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The 5-HT_{1A} receptor active compounds (*R*)-8-OH-DPAT and (*S*)-UH-301 modulate auditory evoked EEG responses in rats

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Summary. Schizophrenics commonly demonstrate abnormalities in central filtering capability following repetitive sensory stimuli. Such sensory inhibition deficits can be mirrored in rodents following administration of psycho-stimulatory drugs. In the present study, male Sprague-Dawley rats were implanted with brain surface electrodes to record auditory evoked EEG potentials in a paired-stimulus paradigm, using 87 dB clicks delivered 0.5 s apart. Amphetamine (1.83 mg/kg, i.p.) produced the expected loss of sensory inhibition, as defined by an increase in the ratio between test (T) and conditioning (C) amplitudes at N40, a mid-latency peak of the evoked potentials. Also, the 5-HT_{1A} agonist (*R*)-8-OH-DPAT caused a significant increase in the TC ratio at the highest dose studied (0.5 mg/kg s.c.), while the 5-HT_{1A} antagonist (*S*)-UH-301 did not significantly affect the TC ratio at any dose studied (0.1–5 mg/kg s.c.). When administered with amphetamine, a lower dose of 8-OH-DPAT (0.1 mg/kg) and the highest dose of UH-301 tested (5 mg/kg, s.c.) were able to reverse the amphetamine-induced increase in TC ratio. The findings suggest that 5-HT_{1A} signaling is involved in sensory inhibition and support the evaluation of 5-HT_{1A} receptor active compounds in conditions with central filtering deficits, such as schizophrenia.

Keywords: Schizophrenia – Sensory inhibition – Auditory evoked potentials – Serotonin – 5-HT_{1A} receptor – UH-301 – 8-OH-DPAT

Abbreviations: 8-OH-DPAT: (*R*)-8-hydroxy-2-(di-n-propyl-amino)tetralin; UH-301: (*S*)-5-fluoro-8-hydroxy-2-(di-n-propyl-amino)tetralin; EEG: electro-encephalography; s.c.: subcutaneous; i.p.: intra-peritoneal; PPI: pre-pulse inhibition; TC ratio: test amplitude/condition amplitude; MANOVA: multivariate analysis of variance; 5-HT: serotonin; DA: dopamine; PET: positron emission tomography; DOI: (2,5-dimethoxy-4-iodoamphetamine.

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Introduction

Sensory inhibition is a phenomenon in which the electrophysiological response to the second of closely-paired identical auditory stimuli is reduced compared to the first. Most humans routinely inhibit their responses to the paired auditory stimuli (Adler et al., 1982; Baker et al., 1987; Freedman et al., 1983, 1987; Waldo and Freedman 1986), as do normal rodents (Adler et al., 1986, 1988; Stevens et al., 1991, 1993). However, the central filtering mechanisms that control sensory inhibition are deficient in certain human mental disorders, such as schizophrenia and mania (Adler et al., 1990a, b; Freedman et al., 1983). This deficit can be mimicked in rodents through the administration of psycho-stimulatory drugs, such as amphetamine or phencyclidine (Adler et al., 1986; Bickford-Wimer et al., 1990; Stevens et al., 1991). Consequently, this rodent model of deficient sensory inhibition has been useful in gaining fundamental understanding of the neurochemical and neuroanatomical basis of central sensory filtering mechanisms. Through these studies, several different transmitter systems and receptors have been implicated in the modulation of sensory inhibition. These include dopamine (Adler et al., 1986, 1990b; de Bruin et al., 2001; Stevens et al., 1991, 1996b), noradrenaline (Adler et al., 1988; Stevens et al., 1991, 1993), acetylcholine (Freedman et al., 1994; Luntz-Leybman et al., 1992; Miller and Freedman, 1993; O'Neill et al., 2003; Simosky et al.,

2001; Stevens et al., 1996a, 1998), GABA (Hershman et al., 1995) and serotonin (Johnson et al., 1998).

Several neuroleptics appear to exert their activity through serotonin (5-HT) receptors (Busatto and Kerwin, 1997; Gurevich and Joyce, 1997; Meltzer, 1999) suggesting that this system may be critically involved in schizophrenia. Though only a single study has assessed 5-HT involvement in the paired-identical stimulus mode of sensory inhibition (Johnson et al., 1998), several studies have used the pre-pulse inhibition (PPI) model to address the role of 5-HT receptors. PPI uses a non-startling auditory pre-pulse before a startle-eliciting stimulus, which normally reduces the behavioral reflex (Geyer, 1996; Geyer et al., 2001). To date, studies have assessed the roles of 5-HT_2 and 5-HT_3 receptors in these two paradigms, in both humans and rodents (Alder et al., 2005; Farid et al., 2000; Geyer, 1996; Hashimoto et al., 2005; Johnson et al., 1998; Koike et al., 2005).

The 5-HT_{1A} receptor is another major 5-HT receptor thought to be implicated in the symptomatology of schizophrenia and antipsychotic drug action (Bantick et al., 2001; Millan, 2000). 5-HT_{1A} receptor density and/or its mRNA have been shown to be increased in the post-mortem schizophrenic brain (Burnet et al., 1996, 1997; Gurevich and Joyce, 1997; Hashimoto et al., 1993; Sumiyoshi et al., 1996), however, PET studies of 5-HT_{1A} receptor binding show conflicting results (Bantick et al., 2004; Tauscher et al., 2002). Several atypical antipsychotic drugs, such as clozapine, quetiapine and ziprasidone, act as partial agonists at the 5-HT_{1A} receptor (Sprouse et al., 1999; Millan, 2000). In animal studies, several 5-HT_{1A} agonists have been shown to possess antipsychotic-like actions (Ahlenius, 1989; Bantick et al., 2001; Millan, 2000) and occasional clinical studies have reported improvement of certain symptoms in schizophrenics (Sumiyoshi et al., 2001). Of particular interest is 5-HT_{1A} agonist (*R*)-8-hydroxy-2-(di-n-propyl-amino)tetralin (8-OH-DPAT) (Arvidsson et al., 1981; Cornfield et al., 1991) which can prevent neuroleptic-induced catalepsy in animal models, while 5-HT_{1A} antagonists demonstrate an opposite action (Wadenberg, 1996; Wadenberg and Hillegaart, 1995; Wadenberg et al., 1994). In the PPI model, studies of 5-HT_{1A} receptor actions have shown equivocal results. 5-HT_{1A} receptor agonists have been reported to either decrease (Gogos and van der Buuse, 2003; Rigdon and Weatherspoon, 1992, Sipes and Geyer, 1994, 1995) or increase PPI (Dulawa et al., 1997; Dulawa and Geyer, 2000). Interestingly, atypical antipsychotics with high affinity for the 5-HT_{1A} receptor, have been found to restore deficits in PPI induced by the psycho-stimulant MK-801 (Bubenikova et al., 2005).

