J Pharmacol Sci **122**, 84 – 92 (2013)

Journal of Pharmacological Sciences

Full Paper

Tandospirone Suppresses Impulsive Action by Possible Blockade of the 5-HT$_{1A}$ Receptor

Yu Ohmura[1,*], Haruko Kumamoto[1], Iku Tsutsui-Kimura[1,3], Masabumi Minami[2], Takeshi Izumi[1], Takayuki Yoshida[1], and Mitsuhiro Yoshioka[1]

[1]*Department of Neuropharmacology, Hokkaido University Graduate School of Medicine, N15 W7 Kita-ku, Sapporo 060-8638, Japan*
[2]*Department of Pharmacology, Hokkaido University Graduate School of Pharmaceutical Sciences, N12 W6 Kita-ku, Sapporo 060-0812, Japan*
[3]*Research Fellow of the Japan Society for the Promotion of Science*

Received December 2, 2012; Accepted April 2, 2013

Abstract. Higher impulsivity is observed in several psychiatric disorders and could be a risk factor for drug addiction, criminal involvement, and suicide. Although the involvement of the 5-HT$_{1A}$ receptor in impulsive behavior has been indicated, the effects of clinically relevant drugs have been rarely tested. In the present study, we examined whether (3a*R*,4*S*,7*R*,7a*S*)-rel-hexahydro-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-4,7-methano-1H-isoindole-1,3(2H)-dione hydrochloride (tandospirone), an anxiolytic and a partial agonist of the 5-HT$_{1A}$ receptor, could affect impulsive action in the 3-choice serial reaction time task. Rats were acutely administered tandospirone (0, 0.1, and 1 mg/kg, i.p.). Tandospirone decreased the number of premature responses, an index of impulsive action, in a dose-dependent manner. *N*-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate salt (WAY100635; 0.3 mg/kg, s.c.), a 5-HT$_{1A}$ receptor antagonist, did not reverse the suppressing effects of tandospirone on impulsive action. Moreover, a higher dose of WAY100635 (1 mg/kg, s.c.) suppressed impulsive action without tandospirone. Thus the effects of tandospirone on impulsivity might be due to the antagonistic action. Tandospirone could be a therapeutic candidate for impulsivity-related disorders.
[Supplementary Figures: available only at http://dx.doi.org/10.1254/jphs.12264FP]

Keywords: impulsive behavior, inhibitory control, behavioral inhibition, anxiolytic

Introduction

Higher impulsivity has been suggested to be a risk factor for drug addiction (1, 2), criminal involvement (3), and suicide (4, 5). Moreover, higher impulsivity is observed in several psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD) (6), schizophrenia (7), substance abuse (8), bipolar disorder (9), and borderline personality disorder (10).

Many rat and human studies have demonstrated that decreased 5-hydroxytryptamine (5-HT) levels in the brain are associated with impulsive behavior (11 – 13). A rat study using a full agonist for the 5-HT$_{1A}$ receptor [8-OH-DPAT; 8-hydroxy-2-(di-n-propylamino)tetralin], which is a research chemical, showed that activation of the 5-HT$_{1A}$ receptor stimulated impulsive action (14). However, another study did not replicate the results (15). Thus, it is of interest to examine the effects of clinically relevant drugs acting on the 5-HT$_{1A}$ receptor on impulsive action.

In the present study, we examined the effects of (3a*R*,4*S*,7*R*,7a*S*)-rel-hexahydro-2-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-4,7-methano-1H-isoindole-1,3(2H)-dione hydrochloride (tandospirone), a 5-HT$_{1A}$ receptor partial agonist that is widely used in Japan and China, on impulsive action in an animal model. To assess impulsive action, we used a 3-choice serial reaction time task (3-CSRTT) (16 – 18), which is a simpler version of the

*Corresponding author. gwd0701@yahoo.co.jp
Published online in J-STAGE on May 24, 2013
doi: 10.1254/jphs.12264FP

5-choice serial reaction time task (5-CSRTT) (19). This task is performed in an operant chamber containing a horizontal array of three holes. A light in the aperture of one of the three holes is briefly flashed in a random order. Animals are required to wait until the light is flashed and to make a nose-poke response into the hole in which the light flashed in order to get a food pellet. Responses that occur before the presentation of the stimulus light are described as premature responses and result in a 5-s time-out period. These responses are regarded as a form of impulsive-like action and a failure in impulse control (20). Thus, the 3-CSRTT is a suitable test for examining the effects of drugs on impulsive action.

Material and Methods

Animals

Thirty-seven male Wistar/ST rats were supplied by Nippon SLC Co., Ltd. (Hamamatsu). Of these rats, 9 were used to test the dose–response effects of tandospirone (experiment 1) on impulsive action. Eight rats were used for a simple food consumption test (experiment 2). Twelve rats were used to examine whether a 5-HT_{1A} antagonist could reverse the effects of tandospirone on impulsive action (experiment 3). Eight rats were used to examine the effects of a higher dose of 5-HT_{1A} antagonist on impulsive action (experiment 4). They were housed in groups of four under an alternating light–dark cycle (light from 7 p.m. to 7 a.m.) at approximately 21°C and a relative humidity of 40% – 50%. When the rats were 9-week-old (270 – 290 g), we began to restrict their food intake to maintain their body weight at 85% of that under free-feeding conditions. The daily food of the rats in the home cage was purchased from CLEA JAPAN, Inc. (CE-2, Tokyo) and was given after their daily sessions. Water was available ad libitum. The treatment of animals complied with the Guidelines for the Care and Use of Laboratory Animals of the Animal Research Committee of Hokkaido University.

