Published in final edited form as:

Behav Brain Res. 2011 May 16; 219(1): 123–131. doi:10.1016/j.bbr.2010.12.031.

Differential Effects of 5-HT_{2A} and 5-HT_{2C} Receptor Blockade on Strategy-Switching

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Abstract

Recent experiments indicate that blockade of serotonin (5-HT) 2A and 2C receptors have differential effects on reversal learning. The present experiments investigated the effects of the 5-HT_{2A} receptor antagonist, ketanserin and 5-HT_{2C} receptor antagonist, SB242084 on acquisition and strategy-switching in a visual cue – response paradigm. Long-Evans rats were trained in a cross-maze to enter an arm based on color (visual cue version) or a specific turn response (response version). Systemic treatment with ketanserin did not affect initial learning of a visual cue or response discrimination, but ketanserin at 0.5 mg/kg significantly enhanced a switch between visual cue and response strategies. Ketanserin facilitated strategy-switching by inhibiting responses to a previously relevant strategy without affecting choices to never-reinforced strategies. Treatment with SB242084 (0.5, 1.0 or 2.0 mg/kg) did not affect acquisition of a visual cue or response discrimination. SB242084 treatment also did not affect strategy-switching. The present findings suggest that blockade of 5-HT_{2A}, but not 5-HT_{2C}, receptors enhance strategy switching.

Keywords

Serotonin; Strategy-Switching; Cognitive Flexibility; Learning; Ketanserin; Rat

Introduction

The ability to employ new choice patterns when contingencies change is important for survival in complex environments. However, evidence suggests that there are different types of cognitive flexibility, e.g. strategy shifting or reversal learning, which may be dissociable among different brain circuitry [44], or neurotransmitter systems [46]. Furthermore, cognitive flexibility deficits occur across a wide variety of neurological and psychiatric populations, but often specific cognitive flexibility impairments occur within a particular

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disorder [50]. Therefore, a significant amount of research is aimed to understand how different brain regions or neurotransmitter systems may contribute to specific types of cognitive flexibility in order to further refine pharmacological interventions.

There is accumulating evidence that the neurotransmitter, serotonin (5-HT) supports behavioral flexibility when task contingencies switch, requiring inhibition of a previously learned choice pattern and learning of a new choice pattern [7, 13, 14]. In particular, 5-HT depletion produces reversal learning impairments both through pharmacological means [13], as well as by chronic intermittent cold stress [33]. Conversely, 5-HT output increases in the rat orbitofrontal cortex during behavioral flexibility tests [14] and treatment with selective serotonin reuptake inhibitors can enhance behavioral flexibility [1, 56]. Taken together, the results suggest that an increase in forebrain 5-HT output enhances behavioral flexibility when conditions require inhibition of one learned choice pattern while switching to a different or new choice pattern.

Other findings suggest that the role of 5-HT in behavioral flexibility is more complex than just a broad increase in forebrain 5-HT levels leading to optimal performance. For example, although there is evidence that 5-HT reuptake inhibitors can enhance reversal learning, treatment with 5-HT reuptake inhibitors has also been found to impair reversal learning [1, 12]. Moreover, other results suggest that blocking 5-HT transmission at specific 5-HT receptors may enhance or impair response inhibitory processes that are important for behavioral flexibility [18, 54]. Because 5-HT acts at seven different receptor families with multiple subtypes [5], a global increase in brain 5-HT levels may not be the optimal strategy for enhancing cognitive processes [24].

Several studies investigating the 5-HT₂ receptor family, which consists of the 5-HT_{2A}, 2B, 2C subtypes, have shown that blockade of specific 5-HT₂ receptors improves response inhibition that may be critical for optimally switching choice patterns when contingencies change [10, 18, 26, 53, 54]. For example, in the 5-choice serial reaction time test rats must attend to a brief visual stimulus and respond based on the location of the visual stimulus. A premature response in this task occurs when a rat makes a choice prior to stimulus presentation. Premature responses are used as a measure of response inhibition with few premature responses considered to reflect better response inhibition. In this task, administration of the 5-HT_{2A} receptor antagonist, (±)2,3-dimethoxyphenyl-1-[2-(4-(piperidine)-methanol)] (M100907) or ketanserin decreases premature responding [10, 18, 26, 53, 54]. In contrast, treatment with the 5-HT_{2A/2C} receptor agonist (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) increases premature responding. Conversely, the 5-HT_{2C} receptor antagonist, 6-chloro-5-methyl-1-[2-(2-methylpyridyl-3-oxy)-pyrid-5-ylcarbonyl] indoline [SB242084]) significantly increases premature responding [18]. Collectively, the findings suggest that response inhibitory processes underlying premature responding can be increased or decreased through blockade of 5-HT_{2A} or 5-HT_{2C} receptors, respectively.

The findings from recent experiments also suggest that 5-HT₂ receptors are involved in reversal learning. Systemic injection of the 5-HT_{2A} receptor antagonist, M100907, impairs spatial reversal learning, while systemic treatment with the 5-HT_{2C} receptor antagonist, SB242084, enhances spatial reversal learning [6]. The enhancing effect of 5-HT_{2C} receptor blockade in reversal learning may be due to actions in specific frontal cortex areas as a microinjection of M100907 into the orbitofrontal cortex, medial prefrontal cortex or nucleus accumbens does not affect spatial reversal learning [7]. However, similar to systemic treatment, infusion of SB242084 into the orbitofrontal cortex enhances spatial reversal learning [7]. These findings suggest that 5-HT_{2A} and 5-HT_{2C} receptors differentially contribute to reversal learning. More specifically, opposite to that observed with premature

responding in the 5-choice serial reaction time test, blockade of 5-HT_{2C} receptors appears to selectively enhance reversal learning.