The present study assessed two 5-HT_{1A} compounds in the chronically-implanted, awake-rat model of sensory inhibition (Adler et al., 1986; Stevens et al., 1991, 1996b). The agonist (*R*)-8-hydroxy-2-(di-n-propyl-amino)tetralin (8-OH-DPAT) (Arvidsson et al., 1981; Cornfield et al., 1991) and the antagonist (*S*)-5-fluoro-8-hydroxy-2-(di-n-propyl-amino)tetralin (UH-301) (Hillver et al., 1990; Björk et al., 1991; Arborelius et al., 1993) were assessed alone, or in combination with d-amphetamine-induced deficit in sensory inhibition (Stevens et al., 1991).

Materials and methods

Animals and surgery

Male Sprague-Dawley rats (Harlan Laboratory, Indianapolis IN) (300–350 g) were stereotaxically implanted with a skull-screw electrode for the recording of auditory evoked potentials. Details of the implantation surgery have been published elsewhere (Stevens et al., 1991). In brief, under sodium pentobarbital (50 mg/kg, i.p.) anesthesia with methoxyflurane as auxiliary, a stainless steel screw soldered to a teflon coated 0.127 mm diameter wire was placed on the brain surface at "vertex" (4.0 mm posterior to bregma, on midline). Reference electrodes, consisting of a pair 0.254 mm diameter teflon-coated wires were placed on dura at 3.0 mm anterior to bregma, to either side of midline. The electrode ends were gathered into a headpiece (Ginder Scientific, Ottawa, Canada), which was secured to the skull with stainless steel screws and acrylic dental cement. Animals were permitted to recover until pre-surgical body weight was achieved (approximately 8 days) before recording sessions were begun. The experiments were carried out in compliance with standard animal ethics regulations and approved by local animal ethics authorities (VAMC IACUC, protocol number 99016).

Apparatus and recording procedures

The recording system has also been described in detail elsewhere (Stevens et al., 1991). Briefly, a plexiglas recording chamber was enclosed in a sound-dampening exterior chamber. The rat was connected to the recording electronics via a cable attached to the rat's headpiece and a commutator atop the recording chamber, thus permitting free movement of the rat within the recording chamber. A speaker, located on the recording chamber, emitted the auditory stimuli at a sound level of 87 dB (SPL), as measured by a sound meter (Model GR1982, GenRad Corp.), at 7.5 cm above the floor of the chamber. The stimuli consisted of computer-delivered paired clicks of 0.5 msec duration, 0.5 sec apart, at 15 sec intervals. A ventilation fan on the chamber provided low-level background noise throughout the experiments. Auditory evoked potentials were amplified, filtered and recorded by a computer (EPMax, Eclectic Engineering Studio, Canton, MA) and stored for later analysis.

Animals were handled for several minutes prior to connection to the recording system and were allowed several more minutes of acclimation once in the chamber. The behavioral state of the animal was noted at the presentation of each trial, and only trials which occurred while the animal was still and alert were accepted for analysis. Normally, 20–30 trials were accumulated for each recording session.

Ten base-line recording sessions (1 per day) were taken for each animal. Still-alert trials from within a single session were averaged together and latency and waveform amplitudes evoked by the first, condition (C), click

and second, test (T), click were determined by computer analysis. Evoked potential amplitudes were determined from peak of the wave to a baseline calculated from activity for the 100 msec prior to stimulus onset. The N40 auditory evoked potential was identified as the largest negative going wave with a peak occurring between 30 and 50 msec from onset of stimulus. A TC ratio (test amplitude/condition amplitude) of 0.4 or less was indicative of normal gating (Stevens et al., 1991). All animals exhibited gating by the tenth recording session and were used in subsequent pharmacological studies.

Pharmacology

Animals were tested using one or more of the following drugs: d-amphetamine sulfate (1.83 mg/kg, i.p.; Sigma Chemicals, St Louis, MO), UH-301 (0.1, 0.5 and 5 mg/kg, s.c.; AstraZeneca, Sweden) and 8-OH-DPAT (0.01, 0.1 and 0.5 mg/kg, s.c.; Sigma Chemicals, St Louis, MO). The order of presentation of drugs or drug combinations was randomized for each rat and a minimum of three days elapsed between testing sessions using UH-301 and/or amphetamine, while a minimum of 14 days were left between sessions testing 8-OH-DPAT to avoid drug-induced changes in the receptors. All drugs were dissolved in 0.9% saline. Since the onset of the amphetamine effect is slower than UH-301 or 8-OH-DPAT, amphetamine was administered 20 min prior to the other drugs. Post drug trials were acquired at 20–40 min (time frame 1), 40–60 min (time frame 2) and 60–80 min (time frame 3) after amphetamine administration; and 0–20 min (time frame 1), 20–40 min (time frame 2) and 40–60 min (time frame 3) after UH-301 or 8-OH-DPAT injection.

Data analysis

All data were analyzed using the computer program SPSS PC+. Accumulated trials (20–30) from each recording session were averaged and the amplitude of the condition (C) response, the amplitude of the test (T) response and the ratio of the amplitudes of the test to the condition responses (TC ratio) were determined. The data obtained from the experiments met the assumption of homogeneity of variance as calculated by Bartlett's Box F and Cochran's C tests; thus, data were analyzed by multivariate analysis of variance (MANOVA), with the time frames recorded as the repeated measure and drug dose nested within drug. Fisher's LSD *a posteriori* analyses were performed where appropriate. A significance level of $p < 0.05$ was maintained throughout the analyses.

