings, SERT mRNA expression in the raphe nucleus was unaltered. These findings suggest that changes in SERT density and function are not related directly to changes in SERT gene regulation. One mechanism to explain these findings may be related to antidepressant-induced changes in SERT trafficking and internalization. Indeed, it has been convincingly shown that insertion and removal of the SERT from the cell surface membrane is highly regulated.

Other In Vivo Properties

A number of other biochemical changes have been reported to occur after paroxetine administration; however, their importance or consistency is not well established. Thus, chronic paroxetine has been reported to decrease 5-HT synthesis[31,32] and to decrease 5-HT_{1A} and 5-HT_{2A} receptor density,[33] 5-$HT_{2C/2B}$ responsivity,[34] and 5-HT_{1B} receptor number within the dorsal raphe nucleus.[35] Chronic paroxetine administration has been reported to increase binding of [^{3}H]-nociceptin to opioid receptor-like receptors in the dorsal raphe, although the significance of this finding is obscure.[36]

Of considerable theoretical interest is the observation that SSRIs, including paroxetine, increase the synthesis of allopregnanolone (3α-hydroxysteroid-5α-pregnan-20-one) in brain tissue, apparently by increasing the affinity of the enzyme 3α-hydroxysteroid dehydrogenase for its substrate.[37,39] 3α-hydroxysteroid dehydrogenase converts 5α-dihydroprogesterone into allopregnanolone. The neurosteroid allopregnanolone is a potent, positive, allosteric modulator of $GABA_A$ receptors and is a powerful, anxiolytic, anticonvulsant, and anesthetic agent. It is logical to speculate that this mechanism might play some role in the well-established antianxiety effects of paroxetine.

Effects of Chronic Paroxetine Administration

Led primarily by seminal studies from de Montigny and Blier, the effects of chronic antidepressant treatment on the serotonergic system have provided the rationale for new treatments, and provided some insight into the putative mechanism(s) responsible for antidepressant

efficacy. Because SSRIs block the SERT and increase extracellular 5-HT concentrations, one of the most consistent effects of paroxetine and other SSRIs is the decrease in the spontaneous firing rate of serotonergic neurons within the dorsal raphe following initial SERT blockade. This is explained by acute increases in extracellular 5-HT activating inhibitory 5-HT_{1A} autoreceptors on serotonin neuronal dendrites within the dorsal raphe. Of particular importance is the observation that after chronic paroxetine treatment, desensitization of this response occurs and serotonergic neuronal firing rates return to baseline frequencies. In addition, SSRIs such as paroxetine also decrease the function of terminal 5-$HT_{1B/1D}$ autoreceptors. Thus, chronic paroxetine administration results in continuous blockade of the cell surface SERTs, perhaps a loss of SERTs from the cell surface (*vida supra*), maintenance of normal firing rates (a result of functionally desensitized 5-HT_{1A} somatodendritic autoreceptors), maintenance of 5-HT release from terminals (functionally desensitized 5-HT terminal autoreceptors), and ultimately a chronic augmentation of postsynaptic 5-HT_{1A} receptor activation.[40-44] Although chronic paroxetine treatment does not modify the function of α_2-heteroceptors on 5-HT terminals,[45] coadministration of drugs that do decrease α_2-heteroceptor function and paroxetine results in even greater augmentation of serotonergic neurotransmission.[46] These findings of augmented serotonergic neurotransmission have been studied in the rat hippocampus. Whether these findings generalize to all, or any other, brain regions is not known, nor is it known whether these findings within the hippocampus are those that are responsible for antidepressant efficacy. More recently, involvement of other transmitter systems and subcellular proteins has gained increasing importance in our theories regarding antidepressant mechanisms, but this area is beyond the scope of our current review.