Unclear, however, is whether 5-HT₂ receptors also play a role in strategy-switching. Based on findings from depletion of specific monoamines in the brain, 5-HT has been suggested to play a specific role in reversal learning, while other monoamines, i.e. dopamine and norepinephrine support strategy-switching [45]. Although, the atypical antipsychotics risperidone and clozapine, which in part block 5-HT₂ receptors [21, 25], attenuate phencyclidine-induced strategy-switching deficits [37]. These results suggest that 5-HT₂ receptors may indeed play a role in strategy-switching. However, these atypical antipsychotics do not selectively block specific 5-HT₂ receptor subtypes, limiting the understanding of whether specific 5-HT₂ receptor subtypes support strategy-switching.

To better understand the role of 5-HT₂ receptors in strategy-switching, the present experiments investigated the effects of the 5-HT_{2A} receptor antagonist, ketanserin and 5-HT_{2C} receptor antagonist, SB242084 on acquisition and strategy-switching of visual cue and egocentric response discriminations. Ketanserin is about 20 times more selective for the 5-HT_{2A} over the 5-HT_{2C} receptor [48]. However, ketanserin does show some affinity as an antagonist for the α -1 adrenergic receptor [27]. To control for any possible effects of ketanserin due to blockade of α -1 adrenergic receptors, the effects of prazosin, an α -1 adrenergic receptor antagonist, was administered during strategy-switching.

Materials & Methods

Subjects

Male Long-Evans rats were purchased from Harlan Laboratories (Indianapolis, IN) weighing between 325–375g. Rats were housed singly in plastic cages (20.3 cm × 20.3 cm × 41.9 cm) in an environmentally controlled room (23°C, 30% humidity) on a 12h:12h light: dark cycle (lights on at 7:00 am). After at least four days to acclimate to the colony room, rats were handled for 10 minutes per day for four days to adjust to being handled during training and testing. At the same time rats began to be handled, rats were also food restricted to reduce their weight to 85–90% of their *ad libitum* weight. Rats had free access to water throughout the experiment. Animal care and use conformed to the guidelines of the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and was approved by the Institutional Laboratory Animal Care and Use Committee at the University of Illinois at Chicago.

Apparatus

Training and behavioral testing were carried out in a cross maze made of translucent black acrylic. Each arm measured 55 cm long, 10 cm wide, and 15 cm in height. A circular food well, with a diameter of 3.2 cm and a depth of 1.6 cm was placed 3 cm from the end of each arm. The maze was placed on a table with a height of 72 cm. Extra-maze cues were placed throughout the testing room. Each arm was arbitrarily named North, South, East, or West, and was consistent throughout the experiment.

Training

Each rat received a training procedure similar to previous studies [42, 43]. The training procedure allowed a rat to acclimate to the maze and learn to consume a quarter piece of Froot Loops cereal (Kelloggs, Battle Creek, MI) found in each food well. The training procedure lasted 4–6 daily sessions. In the final two days of training, black and white poster board was placed in each maze arm which served as visual cues. There were two black boards and two white boards. Each colored board extended the length of the maze arm

covering the base, as well as the side walls. The final training session consisted of 7 trials to determine a rat's turn bias or bias toward a particular visual cue comparable to a previous experiment [42]. For each trial a black acrylic block (9 cm × 13 cm × 9 cm) was placed in the maze such that it blocked entry into one arm, effectively turning the cross maze into a T shape. A rat was placed in the stem arm and the other two arms served as choice arms. Each choice arm was baited and contained a black or white visual cue. A rat was allowed to enter a choice arm and consume the cereal piece. Both the colored visual cue and turn response (right or left) a rat chose on the first entry of a trial was recorded. The color cue and turn direction a rat made on a majority of trials was considered its color and turn bias, respectively. After the completion of this training session, the testing phase began the following day.

Behavioral Testing

Experiment 1: The effects of ketanserin treatment on acquisition and switch between a visual cue and response strategy—The purpose of this experiment was to determine the effects of the 5-HT_{2A} receptor antagonist, ketanserin on acquisition of a visual cue discrimination and switch to response discrimination, as well as vice versa. Testing occurred across two consecutive days, the acquisition and switch phases. In the visual cue strategy, a rat was required to enter the same arm based on color (black or white) in order to receive a ½ cereal piece. The visual cue associated with reinforcement for a rat was always opposite to the colored cue a rat preferred in the last training session. For the response strategy, a rat was required to turn in a particular direction (left or right) in order to enter an arm and receive a ½ cereal piece. In each test, a rat was pseudorandomly started from one of two arms (“west” or “south”) such that the same start arm was never used more than two consecutive trials. The visual cues were pseudorandomly switched between choice arms such that a particular cue was associated with the same turn direction (left or right) a maximum of three consecutive trials and was equally associated with each turn direction across consecutive blocks of 12 trials.