Results

By the 10th baseline recording session, all rats had TC ratios within the range defined as normal gating (mean = 0.30 ± 0.02). After amphetamine administration (1.83 mg/kg, i.p.), all rats showed the typical stereotypies and increased locomotor activity, concurrent with a loss of auditory gating, as had been previously reported (Stevens et al., 1991) (Fig. 1).

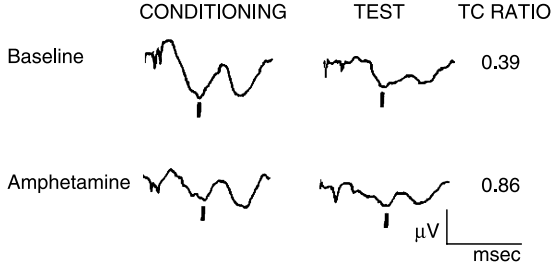

Fig. 1. Representative auditory evoked EEG potentials, induced by paired 87 dB clicks delivered 0.5 s apart, from a rat under baseline recordings and after it has received amphetamine (1.83 mg/kg, i.p.). The test (T) and conditioning (C) potentials are shown together with the resulting TC ratio. Calibration is 50 μvolts (μV), 50 msec

Effects of 8-OH-DPAT on general behavior and auditory evoked potentials

8-OH-DPAT produced a quiet, prone posture, concurrent with a drooping lower lip. These behavioral modifications were observed even after amphetamine co-administration, although in these animals, the quiet, prone posture alternated with a prone, crawling activity and a high degree of sniffing and head bobbing.

Repeated measures analysis of recording time by dose nested within drug for the effect of amphetamine and/or 8-OH-DPAT on TC ratio showed a significant effect of treatment ($F_{(15,222)} = 2.20$, $p = 0.007$). *A posteriori* analysis revealed a significant increase in TC ratio with amphetamine administration at all three frames as well as a significant increase at the highest dose of 8-OH-DPAT (0.5 mg/kg) alone at the first 2 time frames. When administered together with amphetamine, the middle dose of 8-OH-DPAT (0.1 mg/kg) reversed the amphetamine-induced increase in TC ratio (Fig. 2).

For conditioning amplitude, there was neither a significant effect of time by dose within drug, nor an effect of dose within drug (Fig. 3). There was a significant effect of time by dose within drug on test amplitude ($F_{(15,222)} = 1.91$, $p = 0.023$). *A posteriori* analysis showed a significant increase in the third time frame with amphetamine alone (Fig. 4). When 8-OH-DPAT was administered alone, there were significant decreases in test amplitudes for the 2 lowest doses (0.01 and 0.1 mg/kg) in the first time frame. When administered with amphetamine, 8-OH-DPAT reversed the increase in test amplitude produced by amphetamine alone and in fact, the lowest doses actually reduced test amplitude below baseline levels.

Effects of UH-301 on general behavior and auditory evoked potentials

UH-301 produced minimal behavioral alterations when administered alone, but moderated the locomotor hyperactivity when administered after amphetamine. In some animals, an arched spine was observed after the combined UH-301 and amphetamine treatment.

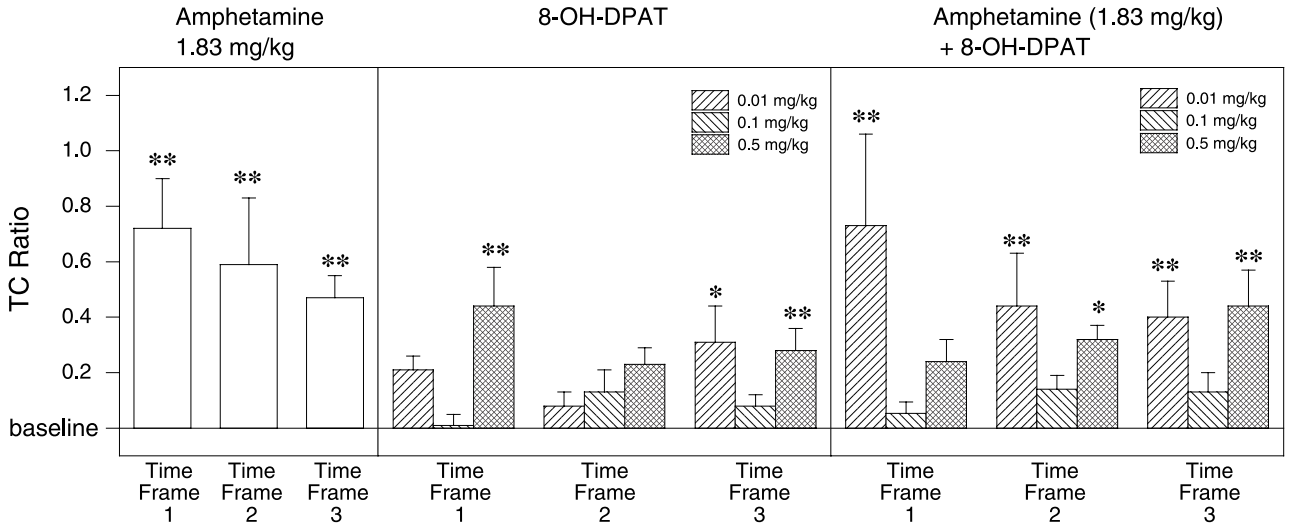

Fig. 2. The effects of amphetamine and 8-OH-DPAT on TC ratio. Data are presented as change from baseline. Since amphetamine has a delayed onset compared to 8-OH-DPAT, it was injected 20 min earlier than 8-OH-DPAT. Thus, Time Frame 1 refers to 20–40 min after amphetamine administration and/or 0–20 min after 8-OH-DPAT administration, Time Frame 2 refers to 40–60 min after amphetamine administration and/or 20–40 min after 8-OH-DPAT administration and Time Frame 3 refers to 60–80 min after amphetamine administration and/or 40–60 min after 8-OH-DPAT administration. Data are change mean + SEM, $^{*}p<0.05$; $^{**}p<0.01$ by Fisher's LSD compared to baseline. Amphetamine $n=20$; 8-OH-DPAT 0.01 mg/kg $n=7$; 8-OH-DPAT 0.1 mg/kg $n=19$; 8-OH-DPAT 0.5 mg/kg $n=11$; amphetamine + 8-OH-DPAT 0.01 and 0.1 mg/kg $n=7$; amphetamine + 8-OH-DPAT 0.5 mg/kg $n=9$