Actions on the NET

As expected from its pharmacology, acute and chronic paroxetine administration increases extracellular concentrations of 5-HT as demonstrated by in vivo microdialysis techniques.[47-50] Acute administration of paroxetine did not alter extracellular norepinephrine concentrations; however, there was a dose-dependent 2-fold increase in hippocampal extracellular norepinephrine concentrations following chronic paroxetine treatment.[47,48]

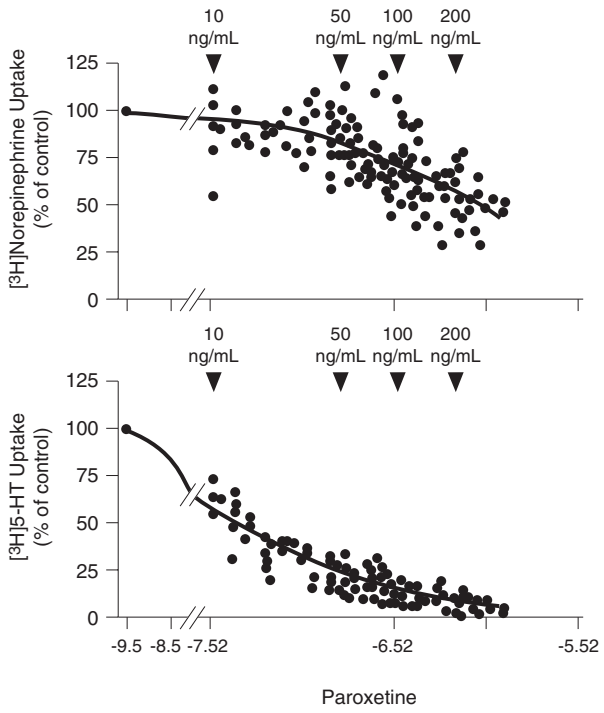
When taken together with the in vitro binding and uptake data reviewed earlier (Table 2), this finding suggests that in addition to its pronounced SERT antagonism, paroxetine may inhibit the NET at certain concentrations in vivo. Indeed, we have previously reported that chronic administration of paroxetine to rats dose-dependently blocks the NET

in vivo.[51] In that study, serum paroxetine concentrations between 100 and 500 ng/mL produced a 21% inhibition of the NET. These concentrations would be associated with nearly complete SERT blockade.

In an attempt to determine whether paroxetine inhibits the NET in humans during treatment, we used a novel ex vivo assay to assess NET inhibition in depressed patients treated for depression.[52] As shown in Figure 2, paroxetine treatment resulted in a concentration-dependent inhibition of the SERT and NET. We observed that at low serum concentrations, associated with low doses, paroxetine is a potent inhibitor of the SERT. However, paroxetine also exhibited some NET inhibition at higher concentrations (ie, higher doses) as predicted in in vitro studies[15,16,18,40] and a recent in vivo study.[51] There is a direct correlation

FIGURE 2

UPTAKE OF NOREPINEPHRINE IN PATIENTS TREATED WITH PAROXETINE



Curves were generated from data from 27 patients who received paroxetine. Classic 1-site competition curves used to describe drug-transporter interactions resulted in goodness-of-fit values of R2=0.51 for norepinephrine uptake in patients taking paroxetine and R2=0.96 for 5-HT uptake in patients taking paroxetine. In the panel depicting norepinephrine uptake for paroxetine, 6 data points ranging from 125%-150% of control are not shown to assist in visual comparison among the panels. These data points were used, however, to generate the competition curves. The 100% control data points are obtained from the individual patient's serum obtained prior to initiation of drug treatment. X-axis scale is paroxetine serum concentrations in log [mol/L]. Data from reference 52.

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between dose and serum concentration of paroxeltine, and low doses of paroxetine (20 mg/d) are associated with considerable SERT inhibition. Significant NET inhibition by paroxetine is not observed until higher doses of paroxetine (≥40 mg/d) are administered.

It is not known at this time whether the observed partial inhibition of the NET by paroxetine physiologically alters the clearance of norepinephrine from extracellular fluid or whether this contributes to the efficacy of paroxetine. However, preliminary data obtained from NET knockout mice undergoing classic behavioral testing for antidepressant efficacy suggest that both paroxetine and bupropion may utilize the NET to elicit their pharmacological actions in vivo.[53]

CONCLUSION

In summary, paroxetine is similar to, but distinct from, other members of the SSRI class. It is a very potent SERT antagonist in vitro. However, paroxetine does possess moderate affinity for the NET, and some NET inhibition appears to occur during treatment with clinically relevant doses. These data suggest that at higher doses, paroxetine is not merely an SSRI but a serotonin/norepinephrine reuptake inhibitor (SNRI). The clinical significance of this action on norepinephrine uptake is unknown, but this action may contribute to the broad therapeutic efficacy of paroxetine in the treatment of depression, panic disorder, social anxiety disorder, posttraumatic stress disorder, and generalized anxiety disorder. ✤

DISCLOSURE

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