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Comparison of the Effects of Sertraline and Its Metabolite Desmethylsertraline on Blockade of Central 5-HT Reuptake In Vivo

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N-demethylation of the selective serotonin reuptake inhibitor sertraline to desmethylsertraline yields a compound with 10- to 20-fold less potency at blocking serotonin (5-HT) reuptake as measured in vitro. In the present study desmethylsertraline (DMS) was examined in two in vivo models of reuptake inhibition—elevation of extracellular 5-HT in the corpus striatum as measured by microdialysis and inhibition of firing of serotonin-containing dorsal raphe neurons. Whereas sertraline (1, 3.2, and 10 mg/kg SC) produced a dose-dependent increase in extracellular 5-HT and a decrease in 5-HIAA in rat striatum, desmethylsertraline was without effect on either parameter. In similar fashion, desmethylsertraline had no effect on dorsal raphe cell firing at a dose (1,000 μg/kg IV) nearly 20-fold the ED_{50} for sertraline (52 μg/kg). Taken together, these data suggest that DMS does not contribute to the blockade of central 5-HT reuptake produced by sertraline in vivo and therefore would be expected to play a negligible role in its clinical activity.
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KEY WORDS: *Selective serotonin reuptake inhibitor; Sertraline; Desmethylsertraline; Microdialysis; Electrophysiology; Dorsal raphe nucleus; Striatum*

Sertraline (Zoloft®) is a potent and selective serotonin reuptake inhibitor (SSRI) that has proven to be a clinically effective and well-tolerated treatment of depression and obsessive-compulsive disorder. Like many reuptake inhibitors, sertraline undergoes biotransformation via N-demethylation in vivo to form the desmethyl metabolite (Tremaine et al. 1989) (Figure 1). In general N-demethylation of reuptake inhibitors can have a variety of effects on the pharmacological activity of the parent drug. For example, the N-demethylation of fluoxetine to norfluoxetine results in a retention of potency in blocking 5-HT reuptake (Wong et al. 1975; Bolden-Watson and Richelson 1993) whereas biotransformation of citalopram to desmethylcitalopram produces a compound with reduced inhibitor potency (Pawlowski et al. 1985). In in vitro measures of 5-HT reuptake and binding to the reuptake site, desmethylsertraline (DMS) was shown to be 10- to 20-fold less potent than the parent compound (Koe et al. 1983; 1990; Bolden-Watson and Richelson 1993); however, little information is available regarding the metabolite in in vivo measures of 5-HT reuptake.

In this communication desmethylsertraline is characterized in two in vivo models in which SSRIs have been shown to be active—elevation of extracellular 5-HT in corpus striatum as measured by microdialysis (Fuller 1994) and inhibition of firing of serotonin-containing dorsal raphe neurons (Sheard et al. 1972). The activity of the SSRIs in each model is thought to be a consequence of their ability to block 5-HT reuptake. On nerve endings SSRIs block the reuptake carrier that normally removes released 5-HT from the synapse, and in doing

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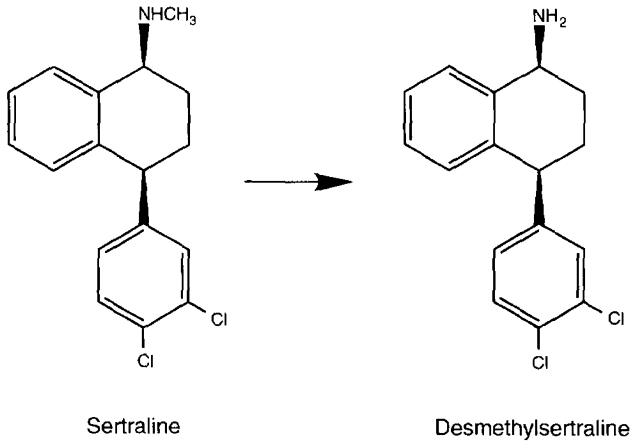

Figure 1. N-demethylation of sertraline to desmethylsertraline.

so they elevate extracellular 5-HT. At the same time SSRIs also block the reuptake carrier located on the cell bodies; the elevated 5-HT within the raphe nucleus in turn activates 5-HT autoreceptors that negatively modulate firing rate.

The results of these experiments with DMS are discussed in terms of the relative role of the metabolite in the reuptake blocking activity of the parent compound and consequently its clinical properties. Portions of this work were previously reported in abstract form (Sprouse et al. 1994).