During the acquisition phase, rats were either trained on the visual cue discrimination or the response strategy. Rats were required to enter the goal arm to receive a cereal reinforcement. If a rat chose the goal arm, it was allowed to proceed to the end of the arm and consume the cereal piece. Subsequently, it was placed in a holding chamber set on a table near the maze. If the incorrect arm was selected, a rat was allowed to proceed to the end of the arm, explore the empty food well and was then removed. Between trials, the maze, block, and visual cues were wiped down with a 2% Quatricide solution to minimize use of olfactory cues. As in previous experiments [36, 38, 42], the maze was rotated 90° every four trials to prevent a rat from potentially using intramaze cues other than the colored boards. Acquisition criterion was achieved when a rat entered the correct arm in 10 consecutive trials.

The day following the acquisition phase, each rat was tested on the switch to the other strategy. Prior to starting the switch phase, two retention trials were given such that a rat was reinforced for choosing the arm associated with reinforcement in acquisition. One trial was started from the “south” arm and other from the “west” arm. If a rat made the incorrect choice on a retention trial, then it was immediately repeated until a rat made the correct choice. In subsequent trials, a rat was required to switch from the strategy learned during the acquisition phase (either visual cue or response) to the alternative strategy. Again, the visual cues were pseudorandomly switched between choice arms such that a particular cue was associated with the same turn direction (left or right) a maximum of three consecutive trials and was equally associated with each turn direction across consecutive blocks of 12 trials. The learning criterion in the switch phase was also 10 consecutive correct arm choices.

In the switch phase, the errors committed were analyzed as in previous studies [36, 42, 43]. Specifically, an analysis was carried out to determine whether treatments altered perseveration or reversions back to the previously correct response pattern after perseveration had ceased. Perseveration involved continuing to make the same choice based on the strategy learned during acquisition, when a trial required a choice based on the other strategy. For every consecutive 12 trials in a session, half the trials consisted of these trials. As in a previous experiment [42], these trials were separated into consecutive blocks of 4 trials each. Perseveration was defined as entering the incorrect arm in 3 or more trials per block. This is a similar criterion as used in previous experiments measuring perseveration [15, 28, 41, 42]. Once a rat made less than three errors in a block the first time, all subsequent errors were no longer counted as perseverative errors. After a rat stopped perseverating as defined above, the numbers of errors were counted when a rat reverted back to the previously correct choice on the types of trials that required turning the opposite direction from the previous strategy. These errors are referred to as regressive errors. During the switch, a third type of error could be made on the other half of the trials in which a correct turn was the same as the choice required in the acquisition phase. For example, during acquisition a rat might be required to always choose the black cue. During the switch, a rat is then required to always turn right. For half of the trials, the black visual cue was in the arm on the right. However, a rat may make an error by turning left into an arm. These errors are referred to as never-reinforced errors because neither entering the white visual cue nor turning left was a reinforced strategy. The regressive and never-reinforced measures provide an index of the ability to maintain a new discrimination strategy.

Thirty minutes prior to each test session, a rat received an intraperitoneal injection of either water or ketanserin. Ketanserin was dissolved in sterile water. Selected doses were similar to those used in previous studies [6, 18]. In one experiment, rats were tested on visual cue acquisition and shift to a response strategy. In another experiment with a different set of naïve rats, subjects were tested on response acquisition and shifted to a visual cue strategy. Group assignment was determined by the treatment administered during each test phase (acquisition/strategy-switching). The final sample size, represented in parentheses, for each group in the visual cue shift to a response test was as follows: vehicle - vehicle (n=9); ketanserin 0.5 mg/kg - vehicle (n=8); vehicle - ketanserin 0.05 mg/kg (n=7); vehicle - ketanserin 0.5 mg/kg (n=9). In the response switch to visual cue test, the groups were as follows: vehicle - vehicle (n=9); ketanserin 0.5 mg/kg - vehicle (n=8); vehicle - ketanserin 0.05 mg/kg (n=7); vehicle - ketanserin 0.5 mg/kg (n=8).

Experiment 2: The effects of ketanserin treatment administered on both acquisition of a visual cue and switch to a response discrimination—Related to experiment 1, initial learning following ketanserin treatment could result in state-dependent learning that affects performance in the switch phase when a rat is administered vehicle treatment. To control for any state-dependent learning effects, another experiment was performed that investigated the effects of ketanserin administered prior to the acquisition and prior to the switch phase in the same group of rats. If ketanserin leads to state-dependent learning, then repeated ketanserin treatment may impair performance on the switch because initial learning occurred in a drug-state. Alternatively, if ketanserin selectively enhances strategy switching, then repeated administration of the drug should still facilitate performance on the switch phase. To specifically test this, ketanserin at 0.5 mg/kg was administered during both phases of the task. Because ketanserin treatment had the same effect on both a visual cue to response and response to visual cue switch, the effects of repeated ketanserin administration was only tested in a single type of switch, specifically a visual cue to response switch. Group assignment was determined by the treatment administered during each test phase (acquisition/strategy-switching) as follows: vehicle - vehicle (n=8); ketanserin 0.5 mg/kg - ketanserin 0.5 mg/kg (n=10).

Experiment 3: The effects of prazosin treatment on a switch from a visual cue to response discrimination—To determine whether any effects of ketanserin observed in Experiment 1 were due to its ability to bind and antagonize $\alpha 1$ -adrenergic receptors ($pK_i=7.7$) [29], prazosin, a selective $\alpha 1$ -adrenergic antagonist was administered to rats using the same procedure described in Experiment 1. Because ketanserin selectively enhanced a switch in strategies, the effect of prazosin was only investigated during the switch phase. In both the acquisition and switch phases, rats received an intraperitoneal injection thirty minutes prior to testing. Group assignment was determined by the treatment administered during each test phase (acquisition/strategy-switching) as follows: vehicle - vehicle (n=6); vehicle - prazosin 0.5 mg/kg (n=6); vehicle - prazosin 2.0 mg/kg (n=6). Prazosin was dissolved in a 2:1 mixture of sterile water to propylene glycol. The doses chosen were based on previous experiments that investigated prazosin on attention and memory tests [40, 57].