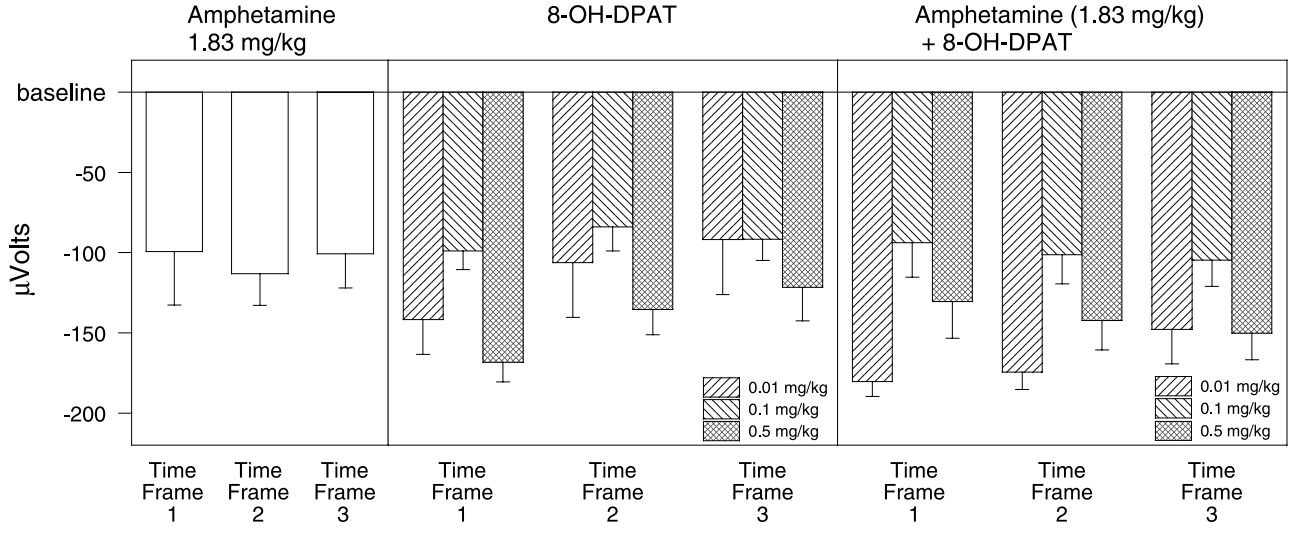

Fig. 3. The effects of amphetamine and 8-OH-DPAT on conditioning amplitude. Data are presented as change from baseline. Since amphetamine has a delayed onset compared to 8-OH-DPAT, it was injected 20 min earlier than 8-OH-DPAT. Thus, Time Frame 1 refers to 20–40 min after amphetamine administration and/or 0–20 min after 8-OH-DPAT administration. Time Frame 2 refers to 40–60 min after amphetamine administration and/or 20–40 min after 8-OH-DPAT administration and Time Frame 3 refers to 60–80 min after amphetamine administration and/or 40–60 min after 8-OH-DPAT administration. Data are change mean ± SEM, $^{*}p<0.05$; $^{**}p<0.01$ by Fisher's LSD compared to baseline. Amphetamine $n=20$; 8-OH-DPAT 0.01 mg/kg $n=7$; 8-OH-DPAT 0.1 mg/kg $n=19$; 8-OH-DPAT 0.5 mg/kg $n=11$; amphetamine + 8-OH-DPAT 0.01 and 0.1 mg/kg $n=7$; amphetamine + 8-OH-DPAT 0.5 mg/kg $n=9$

Repeated measures analysis of variance for recording time with dose nested under drug, for TC ratio among animals which had received amphetamine and/or UH-301, showed a trend toward a significant effect of dose within drug by time ($F_{(15,144)}=1.71$, $p=0.056$). Fisher's LSD *a posteriori* analysis showed that there was the expected significant loss of gating following amphetamine administration as well as a significant loss of gating following administration of amphetamine and the two lowest doses of UH-301 (0.1 and 0.5 mg/kg) at all three time