Drugs

Tandospirone hydrochloride, a 5-HT_{1A} receptor partial agonist, was purchased from Tocris Bioscience (Bristol, UK). Tandospirone was dissolved in saline and administered intraperitoneally at a volume of 2 ml/kg. *N*-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamid maleate salt (WAY100635), a selective 5-HT_{1A} receptor antagonist, was purchased from Sigma-Aldrich (St. Louis, MO, USA). WAY100635 was dissolved in 0.01 M phosphate-buffered saline (PBS). WAY100635 was administered subcutaneously at a volume of 1 ml/kg. The concentration of tandospirone was calculated as the salt form, and the concentration of WAY100635 was calculated as the free base.

Apparatus

Aluminum operant chambers measuring 26 × 26 × 26 cm (Med Associates Inc., St. Albans, VT, USA) were used. The curved rear wall of each chamber contained nine 2.5-cm^2 holes, 2.2-cm deep. Each hole had an infrared photocell beam to detect nose poke responses and a 2.8-W bulb at its rear. Every other hole was sealed so that only the central three holes were accessible. A food magazine was located on the opposite wall of the chamber, and a house light was located at the top of this wall. The apparatus was controlled by a computer program written in the MED-PC language (Med Associates Inc., St. Albans, VT, USA).

3-CSRTT

The training procedure and the task sequence employed in the 3-CSRTT have been described in detail in previous reports (16, 21). Briefly, when the task began, the house light was illuminated. After a fixed intertrial interval (ITI, 5 s), one of the three holes was illuminated briefly (stimulus duration: 1 s) in a random order. Nose poking during the ITI was recorded as a premature response, an index of impulsive-like action. Nose poking into the lit hole while it was illuminated or within 5 s of limited hold was recorded as a correct response and was rewarded by the immediate delivery of a palatable food pellet (45 mg each, dustless precision pellets; Bio-serv, Frenchtown, NJ, USA) to the food magazine. That is, even after the hole light turned off, nose poking into the lit hole caused reward delivery if the response occurred within 5 s. Nose poking into another hole was recorded as an incorrect response. When a rat failed to nose poke within the time limit, it was recorded as an omission. After the delivery and collection of the food pellet by a rat, the house light was switched off for 2 s to allow the rat to eat the pellet before the next trial automatically began. The beginning of the next ITI was signaled by illumination of the house light. Additional nose poking into any of the three holes prior to food collection was recorded as a perseverative response. Premature responses, incorrect responses, omissions, and perseverative responses resulted in a 5 s time-out period during which the all lights were extinguished. The number of nose-poke responses during the time-out period was also counted, although these responses had no other consequences. Because the trial was initiated automatically, we did not set a time restriction. Each session consisted of 100 trials. All rats in the present study finished 100 trials within 30 min. Training was conducted

for one session per day and five to six sessions per week.

At the beginning of the training schedule, the stimulus duration was 30 s. Depending on individual performances, it was progressively reduced to 1 s (15, 10, 5, 3, 2, 1.5, and 1 s). When a rat attained the criteria of > 80% accuracy (percentage of correct responses) and < 20 omissions in a session, the stimulus duration was reduced in the next session.

We measured six behavioral parameters, as described below. 1) Premature responses (No. per session), 2) Accuracy (percentage of correct responses): [(correct responses) / (correct and incorrect responses)] × 100, 3) Omissions (No. per session), 4) Perseverative responses (No. per session), 5) Correct response latency (s): the mean time between stimulus onset and nose poke to the correct hole, 6) Reward latency (s): the mean time between reward delivery and nose poke to the food magazine.

Training was completed when the animal reached the target phase (stimulus duration 1 s) and maintained stable performance. After the completion of training, the stimulus duration was fixed at 1 s regardless of performance.

Food consumption test

Although omissions and reward latency are an index of appetite/motivation, they are relatively indirect measures. To directly assess appetite and discriminate between drug effects on performance in the 3-CSRTT and motivation for food, we conducted a simple food consumption test with the operant box which was used for 3-CSRTT. A rat was allowed to eat food pellets in the food magazine for 30 min. Twelve grams of food pellets were placed in the food magazine.

Baseline performance assessment and drug treatment schedule

Once the performance of the rats stabilized, the experiments began. Rats were approximately 20-week-old at the beginning of the experiment. We used the data from the last 3 days of training to provide a pre-experimental baseline index of performance. Drug treatments were carried out with a Latin square design or the order was counterbalanced if only two conditions were used. The experimental baseline was assessed on Mondays and Thursdays, and drugs were administered on Tuesdays and Fridays. We kept the time between an experiment and the feeding after training on the previous day constant to stabilize the rats' motivational levels.

Experiment 1: the effects of tandospirone on impulsive action

Nine rats were administered tandospirone (0, 0.1, and 1 mg/kg, i.p.) 20 min before the testing session. We did not use higher doses of tandospirone because a higher dose (10 mg/kg) dramatically increased omissions (> 50) in our preliminary study. The dose of tandospirone (1 mg/kg) was chosen based on our previous reports (22, 23). This dose of tandospirone has consistently exerted anxiolytic actions in rats.

Experiment 2: the effects of tandospirone on appetite

Eight rats were administered tandospirone (0 and 1 mg/kg, i.p.) 20 min before the food consumption test. We used this dose of tandospirone based on the results of experiment 1.

Experiment 3: the effects of 5-HT_{1A} antagonist on the suppressing effects of tandospirone on impulsive action

Twelve rats were administered WAY100635 (0 and 0.3 mg/kg, s.c.) 30 min before the testing session. Tandospirone (0 and 1 mg/kg, i.p.) was administered 10 min after the injection of WAY100635. We used this dose of WAY100635 because a previous study demonstrated that 0.3 mg/kg of WAY100635 reversed the effects of an agonist (15).