METHODS

Microdialysis

I-shaped concentric microdialysis probes (8 mm long with a 4-mm dialysis tip) were constructed according to methods previously described (Santiago and Westerink 1990) and implanted in the striatum (coordinates AP +0.5, ML +3.0, DV −8.0; Paxinos and Watson 1986) of male Sprague-Dawley rats (300–350 g) under ketamine (75 mg/kg IM) and xylazine (10 mg/kg IM) anesthesia. Following surgery the rat was placed in a perspex cage inside an insulation box (BRS/LVE, Laurel, MD, USA), and the probe inlet was connected via flexible PEEK tubing (ID 0.005'') and a dual channel fluid swivel system (Instech Laboratories Inc., Plymouth Meeting, PA, USA), to a CMA/100 microperfusion pump (CMA/Microdialysis, Acton, MA, USA). The probe was perfused overnight with artificial cerebrospinal fluid (ESA Inc., Bedford, MA, USA) at 1.5 µl/minute, and the next day experiments were started by connecting the probe outlet with flexible PEEK tubing to a 30-µl sample loop of an HPLC valve with actuator (Valco Instruments Co., Houston, TX, USA), built in an ANTEC DECADE electrochemical detector (ANTEC, Leiden, Netherlands). Microdialysate samples were thus collected on-line and automatically injected every 25 minutes. Injection frequency and attenuation changes during the chromatographic run were controlled by the timeline program of the ANTEC DECADE. The analytes were separated at 35°C over a Hypersil 150 × 3 mm, C18, 3-µ column (Keystone Scientific, Inc., Bellefonte, PA, USA), using a 75 mM sodium phosphate mobile phase of pH 5.0, containing 0.8 mM octanesulfonate, 5% acetonitrile, 8% methanol, 3 mM triethylamine, and delivered at a flow rate of 0.4 ml/minute by an ESA 580 pump. Amperometric detection of 5-HIAA and 5-HT was performed using the glassy carbon electrode of the ANTEC DECADE detector, set at 500 mV versus Ag/AgCl. Extracellular levels of 5-HIAA and 5-HT were quantified by comparing peak heights with those of standards.

After obtaining a stable baseline (5–8 samples), drugs were administered subcutaneously in a volume of 2 ml/kg. Effects of drug treatments on extracellular 5-HT were followed for at least 4 to 6 hours after drug administration. 8-OH-DPAT (0.5 mg/kg SC) was routinely injected at the end of the experiment to confirm the neurogenic origin of the 5-HT peak in the chromatogram. Dialysate concentrations were not corrected for probe recovery and were expressed as percentages of the basal concentrations (average of last five samples before drug administration). Animals were unanesthetized and unrestrained during the collection periods.

Dorsal Raphe Recordings

Extracellular single-unit recordings were made in chloral hydrate-anesthetized male Sprague-Dawley rats (250–350 g) using standard electrophysiological techniques (Sprouse and Aghajanian 1987). Serotonin-containing neurons were identified on-line by their wide duration action potentials and slow rhythmic firing rate. Cells with these characteristics in the dorsal raphe nucleus have been confirmed to be 5-HT neurons by intracellular double-labeling (Aghajanian and Vandermaelen 1982). Unit activity was integrated over 10-second periods and continuously plotted as a firing rate histogram. Compounds were administered IV in a volume of 1 ml/kg and the effects on firing rate noted. A decrease in firing rate from baseline was taken as an indicator of 5-HT_{1A} autoreceptor activation.

Statistics

In the microdialysis experiments data were expressed as the mean percentage of basal extracellular concentrations ± SEM. Statistical analysis was performed by repeated-measures analyses of variance (ANOVA) with Newman-Keuls post hoc comparisons between baseline and postinjection levels of 5-HT and 5-HIAA. Correlations between the dose of sertraline or DMS and maximal effects on extracellular 5-HT or 5-HIAA levels were

examined by linear regression. In the electrophysiology experiments, the results were expressed as the mean percentage inhibition of baseline dorsal raphe firing rate ± SEM. A single factor ANOVA was employed to probe for dose dependency of the sertraline and DMS effect on cell firing. Potency estimates (ED_{50}) were calculated by linear regression.