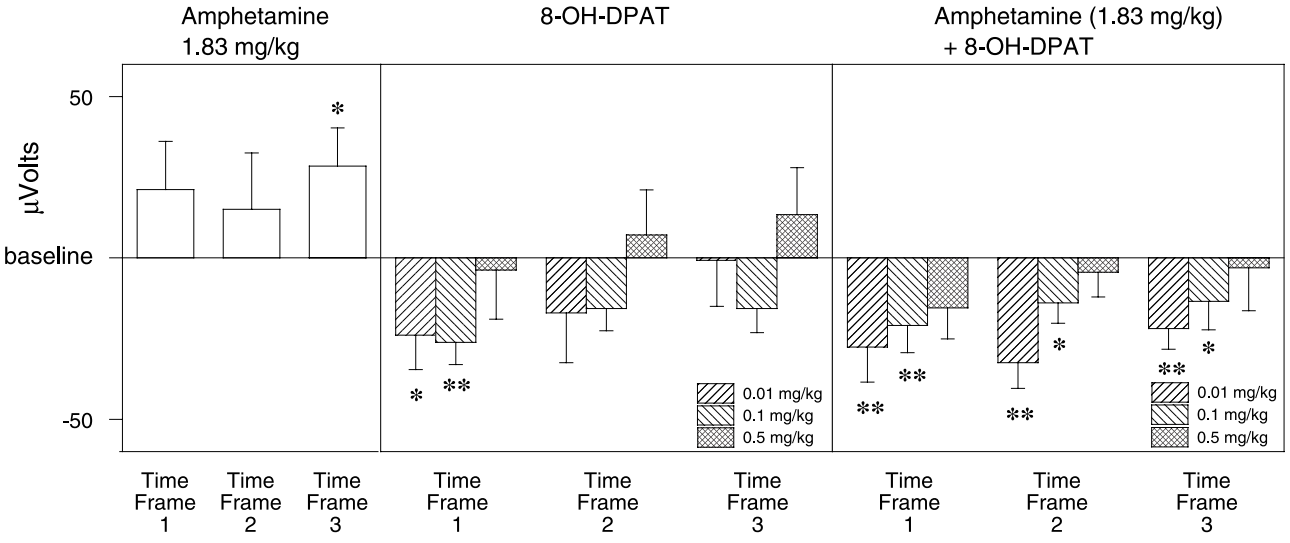

Fig. 4. The effects of amphetamine and 8-OH-DPAT on test amplitude. Data are presented as change from baseline. Since amphetamine has a delayed onset compared to 8-OH-DPAT, it was injected 20 min earlier than 8-OH-DPAT. Thus, Time Frame 1 refers to 20–40 min after amphetamine administration and/or 0–20 min after 8-OH-DPAT administration, Time Frame 2 refers to 40–60 min after amphetamine administration and/or 20–40 min after 8-OH-DPAT administration and Time Frame 3 refers to 60–80 min after amphetamine administration and/or 40–60 min after 8-OH-DPAT administration. Data are change mean ± SEM, $^{*}p<0.05$; $^{**}p<0.01$ by Fisher's LSD compared to baseline. Amphetamine $n=20$; 8-OH-DPAT 0.01 mg/kg $n=7$; 8-OH-DPAT 0.1 mg/kg $n=19$; 8-OH-DPAT 0.5 mg/kg $n=11$; amphetamine + 8-OH-DPAT 0.01 and 0.1 mg/kg $n=7$; amphetamine + 8-OH-DPAT 0.5 mg/kg $n=9$

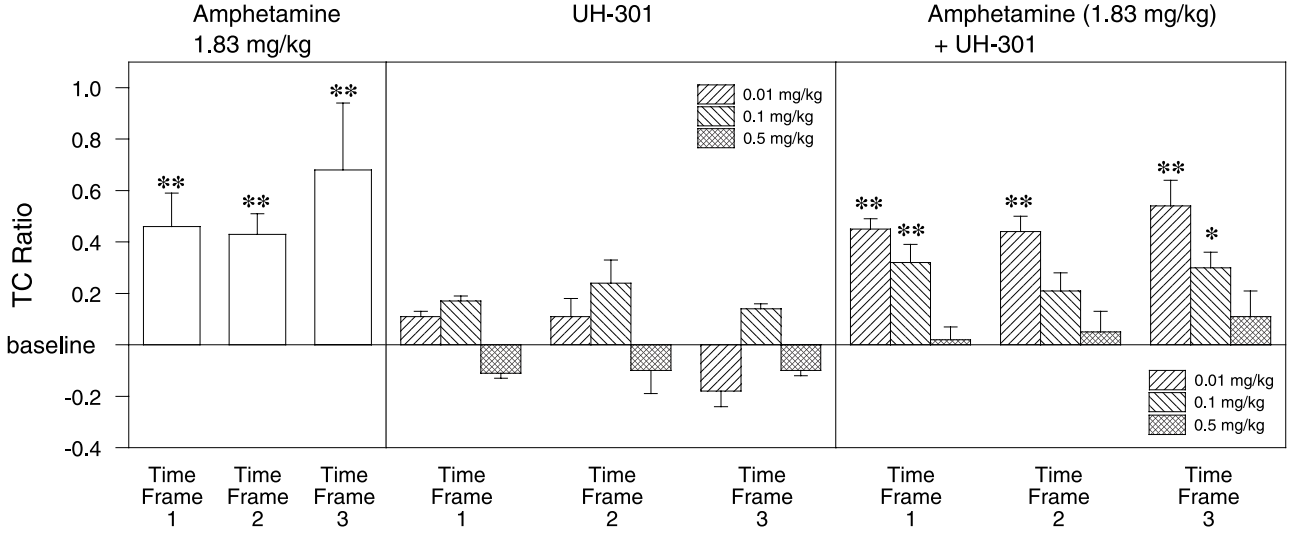

Fig. 5. The effects of amphetamine and UH-301 on TC ratio. Data are presented as change from baseline. Since amphetamine has a delayed onset compared to UH-301, it was injected 20 min earlier than UH-301. Thus, Time Frame 1 refers to 20–40 min after amphetamine administration and/or 0–20 min after UH-301 administration, Time Frame 2 refers to 40–60 min after amphetamine administration and/or 20–40 min after UH-301 administration and Time Frame 3 refers to 60–80 min after amphetamine administration and/or 40–60 min after UH-301 administration. Data are change mean ± SEM, $^{*}p<0.05$; $^{**}p<0.01$ by Fisher's LSD compared to baseline. Amphetamine $n=20$; UH-301 0.1 mg/kg $n=5$; UH-301 0.5 mg/kg $n=5$; UH-301 5 mg/kg $n=7$; amphetamine + UH-301 0.1 and 0.5 mg/kg $n=5$; amphetamine + UH-301 5 mg/kg $n=7$

frames recorded (Fig. 5). The highest dose of UH-301 (5 mg/kg) reversed the amphetamine-induced loss of gating. UH-301 alone did not significantly affect TC ratio at any time frame.