Experiment 4: the effects of a higher dose of 5-HT_{1A} antagonist on impulsive action

Eight rats were administered WAY100635 (0 and 1 mg/kg, s.c.) 30 min before the testing session.

Data analysis

Six behavioral measures were analyzed (accuracy, premature responses, omissions, perseverative responses, correct response latency, and reward latency). Each measure was analyzed separately by two-factor analysis of variance for repeated measures with the rank of dose injection as the between-subject factor and the dose of drug (or the type of drug) as the within subject factor. When the result of Mauchly's sphericity test was significant, The Greenhouse-Geisser correction was used. Multiple comparisons with Bonferroni's correction were also conducted. To test the statistical significance of differences between two conditions, paired *t*-tests were utilized. The alpha level was set at 0.05 for all statistical procedures. All statistical analyses were conducted using SPSS (version 15.0 J).

Results

Experiment 1: the effects of tandospirone on impulsive action

Figure 1, A – F shows the effects of tandospirone on premature responses, accuracy (percent correct responses), omissions, perseverative responses, correct response

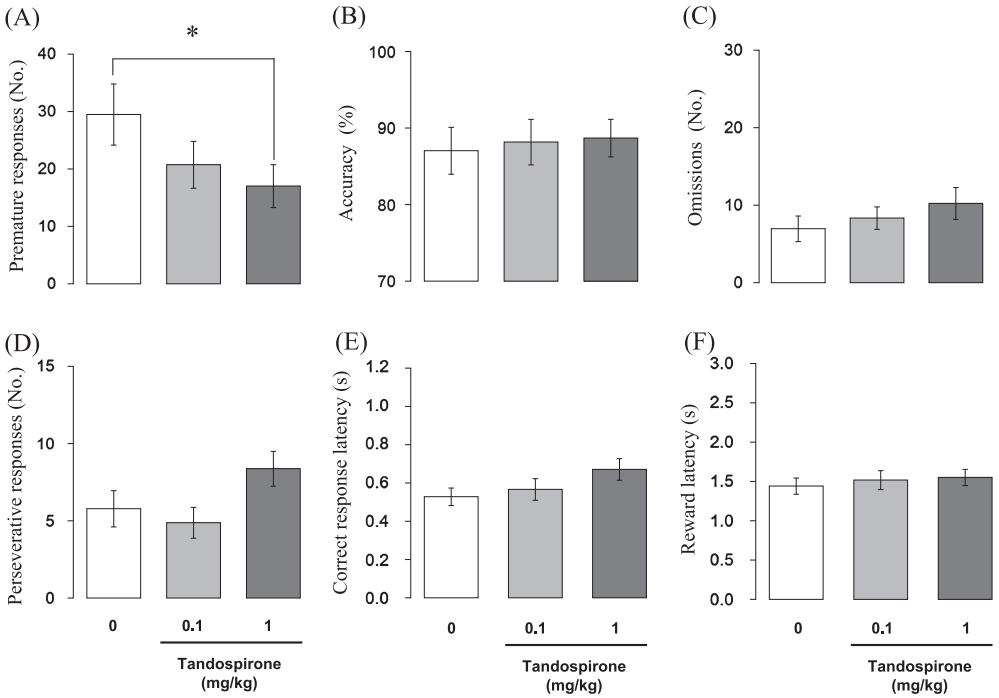

Fig. 1. The effects of tandospirone (A – F) on 3-CSRTT performance. Nine rats were administered tandospirone (0, 0.1, and 1 mg/kg, i.p.) 20 min before the testing session. A multiple comparison revealed that the 1 mg/kg dose of tandospirone significantly decreased the number of premature responses, which is a measure of impulsive action. The bars represent the mean and the lines represent the S.E.M. *$P < 0.05$ (with Bonferroni's correction).

latency, and reward latency. Two-way ANOVA revealed a significant dose effect on premature responses ($F_{2, 12} = 12.33$, $P < 0.01$) and perseverative response ($F_{2, 12} = 5.84$, $P < 0.05$), but not on accuracy ($F_{2, 12} = 0.38$, NS), omissions ($F_{2, 12} = 0.88$, NS), or reward latency ($F_{2, 12} = 1.60$, NS). There was a trend in correct response latency ($F_{1.07, 6.43} = 5.05$, $P = 0.06$, with the Greenhouse-Geisser correction) but the effect was not statistically significant. There was no main effect of rank of dose injection or significant dose × rank of dose injection interaction.

A multiple comparison with Bonferroni's correction revealed that the 1 mg/kg dose of tandospirone significantly decreased the number of premature responses ($P < 0.05$). The effects of tandospirone on the perseverative response did not reach statistical significance in the post hoc tests.

Experiment 2: the effects of tandospirone on appetite

Because tandospirone slightly increased omissions and reward latency, which are an indirect index of appetite, while the effects were not statistically significant (Fig. 1), a more direct measure was additionally used. Figure 2 shows the effects of tandospirone (1 mg/kg) on the amount of food consumption in the operant box.

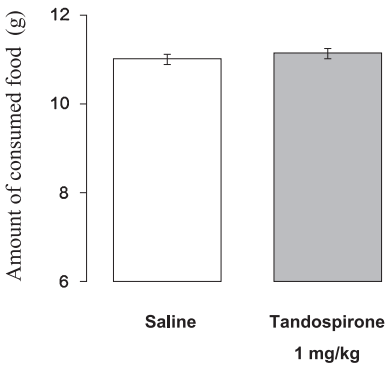

Fig. 2. The effects of tandospirone on the amount of food consumption. Eight rats were administered tandospirone (0 and 1 mg/kg, i.p.) 20 min before the food consumption test. No significant anorexic effects of 1 mg/kg of tandospirone were observed. The bars represent the mean and the lines represent the S.E.M.