Experiment 4: The effects of SB242084 treatment on acquisition and switch between a visual cue and response strategy—The purpose of Experiment 4 was to determine whether blockade of 5-HT_{2C} receptors affects discrimination learning and/or strategy-switching. This was accomplished by investigating the effects of the 5-HT_{2C} antagonist, SB242084 on the acquisition and switch of a visual cue and response strategy discrimination. All aspects of the experiment were the same as described in Experiment 1. The treatment groups for the visual cue acquisition and switch to response experiment were as follows: vehicle - vehicle (n=6); SB242084 0.5 mg/kg - vehicle (n=6); SB242084 1.0 mg/kg - vehicle (n=6); vehicle - SB242084 0.05 mg/kg (n=6); vehicle - SB242084 0.5 mg/kg (n=6); vehicle - SB242084 1.0 mg/kg (n=6). The groups in response acquisition and switch to visual cue experiment were as follows: vehicle - vehicle (n=7); SB242084 0.5 mg/kg - vehicle (n=6); SB242084 1.0 mg/kg - vehicle (n=9); vehicle - SB242084 0.05 mg/kg (n=7); vehicle - SB242084 0.5 mg/kg (n=8); vehicle - SB242084 1.0 mg/kg (n=6). The doses used were similar to those in previous experiments shown to affect learning and behavioral flexibility [6, 18]. SB242084 was dissolved in an 8% cyclodextrine/saline solution containing 25 mM citric acid.

Statistical Analysis

One-way ANOVAs were used to analyze differences in trials to criterion in both the acquisition and switch phases of experiments 1, 3, and 4. Separate, one-way ANOVAs were also used to determine group differences in the amount of perseverative, regressive, and never reinforced errors committed among the groups. Newman-Keuls post-hoc tests were used to determine significant differences between specific treatment groups. An unpaired *t*-test was used in experiment 2 to determine significant difference on trials to criterion and each error type between saline controls and ketanserin-treated rats.

Results

Experiment 1: The effects of ketanserin treatment on acquisition and switch between a visual cue and response strategy

The results on trials to criterion and analysis of errors for Experiment 1 are shown in Table 1. Ketanserin treatment did not significantly affect acquisition of either the visual cue discrimination ($F_{3,34} = 0.84$, $P > 0.05$), or the response discrimination, ($F_{3,31} = 0.12$, $P > 0.05$) [see Figures 1a and 2a, respectively]. The difference in trials to criterion in the switch from a visual cue to a response strategy among groups was significant ($F_{3,34} = 6.38$, $P < 0.01$). Specifically, ketanserin at 0.5 mg/kg facilitated a switch to the response strategy. Post hoc Newman-Keuls tests revealed that the group receiving ketanserin 0.5 mg/kg on the switch to response required significantly less trials to reach criterion compared to all other groups ($P's < 0.05$). Likewise, the groups that were required to switch strategies from a

response to a visual cue discrimination showed a difference in trials to reach criterion, ($F_{3,31} = 9.27, P < 0.01$). Ketanserin 0.5 mg/kg treatment during the shift to the visual cue significantly reduced trials to criterion compared to that of all other treatments (P 's < 0.01).

Immediately preceding the switch phase, rats were required to demonstrate retention of the previously learned strategy. There was not a significant difference in the number of retention trials among the groups for either retention of the visual cue discrimination ($F_{3,26} = 0.58, P > 0.05$) or the response discrimination ($F_{3,25} = 2.31, P > 0.05$).

Figure 1C illustrates errors committed during the switch to a response discrimination. There was a significant treatment effect in the number of perseverative errors ($F_{3,34} = 4.26, P < 0.05$). The ketanserin 0.5 mg/kg – vehicle group had a significantly greater number of perseverative errors compared to that of the other treatment groups (P 's < 0.05). There was also a significant treatment effect for regressive errors ($F_{3,34} = 3.91, P < 0.05$). Ketanserin 0.5 mg/kg treatment during the switch significantly reduced regressive errors compared to that of other treatments (P 's < 0.05). In contrast to perseverative and regressive errors, there was not a significant group difference in the number of never-reinforced errors in the switch to a response strategy ($F_{3,34} = 1.06, P > 0.05$).

Ketanserin treatment altered the error pattern in the switch to the visual cue strategy similar to that observed in the shift to the response strategy (see Figure 2c). Specifically, there was a significant difference in the number of perseverative errors among the groups ($F_{3,31} = 3.32, P < 0.05$). The ketanserin 0.5 mg/kg - vehicle group had a significantly greater number of perseverative errors than the vehicle - ketanserin 0.5 mg/kg group ($P < 0.05$), but not compared to that of the vehicle - vehicle or vehicle - ketanserin 0.05 mg/kg groups (P 's > 0.05). Additionally, there was a significant treatment effect for the number of regressive errors ($F_{3,31} = 4.12, P < 0.05$). Administration of ketanserin 0.5 mg/kg on the switch led to significantly fewer regressive errors than all other treatment groups (P 's < 0.05). Analysis of the never-reinforced errors indicated that the various groups committed a similar number of errors ($F_{3,31} = 0.22, P > 0.05$).