Chemicals and Drugs

All reagents were analytical grade and dissolved in nanopure water. Sertraline and DMS were synthesized in the Medicinal Chemistry Department of Pfizer Central Research (Groton, CT, USA). For the microdialysis experiments, sertraline and DMS were dissolved in a mixture of 60% propyleneglycol and 40% saline and injected SC. For the dorsal raphe recordings, sertraline was dissolved by sonification in warm acidified water; DMS was dissolved in warm 5% DMSO and 95% saline. 8-Hydroxy-dipropylaminotetralin (8-OH-DPAT HBr; Research Biochemicals International, Natick, MA, USA) dissolved in saline was used in both the microdialysis and electrophysiological experiments to confirm the serotonergic nature of the system or neuron under study.

RESULTS

Effect of Sertraline and Desmethylsertraline on 5-HT Reuptake as Measured by Microdialysis in Rat Striatum

Prior to sertraline or DMS administration, basal levels of 5-HT in rat striatal microdialysates averaged 1.28 ± 0.11 pg/30-μl sample (n = 26); basal levels of 5-HIAA were substantially higher at 1760 ± 128 pg/30-μl sample (n = 26). Injections of sertraline (1, 3.2, and 10 mg/kg SC) resulted in a rapid, dose-dependent increase in extracellular 5-HT concentrations, while 5-HIAA levels decreased to about 70% of basal levels (Figures 2 and 3). 5-HT levels were significantly different from basal levels 2 hours after injection of 1 and 3.2 mg/kg sertraline and 25 minutes after 10 mg/kg sertraline ($p < .05$). Maximal 5-HT increases were 160% after 1 mg/kg, 250% after 3.2 mg/kg, and 450% after 10 mg/kg sertraline, these effects being reached about 3 to 4 hours after injection and in the case of the 10-mg/kg dose remaining elevated for at least 20 hours (Figure 4). Linear regression showed a strong correlation between the dose of sertraline and the maximal 5-HT increase (r = 0.83, $p < .001$); the dose-response relationship for the effects on 5-HIAA narrowly missed statistical significance ($r = 0.50$, $0.1 > p > .05$).

In contrast to the pronounced effects of sertraline on extracellular 5-HT, administration of DMS (1, 3.2, or 10 mg/kg SC) had no significant effects on 5-HT or 5-HIAA dialysate concentrations (Figures 2 and 3). At the highest dose tested, 10 mg/kg, only a small nonsignificant increase in extracellular 5-HT was observed 3 hours after injection while the 5-HIAA levels appeared to decrease slightly (to 90% of basal levels). As expected, changes in extracellular 5-HT or 5-HIAA did not correlate with the dose of DMS (r = 0.43 and r = 0.10, respectively, $p > .1$).

The neurogenic origin of the 5-HT collected in the dialysate was verified by injection of 8-OH-DPAT (0.5 mg/kg SC), a potent and selective cell-body autoreceptor agonist. As previously reported (Rutter and Auer-