There was no significant anorexic effect of tandospirone ($t_7 = 0.71$, NS).

Experiment 3: the effects of 5-HT$_{1A}$ antagonist on the suppressing effects of tandospirone on impulsive action

Figure 3, A – F shows the effects of tandospirone and

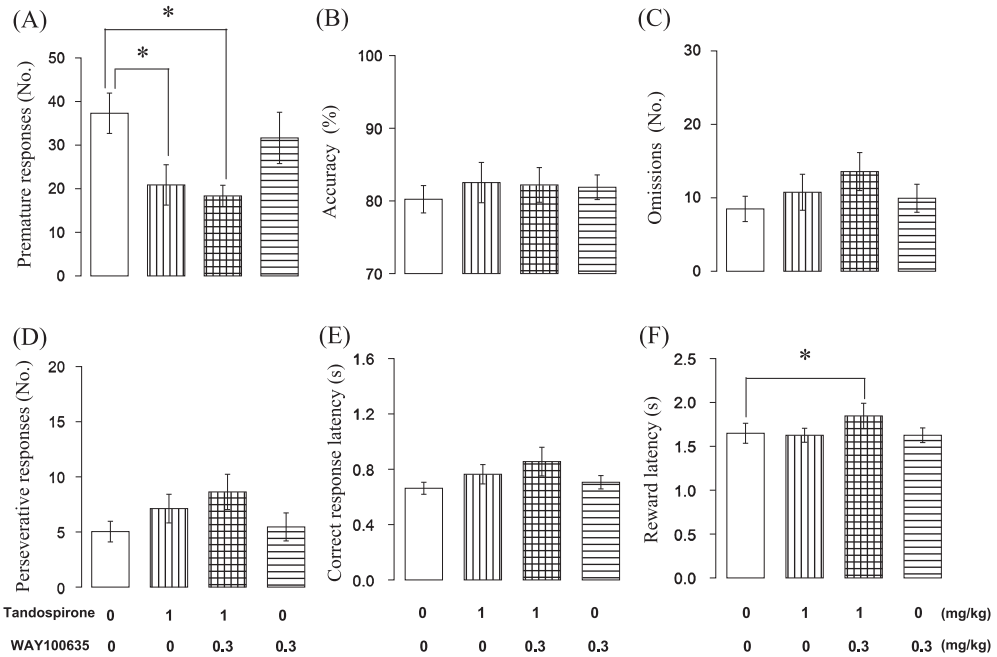

Fig. 3. The effects of tandospirone and 5-HT_{1A} antagonist (A – F) on 3-CSRTT performance. Twelve rats were administered WAY100635 (0 and 0.3 mg/kg, s.c.) 30 min before the testing session. Tandospirone (0 and 1 mg/kg, i.p.) was administered 10 min after the injection of WAY100635. A multiple comparison revealed that the 1 mg/kg dose of tandospirone and tandospirone with WAY100635 significantly decreased the number of premature responses, indicating that 5-HT_{1A} antagonist failed to attenuate the effects of tandospirone. Moreover, a multiple comparison revealed that the 1 mg/kg dose of tandospirone with 0.3 mg/kg of WAY100635 significantly prolonged reward latency. The bars represent the mean and the lines represent the S.E.M. *$P < 0.05$ (with Bonferroni's correction).

WAY100635 on premature responses, accuracy (percent correct responses), omissions, perseverative responses, correct response latency, and reward latency. Two-way ANOVA revealed a significant effect of the type of drug on premature responses ($F_{3, 24} = 7.90$, $P < 0.01$) and reward latency ($F_{3, 24} = 5.33$, $P < 0.01$), but not on accuracy ($F_{3, 24} = 0.41$, NS), omissions ($F_{3, 24} = 1.55$, NS), perseverative response ($F_{3, 24} = 2.39$, NS), or correct response latency ($F_{1.46, 11.68} = 2.37$, NS, with Greenhouse-Geisser correction). There was no main effect of rank of dose injection or significant dose × rank of dose injection interaction.

A multiple comparison with Bonferroni's correction revealed that the 1 mg/kg dose of tandospirone significantly decreased the number of premature responses ($P < 0.05$), consistent with the results of experiment 1. However, tandospirone with WAY100635 still significantly decreased the number of premature responses ($P < 0.05$), indicating that WAY100635 did not reverse the effects of tandospirone at all. Moreover, a multiple comparison with Bonferroni's correction revealed that the 1 mg/kg dose of tandospirone with 0.3 mg/kg of WAY100635 significantly prolonged reward latency ($P < 0.05$).

Experiment 4: the effects of a higher dose of 5-HT_{1A} antagonist on impulsive action

Figure 4, A – F shows the effects of WAY100635 (1 mg/kg) on premature responses, accuracy (percent correct responses), omissions, perseverative responses, correct response latency, and reward latency. The paired *t*-test revealed a significant effect of WAY100635 on premature responses ($t_7 = 3.39$, $P < 0.05$), but not on omission ($t_7 = 0.00$, NS), correct response latency ($t_7 = 1.19$, NS), accuracy ($t_7 = 0.25$, NS), perseverative responses ($t_7 = 1.22$, NS), or reward latency ($t_7 = 0.02$, NS).