Experiment 2: The effects of ketanserin treatment administered on both acquisition of a visual cue and switch to a response discrimination

Similar to that observed in Experiment 1 with a single injection of ketanserin, ketanserin 0.5 mg/kg administered during acquisition and strategy switching still led to a selective improvement in strategy switching (see Figure 3). Ketanserin 0.5 mg/kg and saline treatment led to a similar learning performance in visual cue acquisition, $t(16) = 1.08, P > 0.05$. Similarly, there was not a significant difference in the retention trials correctly achieved between the groups, $t(16) = 0.42, P > 0.05$. However, the ketanserin 0.5 mg/kg – ketanserin 0.5 mg/kg group required significantly fewer trials to criterion in the switch phase compared to that of the vehicle – vehicle group, $t(16) = 4.45, P < 0.01$.

There was a trend for the ketanserin group to commit fewer perseverative errors, $t(16) = 1.70, P = 0.10$ and regressive errors, $t(16) = 1.75, P = 0.10$, than the vehicle group (see Figure 3c). Specifically, the vehicle group committed 8.00 ± 1.31 mean perseverative errors and 6.25 ± 1.10 mean regressive errors, while the ketanserin group had mean scores of 5.20 ± 1.04 and 3.70 ± 1.04 for perseverative and regressive errors, respectively. There was not a significant difference in never-reinforced errors committed between the groups, $t(16) = 0.80, P > 0.05$.

Experiment 3: The effects of prazosin on visual Cue acquisition and switch to response discrimination

Experiment 1 demonstrated that ketanserin selectively enhanced a switch in strategies. Although ketanserin preferentially blocks 5-HT_{2A} receptors, it exhibits some affinity for blocking α 1-adrenergic receptors. To determine whether the effects of ketanserin might be due to primarily blocking α 1-adrenergic receptors, the effects of prazosin, a specific α 1-adrenergic antagonist, in a switch from a visual cue to response strategy was determined. The mean scores on acquisition and switch phases for trials to criterion and errors are shown in Supplementary Table 2. All the groups received vehicle treatment prior to acquisition. There was not a significant difference in trials to criterion among the groups on acquisition ($F_{2,17} = 0.07$, $P > 0.05$). Additionally, prazosin treatment did not significantly affect retention of the originally learned visual cue strategy ($F_{2,17} = 0.68$, $P > 0.05$) or strategy-switching ($F_{2,17} = 2.17$, $P > 0.05$) [see Figure 4].

Examination of the error pattern during the switch to response discrimination revealed that prazosin treatment also did not affect the error pattern compared to that of vehicle controls. Specifically, there was not an overall group effect for perseverative errors ($F_{2,17} = 0.59$, $P > 0.05$); regressive errors ($F_{2,17} = 0.71$, $P > 0.05$); or never-reinforced errors ($F_{2,17} = 0.78$, $P > 0.05$).

Experiment 4: The effects of SB242084 treatment on acquisition and switch between a visual Cue and response strategy

The results from Experiment 4 are shown in Supplementary Table 2. SB242084 treatment did not significantly affect visual cue acquisition ($F_{5,35} = 0.18$, $P > 0.05$) or response acquisition ($F_{5,42} = 1.03$, $P > 0.05$) [see Figures 5a and 6a, respectively]. Unlike the effects of 5-HT_{2A} receptor antagonism, blockade of 5-HT_{2C} receptors with SB242084 had no significant effect on either the switch from a visual cue to a response discrimination, ($F_{5,35} = 0.50$, $P > 0.05$) [Figure 5b], or from a response to a visual cue strategy ($F_{5,42} = 0.68$, $P > 0.05$) [Figure 6b].

In measuring retention of the originally learned strategy, there was not a significant group effect in retention of the visual cue discrimination ($F_{5,30} = 1.06$, $P > 0.05$), nor was there a significant group effect on retention of the response discrimination ($F_{5,37} = 0.82$, $P > 0.05$).

In the switch to the response strategy, an analysis of the errors indicated that there was no significant difference in perseverative errors ($F_{5,35} = 0.76$, $P > 0.05$), regressive errors ($F_{5,35} = 1.39$, $P > 0.05$), or never-reinforced errors ($F_{5,35} = 0.91$, $P > 0.05$) [see Figure 5c]. In a comparable fashion, there was no significant differences among the groups in the switch to a visual cue strategy for perseverative errors ($F_{5,42} = 2.20$, $P > 0.05$), regressive errors ($F_{5,42} = 1.29$, $P > 0.05$), or never-reinforced errors ($F_{5,42} = 0.99$, $P > 0.05$) [see Figure 6c].

Discussion

The present findings indicate that blockade of 5-HT_{2A} receptors with ketanserin facilitated strategy-switching in a dose-dependent manner. This was the case when subjects were required to switch from using a visual cue strategy to using an egocentric response strategy and in the converse as well. Ketanserin is known to have some affinity for antagonizing α -1 adrenergic receptors, however the present results indicate that ketanserin enhancement of strategy-switching is principally due to its action in blocking 5-HT_{2A} receptors. This is because treatment with the α -1 adrenergic receptor antagonist, prazosin, had no effect on strategy-switching. Moreover, blockade of 5-HT_{2C} receptors using the selective 5-HT_{2C} receptor antagonist, SB242084, did not affect strategy-switching between a visual cue and egocentric response strategy. Taken together, the findings suggest that selectively blocking

5-HT_{2A} receptors enhances behavioral flexibility when conditions require a switch in strategies.