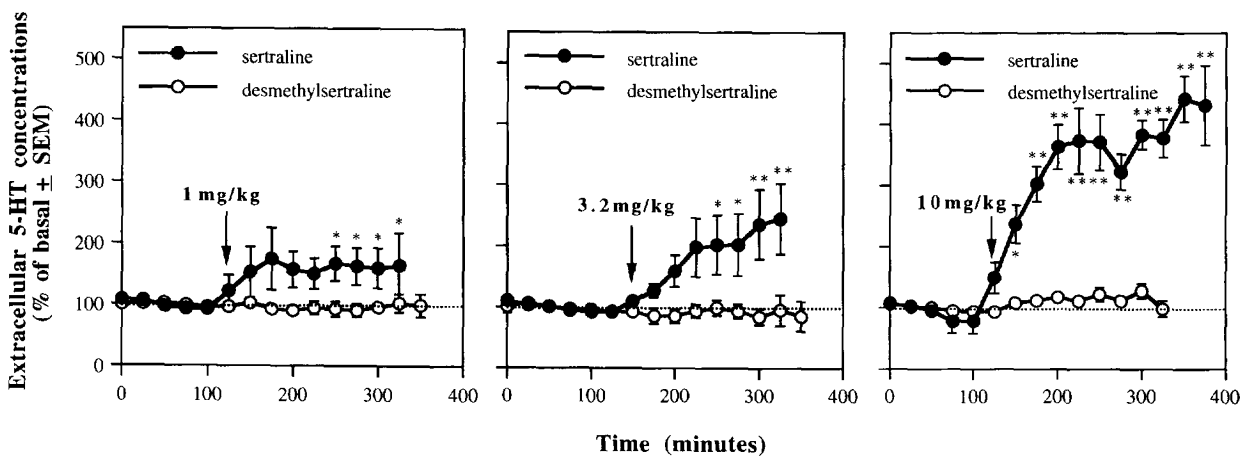

Figure 2. Effect of SC injection (*arrow*) of 1, 3.2, and 10 mg/kg of sertraline (*solid circles*) and desmethylsertraline (*open circles*) on extracellular 5-HT concentrations in rat striatum. Data are expressed as percentages of basal 5-HT levels [i.e., the average of five samples before drug administration ± SEM (n = 4–5)]. *$p < .05$, **$p < .01$ compared to baseline using a one-way repeated-measures ANOVA followed by the Newman-Keuls test.

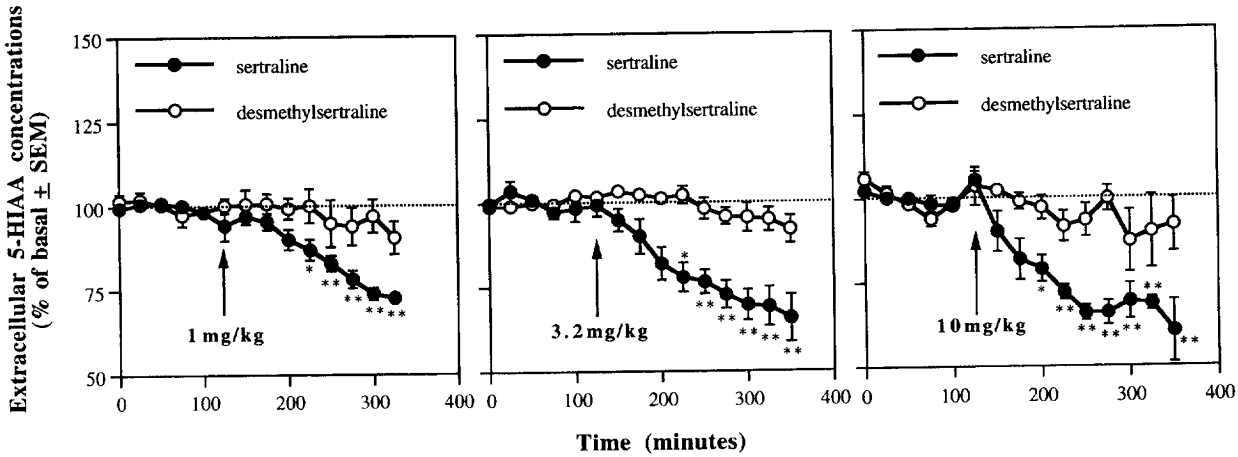

Figure 3. Effect of SC injection (*arrow*) of 1,3.2, and 10 mg/kg of sertraline (*solid circles*) and desmethylsertraline (open circles) on extracellular 5-HIAA concentrations in rat striatum. Data are expressed as percentages of basal 5-HIAA levels, [i.e. the average of five samples before drug administration ± SEM (n = 4–5)]. $^{*}p < .05$, $^{**}p < .01$ compared to baseline using a one-way repeated measures ANOVA followed by the Newman-Keuls test.

bach 1993), administration of 8-OH-DPAT reduced sertraline-induced elevations of extracellular 5-HT (Figure 4). 8-OH-DPAT also reduced basal levels of 5-HT in rats given a high but ineffective dose of DMS, in this manner demonstrating that the preparation was capable of responding to drug effects (Figure 4).

Effect of Sertraline and Desmethylsertraline on 5-HT Reuptake as Measured in Recordings of Dorsal Raphe Neurons

Administration of sertraline (10, 30, 100, and 300 μg/kg IV) inhibited the spontaneous firing rate of dorsal raphe neurons as a function of dose (Figures 5 and 6). In general, the onset of the suppressant effect occurred within the first few minutes following drug injection; recovery to predrug baseline rates was absent or incomplete. The ED_{50}, the effective dose that reduced cell firing to 50% of baseline, was calculated to be 52 μg/kg. A complete dose-response curve for 8-OH-DPAT is included for comparative purposes (Figure 6).