Baseline performance assessment

Figure 5 shows the pre-experimental and experimental baseline for premature responses, accuracy, and omissions for the three groups of rats (experiments 1, 3, and 4) over 6, 7, and 5 sessions, respectively. Repeated-measures ANOVA showed no significant effects of day, in any of the three groups, on premature responses (experiment 1: $F_{5, 40} = 1.58$, NS; experiment 3: $F_{6, 66} = 1.34$, NS; and experiment 4: $F_{4, 28} = 1.18$, NS), omissions (experiment 1: $F_{2.31, 18.50} = 1.93$, NS; experiment 3: $F_{6, 66} = 0.27$, NS; and experiment 4: $F_{4, 28} = 1.35$, NS), or accu-

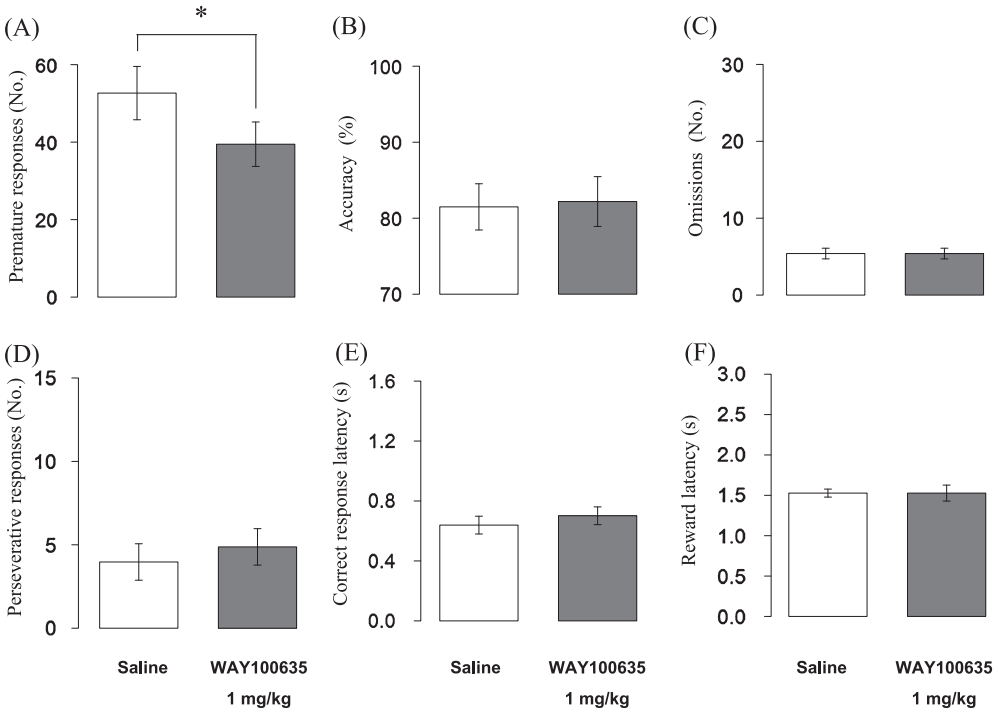

Fig. 4. The effects of a higher dose of 5-HT_{1A} antagonist (A – F) on 3-CSRTT performance. Eight rats were administered WAY100635 (0 and 1 mg/kg, s.c.) 30 min before the testing session. Paired *t*-test revealed a significant effect of WAY100635 on premature responses, which is a measure of impulsive action. The bars represent the mean and the lines represent the S.E.M. *$P < 0.05$.

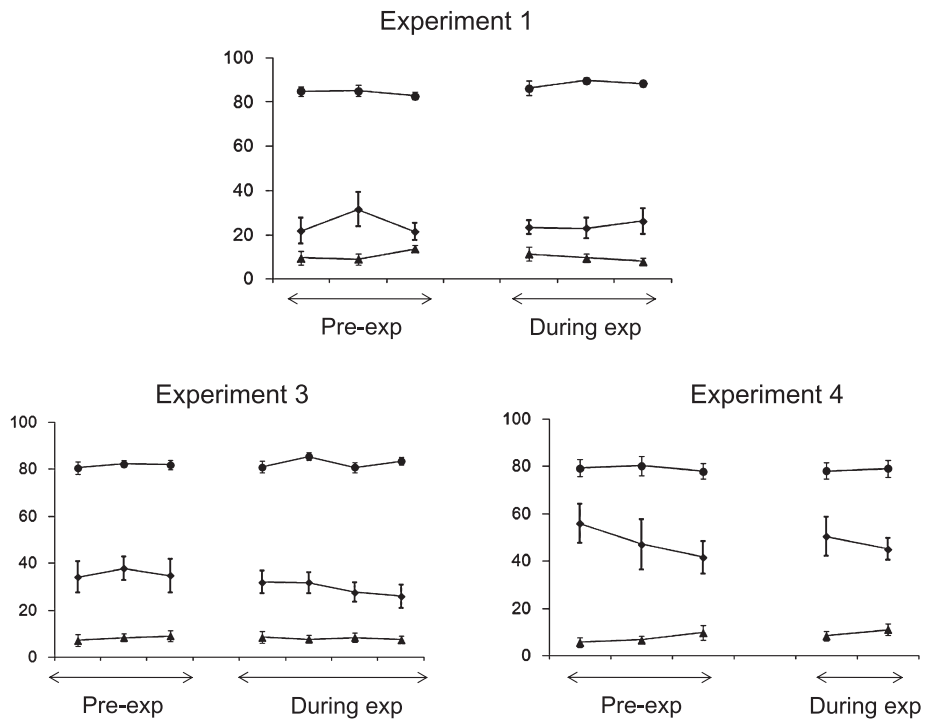

Fig. 5. Baseline session. Pre-experimental (Pre-exp) and experimental (During exp) baseline performance levels of premature responses, accuracy, and percentage response omissions in three groups of rats: experiment 1, n = 9; experiment 3, n = 12; experiment 4, n = 8. Filled circles, accuracy (in percent); filled diamonds, premature responses (number); filled triangles, omissions (number). No significant effects of day were found in any group, except for accuracy in experiment 1. However, the effects of day were not significant when only experimental baseline was analyzed. Baseline performance remained relatively stable in all groups during the experiments. The lines represent the S.E.M.