The enhancement of behavioral performance with 5-HT_{2A} receptor blockade is not limited to conditions requiring a shift in strategies, but has also been observed on premature responding in the 5-choice serial reaction time test. In particular, ketanserin treatment reduces premature responding [18, 53] at the same dose ketanserin enhances strategy-switching. Thus, blockade of 5-HT_{2A} receptors can enhance behavioral flexibility when conditions require inhibition of a previously relevant strategy and learning of a new strategy, as well as when conditions require inhibiting initiation of a response prior to the onset of the proper stimulus. Unknown, at this point, is whether these two set of findings represent a similar underlying process that is affected by 5-HT_{2A} receptor blockade when conditions require inhibition of a pre-potent response.

The findings from other experiments suggest that blockade of 5-HT_{2A} receptors does not improve behavioral flexibility under all conditions. Systemic treatment with M100907 impairs spatial reversal learning, while treatment with SB242084 enhances reversal learning [6]. Furthermore, M100907 does not reverse a phencyclidine-induced reversal learning deficit [46]. Strategy-switching and reversal learning are proposed to require different types of rule learning, or processes to allow appropriate decision-making [55]. In the case of reversal learning, a subject may apply a simple valence to two particular choices, e.g. black object + and white object –, and then the contingencies are reversed. Therefore, in reversal learning the general strategy remains the same, e.g. always base a choice on object. In strategy-switching, however, a subject must fundamentally change how they approach solving a problem and apply a new strategy, e.g. in a switch from a visual cue strategy to an egocentric response strategy. There is accumulating evidence that different neural circuitry supports reversal learning and strategy-switching [13, 20, 35, 44]. Specifically, the orbitofrontal cortex is one brain area found to support reversal learning, but not strategy-switching [4, 31, 47]. Thus, one possibility is that blockade of 5-HT_{2C} receptors predominantly modifies activity in neural circuitry that supports reversal learning, while blockade of 5-HT_{2A} receptors predominantly occurs in the neural circuitry that underlies strategy-switching. Consistent with this idea, direct infusion of a 5-HT_{2C} receptor antagonist into the orbitofrontal cortex enhances spatial reversal learning [7]. In contrast, infusion of a 5-HT_{2C} receptor antagonist into the prelimbic cortex does not affect reversal learning. The prelimbic cortex, unlike the orbitofrontal cortex, does not support reversal learning, but is important for facilitating strategy-switching [41, 44].

In experiment 1, ketanserin enhanced strategy-switching by reducing regressive errors. In experiment 2, there was a modest decrease in both perseverative and regressive errors following ketanserin treatment. Consistent across both experiments was that ketanserin treatment enhanced strategy-switching by inhibiting the expression of the previously relevant strategy without affecting never-reinforced errors. Several experiments indicate that various pharmacological manipulations of the dorsomedial striatum selectively affect regressive errors, suggesting that this area is critical for maintaining a new strategy once selected [37, 39, 42, 43, 44, 51]. In contrast, prefrontal cortex regions appear to be critical for the initial inhibition of a previously relevant strategy and/or generation of a new strategy [19, 20, 31, 41, 44]. Based on the effects of ketanserin in experiments 1 and 2, blockade of 5-HT_{2A} receptors may enhance strategy switching by affecting activity in both prefrontal cortex and striatal circuitry.

One unexpected finding was that in Experiment 1, ketanserin treatment administered prior to acquisition increased perseverative errors during the switch phase. This was the case in both a switch from visual cue to response and in the switch from response to visual cue. Although

ketanserin treatment on acquisition increased perseveration on the switch, it did not lead to a significant increase in trials to criterion in the switch phase. This is because ketanserin had a small, but significant increase in perseverative errors that by definition were all concentrated early in the test phase. This is in contrast to other treatments on these tests that significantly increase perseverative errors, as well as trials to criterion [19, 41]. Furthermore, the effect on increasing errors on the initial trials of a shift is unlike committing a regressive error, which occurs at later points in the test phase and causes a restarting of the learning criterion after potentially making several consecutive correct choices.

In contrast to experiment 1, ketanserin when administered prior to the acquisition phase, as well as prior to the switch phase did not lead to increased perseveration in the switch phase. Instead, ketanserin treatment in experiment 2 trended toward decreasing perseveration and significantly enhanced strategy-switching. Because ketanserin selectively enhanced strategy switching when administered in the acquisition and switch phases, the results suggest that ketanserin does not lead to state-dependent learning. Moreover, ketanserin treatment as administered in Experiment 2 reveal that 5-HT_{2A} receptor blockade enhancement of strategy-switching is not masked by any effects found when administered only during the acquisition phase. This is clearly demonstrated by the similar findings found when ketanserin was only administered in the switch phase (Experiment 1) or when it was administered during both the acquisition and switch phases (Experiment 2). In both cases a facilitation of the switch to a new strategy is observed.

The effect of 5-HT_{2A} receptor blockade on error patterns has also been examined in reversal learning. More specifically, Boulougouris et al. [6] showed that repeated administration with M100907 increased perseverative errors during an initial reversal learning test, but did not affect performance during subsequent reversal learning tests. In this experiment, M100907 was administered repeatedly, along with multiple retention tests prior to the initial reversal of the discrimination. M100907 treatment did not affect retention, but transiently increased perseverative errors only during the first reversal learning test. This raises the possibility that under some conditions 5-HT_{2A} receptor blockade may transiently alter initial inhibition of a previously learned discrimination. However, with more extended drug administration and/or behavioral flexibility testing this increase in perseveration does not occur.