In contrast, injections of DMS produced no discernible changes from the baseline firing rate. A dose of 1,000 μg/kg IV, nearly 20-fold the ED_{50} for sertraline, was without effect in the six cells tested. Higher doses

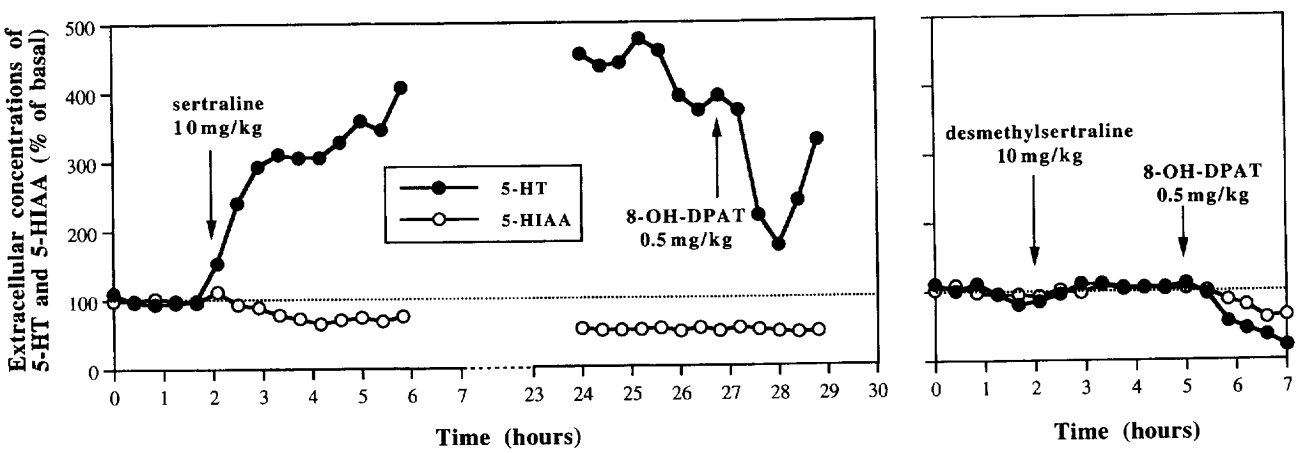

Figure 4. Verification of the neurogenic origin of the 5-HT collected in the dialysate from rat striatum by injection of 8-OH-DPAT (0.5 mg/kg SC). In the example shown in the left panel, an earlier challenge with sertraline (10 mg/kg SC) elevated extracellular 5-HT (*solid circles*) to a maximal of 400% at 6 hours and decreased 5-HIAA levels (*open circles*). Injection of 8-OH-DPAT 25 hours after the sertraline dose, when the maximal effect was still evident, rapidly reduced extracellular 5-HT. In the right panel, desmethylsertraline (10 mg/kg SC) had no effect on extracellular 5-HT (or 5-HIAA). A subsequent dose of 8-OH-DPAT markedly decreased basal extracellular 5-HT. Data are expressed as percentages of basal 5-HT or 5-HIAA levels (i.e., the average of five samples before drug administration).

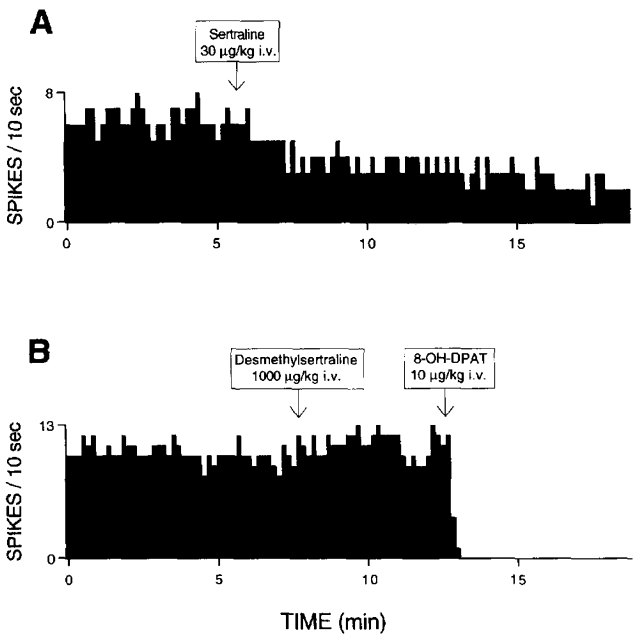

Figure 5. Representative rate histograms showing the effect of sertraline (**A**) and desmethylsertraline (**B**) on the firing of single dorsal raphe neurons. In the example with sertraline (30 µg/kg IV), firing rate was inhibited by 60%, whereas in the example with desmethylsertraline (1,000 µg/kg IV), the metabolite had no effect on unit activity. 8-OH-DPAT (10 µg/kg IV) completely inhibited firing, confirming the serotonergic nature of the neuron.

could not be attempted because of solubility considerations. Cells exposed to 8-OH-DPAT (10 µg/kg IV) given at the end of the experiment were completely inhibited.