racy (experiment 3: $F_{3.63, 39.89} = 1.27$, NS; and experiment 4: $F_{4, 28} = 0.17$, NS), except for accuracy in experiment 1 (experiment 1: $F_{5, 40} = 2.76$, $P < 0.05$). However, the effects of day were not significant when only experimental baseline was analyzed ($F_{2, 16} = 0.96$, NS). This analysis indicated that baseline performance remained relatively stable in all groups during the experiments.

Discussion

Tandospirone suppressed impulsive action in a dose-dependent manner (Fig. 1), and the result was replicated in the subsequent experiment (Fig. 3). The effects of tandospirone on other parameters in the 3-CSRTT were not significant in post hoc tests, indicating that tandospirone selectively suppressed impulsive action. Moreover, tandospirone did not decrease the amount of food consumption in a simple food consumption test (Fig. 2). Thus it is unlikely that the suppressing effects of tandospirone on impulsive action were due to the anorexic effect.

Neither tandospirone nor WAY100635 affected accuracy, which is an index of attentional function, in the 3-CSRTT (Figs. 1B, 3B, and 4B). Although the stimulation or blockade of 5-HT_{1A} receptor might affect memory function (24 – 26), enhanced memory function is not directly related to the performance in the 3-CSRTT because only rats that have been trained for a long time and that reached stable performance are used. Furthermore, the stimulus duration in the 3-CSRTT was 1 s and the duration was longer than correct response latency (0.5 – 0.6 s, see Figs. 1E, 3E, and 4E), indicating that working memory is not required to respond correctly. Severely impaired memory function would non-selectively impair performance in the 3-CSRTT, but selective effects of drugs were observed in the present study. Thus it is unlikely that the effects of tandospirone on impulsive action were due to the effects on other cognitive functions.

The suppressing effects of tandospirone on impulsive action were not reversed by 0.3 mg/kg of WAY100635. It should be noted that this dose and lower dose of WAY100635 have reversed the effects of 5-HT_{1A} agonists (15, 27). It is unlikely that the dose of tandospirone was too high to antagonize the effects because our supplemental data showed that 0.3 mg/kg of tandospirone did not exert a clear antiimpulsive effect and the small effect was not reversed by WAY100635 (Supplementary Fig. 1: available in the online version only).

Our results showed that the 1 mg/kg dose of tandospirone with 0.3 mg/kg of WAY 100635 significantly prolonged reward latency and tended to increase omission and to prolong correct response latency (Fig. 3). In our preliminary study, a larger dose of tandospirone or WAY100635 caused sedation, and resulted in increased omission and prolonged response latency (data not shown). Assuming that the coadministration of drugs with similar effects could mimic the effects of higher doses, it is plausible that WAY100635 acted additively to enhance the effects of tandospirone, but not antagonize them.

Because a higher dose of WAY100635 (1 mg/kg) suppressed impulsive action, it is speculated that tandospirone suppressed impulsive action by blocking 5-HT_{1A} receptors. Although higher doses of WAY100635 could have α_1 adrenoceptor–antagonistic properties (28), a previous study demonstrated that an α_1 adrenergic antagonist did not alter impulsive action (29). Given that tandospirone is a partial agonist for the 5-HT_{1A} receptor, tandospirone could act as an antagonist, but there is so far no direct evidence. At least agonistic action for the 5-HT_{1A} receptor would not account for the suppressing effects of tandospirone on impulsive action because a full agonist for the 5-HT_{1A} receptor stimulated or had no effect on impulsive action (14, 15) (Supplementary Fig. 2: available in the online version only).

Alternatively, tandospirone might suppress impulsive action through affecting receptors other than the 5-HT_{1A} receptor. However, tandospirone is highly selective for the 5-HT_{1A} receptor and acts as a partial agonist for 5-HT_{1A} receptors (30). Although its metabolite, 1-(2-pyrimidinyl)-piperazine, acts as an α_2 adrenergic antagonist (31, 32), a previous study showed that an α_2 adrenergic antagonist stimulated impulsive action (33). Moreover, another partial agonist for 5-HT_{1A} receptor, buspirone, also suppressed impulsive action (Supplementary Fig. 3: available in the online version only). Thus it is not likely that the effects of tandospirone observed in the present study are due to the effects of tandospirone on receptors other than the 5-HT_{1A} receptor or the effects of a metabolite of tandospirone.

To make tandospirone act as an antagonist, increased 5-HT release is necessary. Previous studies have shown that 5-HT release or firing rate of putative serotonergic neurons in the dorsal raphe nucleus is increased when rats suppress their response and wait for reward (34, 35). Thus it is likely that 5-HT release is increased in some specific brain regions when rats were engaged in the 3-CSRTT. Under this situation, it is possible that tandospirone acts as an antagonist in some brain regions and prolongs increased 5-HT release because the activation of presynaptic/postsynaptic 5-HT_{1A} receptor inhibits 5-HT cell firing (36). Indeed, some studies have demonstrated that WAY100635 administration potentiates selective 5-HT reuptake inhibitors (SSRIs)-induced increases in extracellular 5-HT concentrations (37, 38).