Assessment of conditioning amplitude for this group again showed a significant effect of dose within drug by time ($F_{(15,144)}=2.93$, $p<0.001$). *A posteriori* analysis showed the expected decrease in conditioning amplitude

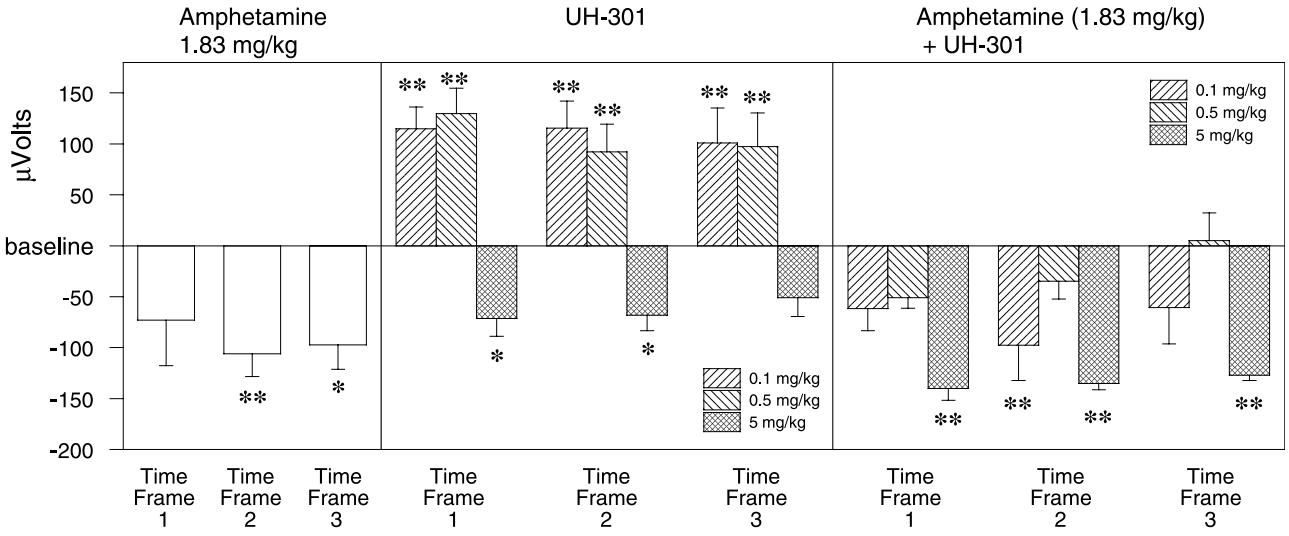

Fig. 6. The effects of amphetamine and UH-301 on conditioning amplitude. Data are presented as change from baseline. Since amphetamine has a delayed onset compared to UH-301, it was injected 20 min earlier than UH-301. Thus, Time Frame 1 refers to 20–40 min after amphetamine administration and/or 0–20 min after UH-301 administration, Time Frame 2 refers to 40–60 min after amphetamine administration and/or 20–40 min after UH-301 administration and Time Frame 3 refers to 60–80 min after amphetamine administration and/or 40–60 min after UH-301administration. Data are change mean ± SEM, $^{*}p<0.05$; $^{**}p<0.01$ by Fisher's LSD compared to baseline. Amphetamine $n=20$; UH-301 0.1 mg/kg $n=5$; UH-301 0.5 mg/kg $n=5$; UH-301 5 mg/kg $n=7$; amphetamine + UH-301 0.1 and 0.5 mg/kg $n=5$; amphetamine + UH-301 5 mg/kg $n=7$

with amphetamine and a significant increase with UH-301 at the 0.1 and 0.5 mg/kg doses (Fig. 6). The highest dose (5 mg/kg) produced significant decreases in conditioning amplitude in the first and third recording time frames. When administered with amphetamine, UH-301 failed to reverse the decrease in conditioning amplitude produced by the amphetamine, and in fact, at the highest dose, exacerbated the decrease (Fig. 6). Analysis of test amplitude failed to show a time by dose within drug effect, though there was a significant effect of dose within drug ($F_{(5,48)}=13.68$, $p<0.001$) (Fig. 7). The lowest doses of UH-301 produced significant increases in test ampli-