The goal of the present experiments was to determine the effects of acute administration of a 5-HT_{2A} and 5-HT_{2C} receptor antagonist on strategy-switching. Only ketanserin, the 5-HT_{2A} receptor antagonist facilitated strategy-switching. It should be noted that acute and chronic administration of a drug can have distinct behavioral and physiological effects. However, both acute and extended repeated administration (two weeks) of ketanserin is effective in reducing nicotine self-administration in rats [34]. Furthermore, repeated administration of either ketanserin or the less selective ritanserin does not affect retention of a learned discrimination [6, 9]. Future experiments that directly investigate the effects of chronic ketanserin treatment will be critical in determining whether such a regimen facilitates strategy switching.

The present findings demonstrating that the 5-HT_{2A} receptor antagonist, ketanserin enhances strategy-switching also has clinical implications. Abnormalities in the 5-HT system have been implicated in several clinical populations including obsessive compulsive disorder (OCD) [2, 16, 17], autism spectrum disorders [8, 49] and schizophrenia [11]. Deficits in cognitive flexibility have been associated with all three of these conditions [3, 23, 32]. Thus, treatment with a selective 5-HT_{2A} receptor antagonist may alleviate the cognitive flexibility deficits observed in these conditions. In the treatment of symptoms in schizophrenia, several atypical anti-psychotics antagonize 5-HT₂ receptors and in some cases are effective in reducing cognitive symptoms [22, 30, 52]. However, often these drugs

have multiple receptor targets, in which the effect of 5-HT_{2A} receptor antagonism may be masked by other receptor activity that counteracts its efficacy (e.g. anticholinergic effects that impair cognitive flexibility) [50]. Future experiments that further explore the behavioral conditions in which 5-HT_{2A} receptor antagonists administered either chronically or acutely to improve cognitive flexibility can provide a better understanding of how such a treatment could be applied in the most effective manner.

In summary, the present experiments demonstrated that acute treatment with the 5-HT_{2A} receptor antagonist, ketanserin enhanced strategy-switching between a visual cue and response strategy. In contrast, blockade of 5-HT_{2C} receptors or α -1 adrenergic receptors did not affect strategy-switching. Thus, treatment with 5-HT_{2A} receptor antagonists may improve cognitive flexibility in various psychiatric and neurological conditions in which cognitive flexibility impairments represent significant aspects of their functional disabilities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by grants AG027951 (MER) and P50 HD055751 (JAS, MER). We appreciate the assistance of Bhavna Balaney, Nisarg Patel and Chiali Lee with behavioral testing.

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Figure 1.

The effect of ketanserin treatment on visual cue acquisition and switch to response. Each rat received an intraperitoneal injection of vehicle (Veh) or one of two doses of ketanserin (Ket) during the acquisition phase or the switch phase 30 minutes prior to testing. The treatments in the legends represent the treatment received prior to acquisition (1st) followed by the treatment received prior to the switch phase (2nd). Treatment given prior to acquisition or the switch phases in bold type. A) Mean ($\pm$ SEM) trials to criterion on acquisition of a visual cue discrimination. Injection of ketanserin had no effect on acquisition. B) Mean ($\pm$ SEM) trials to criterion on a switch to a response strategy. Ketanserin at 0.5 mg/kg dose facilitated a switch to a response strategy. * = $P < .05$ vs. Veh - Veh, Ket 0.5 mg/kg - Veh, Veh - Ket 0.05 mg/kg. C) Mean ($\pm$ SEM) errors committed by type during the switch to a response strategy. Ketanserin 0.5 mg/kg administered prior to the acquisition phase of testing resulted in an increase in perseverative responding during the switch phase. * = $P < .05$ vs. Veh - Veh, Veh - Ket 0.05 mg/kg, Veh - Ket 0.5 mg/kg. Ketanserin 0.5 mg/kg administered prior to the switch to response significantly reduced regressive errors. * = $P < .05$ vs. Veh - Veh, Ket 0.5 mg/kg - Veh, Veh - Ket 0.05 mg/kg. There was no significant group difference in the number of never-reinforced errors committed.

Figure 2.

The effect of ketanserin treatment on response acquisition and switch to visual cue. Each rat received an intraperitoneal injection of vehicle (Veh) or one of two doses of ketanserin (Ket) during either the acquisition or the switch phase 30 minutes prior to testing. The treatments in the legends represent the treatment received prior to acquisition (1st) followed by the treatment received prior to the switch phase (2nd). Treatment given prior to either acquisition or the switch phase is in bold type. A) Mean (± SEM) trials to criterion on acquisition of a response strategy. Injection of ketanserin had no effect on acquisition trials to criterion. B) Mean (± SEM) trials to criterion on switch to a visual cue discrimination. Ketanserin at 0.5 mg/kg dose facilitated the switch to a response strategy. * = $P < .05$ vs. Veh – Veh, Ket 0.5 mg/kg – Veh, Veh – Ket 0.05 mg/kg. C) Mean (± SEM) errors committed by type during the switch to a visual cue discrimination. Ketanserin 0.5 mg/kg administered prior to the acquisition phase of testing resulted in an increase in perseverative responding during the switch phase. * = $P < .05$ vs. Veh – Ket 0.5 mg/kg. Ketanserin 0.5 mg/kg administered prior to the switch to visual cue significantly reduced regressive errors.* = $P < .05$ vs. Veh – Veh, Ket 0.5 mg/kg – Veh, Veh – Ket 0.05 mg/kg. There was no significant difference among the groups in never-reinforced errors.