DISCUSSION

The ability of SSRIs to block 5-HT reuptake has been demonstrated by numerous techniques since the original description of these compounds. Direct evidence for this mechanism, however, has come only recently from in vivo cerebral microdialysis measurements in which inhibition of carrier transport has been shown to result in discernible elevations of synaptic 5-HT (Fuller 1994). The therapeutic effects of the SSRIs are thought to follow from enhanced activation of postsynaptic 5-HT receptors, although modulation of various feedback mechanisms may be an intermediate step (Briley and Moret 1993; Blier and deMontigny 1994).

In the present experiments sertraline produced dose-dependent elevations of extracellular 5-HT in rat striatum (and a lowering of 5-HIAA) similar to those found by previous investigators (Rutter and Auerbach 1993). Consistent with its 10- to 20-fold lower potency in blocking 5-HT reuptake in vitro (Koe et al. 1983, 1990;

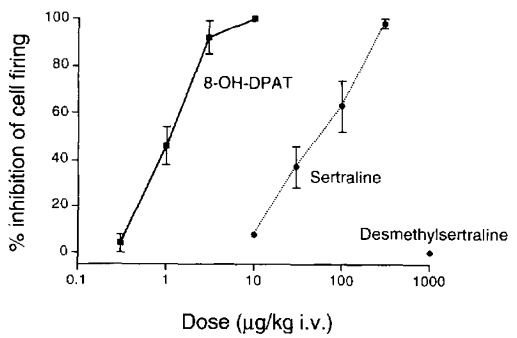

Figure 6. Dose-response curve for sertraline, desmethylsertraline, and 8-OH-DPAT to inhibit dorsal raphe cell firing. Data are expressed as the mean percentage decrease from baseline firing rate ± SEM (n = 2–7). The ED_{50} for sertraline was calculated to be 52 µg/kg IV; the ED_{50} for 8-OH-DPAT, 1 µg/kg IV.

Bolden-Watson and Richelson 1993), DMS did not mimic this capacity of sertraline to elevate extracellular 5-HT (or reduce 5-HIAA). Whereas a dose of 1 mg/kg SC of sertraline produced a significant increase in extracellular 5-HT, a 10-fold higher dose of DMS was without effect. When tested within this dose range, then, DMS would appear to possess little 5-HT reuptake blocking properties in vivo.

The time course of sertraline's action on the reuptake mechanism, still near maximal 20 hours after a single 10 mg/kg SC dose, is consistent with the long-lasting elevations of extracellular 5-HT reported for SSRIs (Rutter and Auerbach 1993). The exact nature of this effect is unknown, although it is unlikely that it is a result of an action of DMS given that the metabolite does not change extracellular 5-HT when given acutely at this dose and does not appear to accumulate in brain during the first 16 hours following a sertraline dose (Tremaine et al. 1989).

As with all SSRIs, these elevations of extracellular 5-HT by sertraline are the result of a delicate balance between the effects of the compound on nerve terminal versus cell body reuptake sites. Previous studies have shown that administration of SSRIs produces a greater increase in extracellular 5-HT in the raphe nuclei than in cortical regions (Invernizzi et al. 1991; Artigas 1993). The increased 5-HT in the raphe enhances the tone on the cell body autoreceptors which in turn produces an inhibition of cell firing, a reduction in impulse flow, and ultimately a decrease in 5-HT release (Sheard et al. 1972; Blier et al. 1988; Hutson et al. 1989; Invernizzi et al. 1991). Presumably the reuptake sites on raphe cell bodies are more sensitive to blockade by SSRIs than those on the nerve terminals in the cortex (Adell and Artigas 1991; Invernizzi et al. 1991). Such an arrangement may account for the smaller increases in extracellular 5-HT

observed in the cortex than in other raphe projection areas (Fuller 1994).