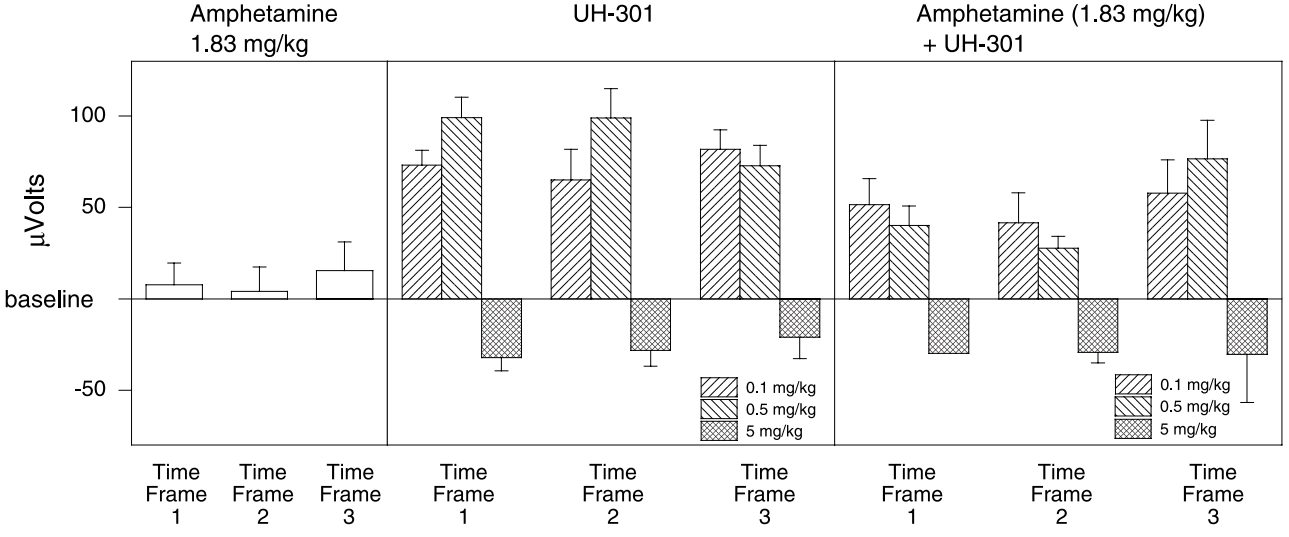

Fig. 7. The effects of amphetamine and UH-301 on test amplitude. Data are presented as change from baseline. Since amphetamine has a delayed onset compared to UH-301, it was injected 20 min earlier than UH-301. Thus, Time Frame 1 refers to 20–40 min after amphetamine administration and/or 0–20 min after UH-301 administration, Time Frame 2 refers to 40–60 min after amphetamine administration and/or 20–40 min after UH-301 administration and Time Frame 3 refers to 60–80 min after amphetamine administration and/or 40–60 min after UH-301 administration. Data are change mean ± SEM, $^{*}p<0.05$; $^{**}p<0.01$ by Fisher's LSD compared to baseline. Amphetamine $n=20$; UH-301 0.1 mg/kg $n=5$; UH-301 0.5 mg/kg $n=5$; UH-301 5 mg/kg $n=7$; amphetamine + UH-301 0.1 and 0.5 mg/kg $n=5$; amphetamine + UH-301 5 mg/kg $n=7$

tude, whether administered alone or together with amphetamine. The highest dose of UH-301 reduced test amplitude, again, regardless of whether administered alone or with amphetamine.

Discussion

The present study assessed the involvement of 5-HT_{1A} neurotransmission in central filtering processes. The 5-HT_{1A} agonist, 8-OH-DPAT, and the antagonist, UH-301, were tested alone and in combination with amphetamine, which is known to disrupt sensory inhibition (Alder et al., 1986; Stevens et al., 1991). There were two main novel findings from this study: 1) administration of a higher dose of 8-OH-DPAT, alone, induced loss of auditory gating; and 2) administration of lower doses of 8-OH-DPAT, or the highest dose of UH-301 reduced d-amphetamine-induced loss of auditory gating.

Administration of 8-OH-DPAT produced some general behavioral changes, such as a prone posture and a drooping lower lip. This behavior was also observed even with amphetamine co-administration, although alternating with a prone, crawling activity and a high degree of sniffing and head bobbing. These behavioral effects of 8-OH-DPAT have been previously documented (Berendsen et al., 1989; Björk et al., 1992) and, when administered together with a psycho-stimulatory drug, such as amphetamine, a combined behavioral response would be expected.

A significant increase in the TC ratio was found following the highest dose of 8-OH-DPAT (0.5 mg/kg). Although this was not produced by statistically significant changes in either conditioning or test amplitudes, there was a strong trend towards a significant reduction in the conditioning amplitude. 8-OH-DPAT has been shown to increase dopamine (DA) release in certain brain areas (Ago et al., 2003; Arborelius et al., 1993; Benloucif and Galloway, 1991; Tanda et al., 1994), similar to amphetamine, which could account for the observed increase in conditioning amplitude. In contrast, there were significant decreases in test amplitudes for the two lower doses of 8-OH-DPAT tested (0.01 and 0.1 mg/kg). While the effect of 8-OH-DPAT alone suggests that the 5-HT_{1A} receptor agonist has the potential to cause loss of sensory inhibition, the middle dose of 8-OH-DPAT (0.1 mg/kg), when administered together with amphetamine, actually reversed the amphetamine-induced increase in TC ratio through blocking the increase in test amplitude produced by amphetamine. These data are in concert with studies showing 8-OH-DPAT reductions in amphetamine-induced increases in DA release in specific brain areas (Ichikawa et al., 1995; Kuroki et al., 2000). Hence there appear to be major differences in the effect of 8-OH-DPAT under basal conditions and after d-amphetamine challenge. The role of DA transmission in causing an increased TC ratio, i.e. loss of sensory inhibition, in rats is well established (de Bruin et al., 2001; Stevens et al., 1991, 1996b). It is therefore likely that the effect seen with 8-OH-DPAT alone on the auditory evoked potentials is, at least partially, related to its DA releasing effects, thereby mimicking an amphetamine action. Alternately, or possibly in parallel, 8-OH-DPAT activity at autoreceptors (Arborelius et al., 1994) in the raphe nuclei, may mediate a reduction in 5-HT release (Ago et al., 2003), which would also lead to a loss in sensory inhibition. This possibility is supported by a study showing that antagonism of postsynaptic 5-HT_2 receptors reduces sensory inhibition, while stimulation enhances inhibition (Johnson et al., 1998). Finally, 8-OH-DPAT, at higher doses, can lose selectivity and act more directly on DA neurotransmission (Arborelius et al., 1993; Smith and Cutts, 1990). The effect of 8-OH-DPAT on amphetamine-induced loss of sensory inhibition is more difficult to explain. However, it is possible that either 5-HT_{1A} receptors directly modulate DA transmission in states of substantially enhanced activity, or that 8-OH-DPAT-mediated inhibition of 5-HT release (Ago et al., 2003) counteracts a component of the amphetamine action that depends on a 5-HT releasing effect (Kuczenski and Segal, 1989). It is also possible that 8-OH-DPAT reduces the size of the releaseable DA pool on which amphetamine acts (Ichikawa et al., 1995).