We speculate that 5-HT release potentiated by the blockade of 5-HT_{1A} receptor is responsible for the suppressing effects of tandospirone on impulsive action because a previous study suggested that stimulation of presynaptic 5-HT_{1A} receptors is involved in stimulating impulsive action (14). That is, tandospirone might enhance increased serotonin release during the 3-CSRTT via the blockade of presynaptic 5-HT_{1A} receptors and thereby suppresses impulsive action. However it should

be noted that the effects of SSRIs on impulsive action are controversial (16, 39) while some studies have demonstrated that serotonin depletion stimulates impulsive behavior (11 – 13).

While it is likely that presynaptic 5-HT_{1A} receptors are involved in impulsive action as stated above, we cannot rule out the possibility that postsynaptic 5-HT_{1A} receptors account for the suppressing effects of tandospirone on impulsive action. To our knowledge, there is so far no study to prove the involvement of postsynaptic 5-HT_{1A} receptors in impulsive action. However it is still possible because 5-HT_{1A} receptors are widely distributed throughout the brain (40).

In summary, our results indicate that tandospirone, a widely used anxiolytic and a 5-HT_{1A} receptor partial agonist, could suppress impulsive action through possible blockade of the 5-HT_{1A} receptor without affecting other cognitive functions or appetite/motivation. However, there is so far no direct evidence that tandospirone actually acts as antagonist to 5-HT_{1A} receptors when conducting the 3-CSRTT. Further studies are required to clarify this issue. Nevertheless, the suppressing effects of tandospirone on impulsive action were repeatedly confirmed in the present study. Higher impulsivity is observed in several psychiatric disorders such as ADHD (6), schizophrenia (7), substance abuse (8), bipolar disorder (9), and borderline personality disorder (10). Because the side effects of tandospirone are relatively mild (41), tandospirone could be a therapeutic candidate for these disorders with comorbid higher impulsivity.

Acknowledgments

This study was supported by a grant for the Interdisciplinary Project for Psychosomatological Research in Hokkaido University and the Strategic Research Program for Brain Sciences (Integrated Research on Neuropsychiatric Disorders) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1 Ohmura Y, Takahashi T, Kitamura N. Discounting delayed and probabilistic monetary gains and losses by smokers of cigarettes. Psychopharmacology (Berl). 2005;182:508–515.
2 Diergaarde L, Schoffelmeer AN, De Vries TJ. Pharmacological manipulation of memory reconsolidation: towards a novel treatment of pathogenic memories. Eur J Pharmacol. 2008;585: 453–457.
3 Babinski LM, Hartsough CS, Lambert NM. Childhood conduct problems, hyperactivity-impulsivity, and inattention as predictors of adult criminal activity. J Child Psychol Psychiatry. 1999;40:347–355.
4 Corruble E, Hatem N, Damy C, Falissard B, Guelfi JD, Reynaud M, et al. Defense styles, impulsivity and suicide attempts in major depression. Psychopathology. 2003;36:279–284.
5 Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. Am J Psychiatry. 2005;162:1680–1687.
6 Losier BJ, McGrath PJ, Klein RM. Error patterns on the continuous performance test in non-medicated and medicated samples of children with and without ADHD: a meta-analytic review. J Child Psychol Psychiatry. 1996;37:971–987.
7 Barr RS, Culhane MA, Jubelt LE, Mufti RS, Dyer MA, Weiss AP, et al. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. Neuropsychopharmacology. 2008;33:480–490.
8 Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Moeller FG. Impulsivity: a link between bipolar disorder and substance abuse. Bipolar Disord. 2004;6:204–212.
9 Strakowski SM, Fleck DE, DelBello MP, Adler CM, Shear PK, McElroy SL, et al. Characterizing impulsivity in mania. Bipolar Disord. 2009;11:41–51.
10 Dom G, De Wilde B, Hulstijn W, van den Brink W, Sabbe B. Behavioural aspects of impulsivity in alcoholics with and without a cluster-B personality disorder. Alcohol Alcohol. 2006;41: 412–420.
11 Schweighofer N, Bertin M, Shishida K, Okamoto Y, Tanaka SC, Yamawaki S, et al. Low-serotonin levels increase delayed reward discounting in humans. J Neurosci. 2008;28:4528–4532.
12 Harrison AA, Everitt BJ, Robbins TW. Doubly dissociable effects of median- and dorsal-raphe lesions on the performance of the five-choice serial reaction time test of attention in rats. Behav Brain Res. 1997;89:135–149.
13 Harrison AA, Everitt BJ, Robbins TW. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. Psychopharmacology (Berl). 1997;133:329–342.
14 Carli M, Samanin R. The 5-HT(1A) receptor agonist 8-OH-DPAT reduces rats' accuracy of attentional performance and enhances impulsive responding in a five-choice serial reaction time task: role of presynaptic 5-HT(1A) receptors. Psychopharmacology (Berl). 2000;149:259–268.
15 Winstanley CA, Chudasama Y, Dalley JW, Theobald DE, Glennon JC, Robbins TW. Intra-prefrontal 8-OH-DPAT and M100907 improve visuospatial attention and decrease impulsivity on the five-choice serial reaction time task in rats. Psychopharmacology (Berl). 2003;167:304–314.
16 Tsutsui-Kimura I, Ohmura Y, Izumi T, Yamaguchi T, Yoshida T, Yoshioka M. The effects of serotonin and/or noradrenaline reuptake inhibitors on impulsive-like action assessed by the three-choice serial reaction time task: a simple and valid model of impulsive action using rats. Behav Pharmacol. 2009;20: 474–483.
17 Tsutsui-Kimura I, Ohmura Y, Izumi T, Yamaguchi T, Yoshida T, Yoshioka M. Endogenous acetylcholine modulates impulsive action via alpha4beta2 nicotinic acetylcholine receptors in rats. Eur J Pharmacol. 2010;641:148–153.
18 Tsutsui-Kimura I, Ohmura Y, Izumi T, Yamaguchi T, Yoshida T, Yoshioka M. Nicotine provokes impulsive-like action by stimulating alpha4beta2 nicotinic acetylcholine receptors in the infralimbic, but not in the prelimbic cortex. Psychopharmacology (Berl). 2010;209:351–359.
19 Carli M, Robbins TW, Evenden JL, Everitt BJ. Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of