The present data show that extracellular 5-HT in the striatum increased following sertraline administration even when cell firing was likely suppressed. Similar findings have been reported in which the SSRI paroxetine produced an increase in cortical extracellular 5-HT during periods of slowed cell firing (Sharp et al. 1994). While a suppressed firing rate would act to mitigate the ability of the reuptake inhibitor to elevate extracellular 5-HT at the nerve terminal, these data suggest that it does not preclude 5-HT release. Rather, 5-HT leakage in addition to firing-dependent release appears to continue during a reduction of impulse flow and yields detectable extracellular 5-HT levels when reuptake is blocked. The elevation of extracellular 5-HT may subsequently be reversed by a cell body autoreceptor agonist such as 8-OH-DPAT that acts further to suppress neuronal firing (Figure 4; see also Rutter and Auerbach 1993). Although not investigated in detail, this scheme would further suggest that the extracellular 5-HT that remains following autoreceptor activation may reflect the action of the SSRI on 5-HT leakage alone.

One explanation for the negligible efficacy of DMS to produce an increase in extracellular 5-HT is that the metabolite has greater efficacy or potency in inhibiting dorsal raphe cell firing than the parent compound. The present results, however, suggest that this is not the case. DMS did not inhibit dorsal raphe neuronal activity at doses in which sertraline produced complete inhibition. While solubility considerations limited the dose of DMS employed to 1000 μg/kg IV, this was nevertheless nearly 20-fold the ED_{50} for sertraline (52 μg/kg). Consequently, in contrast to sertraline, DMS was found to be inactive within the dose range tested at both cell body and nerve terminal reuptake sites. A second explanation for the lack of reuptake blockade by DMS in vivo is that the compound does not achieve brain levels comparable to those achieved by sertraline following systemic dosing. However, previous studies have shown that rats given DMS IP had significant brain levels of the metabolite similar in magnitude to levels of unaltered parent compound following sertraline administration (Fuller et al. 1995). Following its entry into the brain, rapid metabolism of DMS in this tissue would not be expected; clearance is likely a function of lipophilicity and cerebral blood flow.

The conclusions drawn here of negligible efficacy for DMS at blocking the reuptake carrier in vivo are generally consistent with results from previous reports investigating the effects of DMS on p-chloroamphetamine (PCA)—induced depletion of rat brain 5-HT (Fuller et al. 1995). In these studies rats given DMS displayed an ED_{50} value for blockade of 5-HT depletion (20 mg/kg IP) that was 20-fold higher than that for sertraline (1 mg/kg IP), a potency difference similar in magnitude to that observed in earlier measurements of in vitro inhibition of 5-HT reuptake (Koe et al. 1983, 1990; Bolden-Watson and Richelson 1993). The authors, however, suggested that DMS is as active as sertraline as a reuptake blocker in this paradigm. Their reasoning is based on the finding that there appears to be a better relationship of efficacy in blocking PCA-induced depletions with brain levels of DMS than with brain levels of sertraline at the late time points when they are approximately twofold higher than those of sertraline. What may have been overlooked in these experiments is the high potency of sertraline in blocking the reuptake carrier, which is 10- to 20-fold greater than that reported for DMS. Although DMS can reach two to five times higher levels than sertraline 4 to 24 hours after sertraline injection, the much lower potency of DMS would preclude its effects on 5-HT reuptake. When tested in mice, similarities in ED_{50} values for DMS (6 mg/kg IP) and sertraline (4 mg/kg IP) in blocking PCA-induced 5-HT depletion have been reported (Hemrick-Luecke et al. 1994; Fuller et al. 1995). These data are problematic given those generated in the same laboratory with rats and raise the issue of species dependence.

In man steady-state plasma levels of DMS are reported to be 1.6- to 2.1-fold higher than those of sertraline after 14 days of sertraline administration (200 mg/day) (Doogan and Caillard 1988). Although in general it is difficult to mimic clinically obtained drug exposure in animal experiments, the dose-dependent effects on extracellular 5-HT observed in the present study suggest that the dose range employed is comparable in pharmacodynamic terms to that in humans. As a result, it is unlikely that in the clinic DMS contributes significantly to the blockade of central 5-HT reuptake produced by the parent compound. Furthermore, these data suggest that DMS would be expected to play a negligible role in the clinical activity established for sertraline. Similar studies as those presented here examining the desmethyl metabolites of other SSRIs would appear to be warranted, particularly for those compounds reported to have greater in vitro activity than the parent in reuptake assays.

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