Figure 3.

The effect of ketanserin treatment on visual cue acquisition and switch to response. Each rat received an intraperitoneal injection of vehicle (Veh) or ketanserin 0.5 mg/kg (Ket) during both the acquisition phase and the switch phase 30 minutes prior to testing. The treatments in the legends represent the treatment received prior to acquisition (1st) followed by the treatment received prior to the switch phase (2nd). Treatment given prior to acquisition or the switch phases in bold type. A) Mean (± SEM) trials to criterion on acquisition of a visual cue discrimination. Injection of ketanserin had no effect on acquisition. B) Mean (± SEM) trials to criterion on switch to a response strategy. Ketanserin 0.5 mg/kg facilitated a switch to a response strategy. ** = $P < 0.01$ vs. Veh – Veh. C) Mean (± SEM) errors committed by type during the switch to a response strategy. There were trends for a reduction in both perseverative and regressive errors (Ket 0.5 mg/kg – Ket 0.5 mg/kg group vs. the Veh – Veh, $P = 0.10$ for both error types). There was no significant group difference in the number of never-reinforced errors committed.

Figure 4.

The effect of prazosin treatment on switch from visual cue to response strategy. Each rat received an intraperitoneal injection of vehicle (Veh) or one of two doses of prazosin (Prz) during either the acquisition or the switch phase 30 minutes prior to testing. The treatments in the legends represent the treatment received prior to acquisition (1st) followed by the treatment received prior to the switch phase (2nd). Treatment administered in a specific test phase is in bold type. A) Mean ($\pm$ SEM) trials to criterion on acquisition of a visual cue discrimination. All vehicle treated groups achieved acquisition criterion in a similar manner. B) Mean ($\pm$ SEM) trials to criterion during the switch to a response strategy. Injection of prazosin had no effect on the switch to response.

Figure 5.

The effect of SB242084 on visual cue acquisition and switch to response. Each rat received an intraperitoneal injection of Vehicle (Veh) or SB242084 (SB) during the acquisition or switch phase, 30 minutes prior to testing. The treatments in the legends represent the treatment received prior to acquisition (1st) followed by the treatment received prior to the switch phase (2nd). The treatment administered prior to each test phase is in bold type. A) Mean ($\pm$ SEM) trials to criterion on acquisition of a visual cue discrimination. Injection of SB242084 had no effect on visual cue acquisition. B) Mean ($\pm$ SEM) trials to criterion during the switch to a response strategy. Injection of SB242084 had no effect on the switch to response.

Figure 6.

The effect of SB242084 on response acquisition and switch to visual cue. Each rat received an intraperitoneal injection of vehicle (Veh) or SB242084 (SB) during either the acquisition or the switch phase, 30 minutes prior to testing. The treatments in the legends represent the treatment received prior to acquisition (1st) followed by the treatment received prior to the switch phase (2nd). The treatment administered prior to a test phase is in bold type. A) Mean ($\pm$ SEM) trials to criterion on acquisition of response strategy. Injection of SB242084 had no effect on response acquisition. B) Mean ($\pm$ SEM) trials to criterion during the switch to a visual cue discrimination. Injection of SB242084 had no effect on the switch to visual cue.

Table 1

Effects of ketanserin treatment on acquisition and switch phases of a strategy switching task.

	Trials to Criterion		Analysis of Errors		
	Acquisition	Switch	Perseverative	Regressive	Never Reinforced
Visual Cue Switch to Response					
VEH-VEH	43.85 ± 5.02	46.00 ± 6.18	4.00 ± 1.09	6.43 ± 1.90	2.00 ± 0.79
VEH - KET 0.05 mg/kg	49.71 ± 5.02	46.14 ± 4.75	6.28 ± 1.47	4.71 ± 0.86	1.86 ± 0.63
VEH - KET 0.5 mg/kg	40.56 ± 6.34	31.33 ± 3.82*	4.00 ± 1.09	2.44 ± 0.50*	0.89 ± 0.40
KET 0.5 mg/kg - VEH	33.29 ± 2.39	58.14 ± 3.81	10.29 ± 1.19*	5.86 ± 1.56	1.14 ± 0.40
Response shift Visual Cue					
VEH - VEH	30.37 ± 0.94	48.5 ± 3.43	8.00 ± 2.23	4.13 ± 0.61	2.28 ± 0.35
VEH - KET 0.05 mg/kg	28.86 ± 2.85	50.71 ± 5.28	7.43 ± 1.36	5.86 ± 1.28	1.71 ± 0.68
VEH - KET 0.5 mg/kg	32.75 ± 6.10	29.37 ± 3.29*	6.00 ± 1.85	1.50 ± 0.50*	2.50 ± 0.87
KET 0.5 mg/kg - VEH	33.83 ± 2.89	54.50 ± 3.45	12.67 ± 2.40 [†]	4.83 ± 1.22	2.00 ± 0.63

Values are mean ± SEM.

* $P < 0.05$ compared with other groups;[†] $P < 0.05$ compared with VEH - KET 0.5 mg/kg group (ANOVA followed by Neuman-Keuls post hoc). KET = ketanserin.