The 5-HT_{1A} antagonist UH-301 caused no apparent behavioral alterations when administered alone, but it moderated the locomotor hyperactivity caused by amphetamine. This is in agreement with previous studies on the behavioral effects of UH-301, where few actions have been found with UH-301 itself, while induced behavioral arousal can be antagonized (Björk et al., 1992; Moreau et al., 1993). The lowest doses of UH-301 (0.1 and 0.5 mg/kg) produced increases in both test and conditioning amplitudes, while in contrast the highest dose of UH-301 used (5 mg/kg) reduced both the test and conditioning amplitudes. The effects on test and conditioning amplitude occurred regardless of whether UH-301 was administered alone or with amphetamine. These changes point to a general strengthening of the evoked potentials, perhaps due to a cerebral arousal action, after the lower doses of UH-301, however, both the conditioning and test amplitudes were increased thus not altering the TC ratio. Most importantly, the highest dose of UH-301 reversed the amphetamine-induced loss of sensory inhibition, pos-

sibly due to DA D2/D3 receptor blockade (Nomikos et al., 1996), while the lower doses of UH-301 (0.1 and 0.5 mg/kg) failed to do this. It is of interest to note that UH-301 did not reverse the amphetamine-induced decrease in conditioning amplitude. In fact, at the highest dose UH-301 exacerbated the decrease in conditioning amplitude induced by amphetamine, in line with its intrinsic effect. The effect of UH-301 on amphetamine is not unexpected since it counteracts behavioral stimulation in several paradigms as well as reduces DA release (Ahlenius et al., 1999; Nomikos et al., 1996) and midbrain DA cell firing (Arborelius et al., 1993). Consequently, even though the action of UH-301 may not entirely be attributed to a ''silent'' 5-HT_{1A} antagonism (Ahlenius et al., 1999; Darmani and Reeves, 1996; Groenink et al., 1995), its modulation of the auditory evoked potentials supports the interpretation that it blocked 5-HT_{1A} receptor function.

Research into the role of 5-HT in sensory inhibition is in the early stages. Currently, it is difficult to interpret the functional consequences of the effects seen after 8-OH-DPAT or UH-301 administration. The actions of the agonist (8-OH-DPAT) and the antagonist (UH-301) on the auditory evoked potentials were not entirely opposed. Indeed, after amphetamine administration they appeared to act similarly, at least at certain doses (0.1 mg/kg 8-OH-DPAT and 5 mg/kg UH-301), reducing the loss of sensory inhibition induced by amphetamine, as defined by a normalized TC ratio. These findings emphasize the complexity of 5-HT, and 5-HT_{1A} receptors in particular, in central filtering processes as well as point to the likelihood that the effects of 5-HT_{1A} receptor active compounds may depend on the level of cerebral activation and tonus of transmitter signaling. A similar complexity is seen with 5-HT_{1A} receptors in PPI. Agonists have been reported to both decrease PPI (Gogos and van den Buuse, 2003; Rigdon and Weatherspoon, 1992, Sipes and Geyer, 1994, 1995) and increase PPI (Dulawa et al., 1997; Dulawa and Geyer, 2000). It has been suggested that this discrepancy may be attributed to species and strain differences (Dulawa and Geyer, 2000), since 5-HT_{1A} receptor agonist-induced decrease in PPI has generally been seen in rats, while an increase has been found in some, but not all mouse strains. Interestingly, it has been reported that in 5-HT_{1A} receptor knock-out mice, there is no change in PPI compared to wild-type mice (Dirks et al., 2001). These studies suggest that there is an intricate balance between post- and pre-synaptic (autoreceptors) $5HT_{1A}$ receptors as well as various postsynaptic subtypes in the regulation of auditory and sensorimotor inhibition. The picture is further complicated by the presence or absence of psycho-stimulatory activation with drugs such as amphetamine. For example, atypical antipsychotics with high affinity for 5-HT_{1A} receptors, but not those with low or no 5-HT_{1A} affinity, have been found to restore MK-801-induced deficits in PPI (Bubenikova et al., 2005) which appears to be in line with the restoring effects seen with 8-OD-DPAT on the amphetamine-induced deficit in sensory inhibition.

Although there have been limited efforts to study the role of 5-HT neurotransmission in the present model, the literature clearly suggests the involvement of at least three receptor subtype groups; the 5-HT_{1A} receptor (present study), the 5-HT_3 receptor (Hashimoto et al., 2005) and 5-HT_2 receptors (Johnson et al., 1998). 5-HT_3 receptors were recently shown to modulate sensory inhibition in the naturally-deficient DBA/2 mouse (Hashimoto et al., 2005), where the 5-HT_3 receptor antagonist tropisetron improved inhibition in this strain. In the Johnson study, the 5-HT_2 antagonist ketanserin reduced sensory inhibition, while the 5-HT_2 agonist DOI provided an improvement. Moreover, DOI was found to antagonize the disruption of inhibition induced by amphetamine administration. The involvement of 5-HT_2 receptors has also been investigated in the PPI model. The agonist, DOI was found to impair PPI (Farid et al., 2000; Sipes and Geyer, 1997), while some, but not all, 5-HT_2 receptor antagonists were shown to counteract disruption of PPI by psycho-stimulatory drugs (Varty et al., 1999). The PPI studies are quite different from the rat sensory inhibition studies. Hence, both 5-HT_{1A} and 5-HT_2 receptor active compounds behave differently in the two rat models of sensory filtering. It may be argued that basic mechanisms of inhibition are shared between the PPI and the auditory evoked potential models, and in fact similar effects are seen after administration of psycho-stimulatory drugs (Adler et al., 1982; Stevens et al., 1991; Geyer et al., 2001; Swerdlow et al., 1990, 2006). However, the auditory evoked potential model of sensory inhibition is a completely central approach to record inhibitory effects, whereas a behavioral startle reflex (muscle reaction) is determined in PPI. The characteristics of the output measures are therefore distinctly different in the two paradigms, which may explain the dichotomy of the two models in the effects of compounds acting at various neurotransmission systems.

In summary, the 5-HT_{1A} active compounds (R)-8-OH-DPAT or (S)-UH-301 were found to alter auditory evoked EEG potentials in awake, adult rats. These data suggest that 5-HT_{1A} receptors modulate sensory inhibition circuits and provide additional evidence for an involvement of serotonergic pathways in regulating central sensory filtering processing, both under normal conditions and in

psycho-stimulatory drug-induced deficit of sensory inhibition. The findings are particularly intriguing since the 5-HT_{1A} receptor is believed to be implicated in the pathophysiology of schizophrenia and constitutes a target for antipsychotic drug development (Bantick et al., 2001; Millan, 2000). Evidence suggesting a role of 5-HT_{1A} receptors in modulating auditory evoked responses therefore supports further evaluation of the therapeutic potential of 5-HT_{1A} receptor active compounds in conditions with altered central filtering capability, such as schizophrenia.

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