dorsal noradrenergic bundle function based on selective attention and arousal. Behav Brain Res. 1983;9:361–380.
20 Robbins TW. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology (Berl). 2002;163:362–380.
21 Ohmura Y, Yamaguchi T, Futami Y, Togashi H, Izumi T, Matsumoto M, et al. Corticotropin releasing factor enhances attentional function as assessed by the five-choice serial reaction time task in rats. Behav Brain Res. 2009;198:429–433.
22 Matsumoto M, Togashi H, Konno K, Koseki H, Hirata R, Izumi T, et al. Early postnatal stress alters the extinction of context-dependent conditioned fear in adult rats. Pharmacol Biochem Behav. 2008;89:247–252.
23 Koseki H, Matsumoto M, Togashi H, Miura Y, Fukushima K, Yoshioka M. Alteration of synaptic transmission in the hippocampal-mPFC pathway during extinction trials of context-dependent fear memory in juvenile rat stress models. Synapse. 2009;63:805–813.
24 Fernandez-Perez S, Pache DM, Sewell RD. Co-administration of fluoxetine and WAY100635 improves short-term memory function. Eur J Pharmacol. 2005;522:78–83.
25 Manuel-Apolinar L, Meneses A. 8-OH-DPAT facilitated memory consolidation and increased hippocampal and cortical cAMP production. Behav Brain Res. 2004;148:179–184.
26 Sumiyoshi T, Matsui M, Yamashita I, Nohara S, Kurachi M, Uehara T, et al. The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. Biol Psychiatry. 2001;49:861–868.
27 Assie MB, Mnie-Filali O, Ravailhe V, Benas C, Marien M, Betry C, et al. F15063, a potential antipsychotic with dopamine D2/D3 receptor antagonist, 5-HT1A receptor agonist and dopamine D4 receptor partial agonist properties: influence on neuronal firing and neurotransmitter release. Eur J Pharmacol. 2009;607:74–83.
28 Villalobos-Molina R, Lopez-Guerrero JJ, Gallardo-Ortiz IA, Ibarra M. Evidence that the hypotensive effect of WAY 100635, a 5-HT1A receptor antagonist, is related to vascular alpha 1-adrenoceptor blockade in the adult rat. Auton Autacoid Pharmacol. 2002;22:171–176.
29 Puumala T, Riekkinen P Sr, Sirvio J. Modulation of vigilance and behavioral activation by alpha-1 adrenoceptors in the rat. Pharmacol Biochem Behav. 1997;56:705–712.
30 Hamik A, Oksenberg D, Fischette C, Peroutka SJ. Analysis of tandospirone (SM-3997) interactions with neurotransmitter receptor binding sites. Biol Psychiatry. 1990;28:99–109.
31 Miller LG, Thompson ML, Byrnes JJ, Greenblatt DJ, Shemer A. Kinetics, brain uptake, and receptor binding of tandospirone and its metabolite 1-(2-pyrimidinyl)-piperazine. J Clin Psychopharmacol. 1992;12:341–345.
32 Blier P, Curet O, Chaput Y, de Montigny C. Tandospirone and its metabolite, 1-(2-pyrimidinyl)-piperazine--II. Effects of acute administration of 1-PP and long-term administration of tandospirone on noradrenergic neurotransmission. Neuropharmacology. 1991;30:691–701.
33 Puumala T, Bjorklund M, Ruotsalainen S, Riekkinen M, Jakala P, Haapalinna A, et al. Lack of relationship between thalamic oscillations and attention in rats: differential modulation by an alpha-2 antagonist. Brain Res Bull. 1997;43:163–171.
34 Miyazaki KW, Miyazaki K, Doya K. Activation of the central serotonergic system in response to delayed but not omitted rewards. Eur J Neurosci. 2011;33:153–160.
35 Miyazaki K, Miyazaki KW, Doya K. Activation of dorsal raphe serotonin neurons underlies waiting for delayed rewards. J Neurosci. 2011;31:469–479.
36 Sharp T, Boothman L, Raley J, Queree P. Important messages in the “post”: recent discoveries in 5-HT neurone feedback control. Trends Pharmacol Sci. 2007;28:629–636.
37 Dawson LA, Nguyen HQ. Effects of 5-HT1A receptor antagonists on fluoxetine-induced changes in extracellular serotonin concentrations in rat frontal cortex. Eur J Pharmacol. 1998;345:41–46.
38 Sharp T, Umbers V, Gartside SE. Effect of a selective 5-HT reuptake inhibitor in combination with 5-HT1A and 5-HT1B receptor antagonists on extracellular 5-HT in rat frontal cortex in vivo. Br J Pharmacol. 1997;121:941–946.
39 Baarendse PJ, Vanderschuren LJ. Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. Psychopharmacology (Berl). 2012;219:313–326.
40 Pompeiano M, Palacios JM, Mengod G. Distribution and cellular localization of mRNA coding for 5-HT1A receptor in the rat brain: correlation with receptor binding. J Neurosci. 1992;12:440–453.
41 Feighner JP, Boyer WF. Serotonin-1A anxiolytics: an overview. Psychopathology. 1989;22 Suppl 1:21–26.