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Delay aversion: Effects of 7-OH-DPAT, 5-$HT_{1A/1B}$-receptor stimulation and D-cycloserine

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Abstract

Impulsive individuals often display an aversion to waiting for rewards. Delay aversion can be quantified in rats in a delayed reward task, in which animals choose between an immediately available, small reward, and a large reward available after a delay. In previous research conducted at our laboratory and in literature, positive correlations between delay aversion and aggression, substance abuse and persistence during extinction of conditioned responses were found. The correlations suggest a possible shared pharmacology. Therefore, we tested drugs with known effects on these behaviors for possible effects on delay aversion: the dopamine D_3-receptor agonist 7-OH-DPAT, the 5-HT_{1A}-receptor agonist flesinoxan, the $5HT_{1A/1B}$-receptor agonist eltoprazine, and the NMDA-receptor agonist D-cycloserine. The results show that 7-OH-DPAT slightly decreased choice for the large reward. Flesinoxan disrupted task execution by lowering choice for the large reward even at a delay of 0 s. Eltoprazine slightly increased choice for the large reward, but the 5-HT_{1B}-antagonist GR127935 had no effect. Administration of D-cycloserine also had no effect on choice behavior. The data suggest the dopamine D_3-receptor and the 5-HT_{1B}-receptor are interesting targets for treating delay aversion impulsivity. These targets were correctly predicted by the positive correlation between delay aversion and aggressive behavior and the intimate links between delay aversion and substance abuse disorders.

Keywords: Impulsivity; Operant conditioning; Dopamine; Serotinin; Glutamate

1. Introduction

Impulsivity is an important symptom of many psychiatric disorders, in particular aggression, addiction, attention-deficit hyperactivity disorder (ADHD) and mania (DSM-IV, 2000). Patients suffering from impulsivity are unable to adapt current behavior to meet future demands. Instead, their behavior is geared towards immediate action or reinforcement (Evenden, 1999). Different types of impulsivity, or pathways leading to impulsivity, are no longer seen as mutually exclusive, but rather as complementing accounts (Sonuga-Barke, 2005). At least two different types of impulsivity exist: an aversion to delays leading up to rewards (Ainslie, 1975), and an inability to inhibit planned or ongoing behavior (Barkley, 1999), and sometimes both types of impulsivity are present in a single patient (Dalen et al., 2004; Sonuga-Barke et al., 2003). We aim to find new therapeutic targets in impulsive patients unconscious of longterm consequences associated with immediate reward. Rewards available after a delay have a smaller reinforcing value than immediately available rewards, and this loss of value is faster in impulsive individuals (Sagvolden et al., 1998), a phenomenon called delay aversion. The delay does not necessarily cause stress, but is aversive because it reduces the incentive value of the reward. Delay aversion is associated to other measures of impulsivity and hyperactivity in children with ADHD (Solanto et al., 2001). Patients suffering from other impulsivity disorders, such as abuse of alcohol (Petry, 2001a), nicotine (Bickel et al., 1999; Ohmura et al., 2005; Reynolds et al., 2004), cocaine (Coffey et al., 2003), heroin (Kirby et al., 1999), and even gambling (Alessi and Petry, 2003) also display a preference for immediate gratification compared to control groups.

Delay aversion may be measured both in humans and several animal species by repeatedly presenting subjects with a choice between a small, immediately available reward and a large reward available only after a delay (Mazur, 1988; Mazur and

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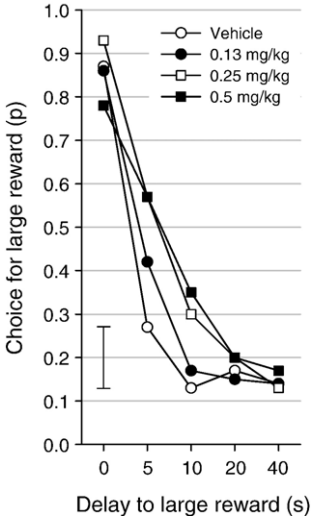

Fig. 1. Effects of D-amphetamine on the preference curve. The *y*-axis represents the proportion (*p*) of choices for the large reward. The *x*-axis displays the delay to the large reward in seconds. A single error bar representing twice the standard error of the mean is shown.

Coe, 1987). In rats, sessions are divided into several blocks. At the start of a session, the delay is set at 0 s, and the delay is increased each block (Evenden and Ryan, 1996, 1999; Logue et al., 1992; Van Gaalen et al., 2006; Winstanley et al., 2003; Winstanley et al., 2005). Alternative tasks in which the delay to the large reward (Mazur and Coe, 1987) or the size of the reward itself (Richards et al, 1997, 1999; Wade et al., 2000) is dynamically adjusted are sometimes used, but such approaches may in some cases measure different processes than intended (Cardinal et al., 2002).

Current pharmacological studies of impulsive behavior and delay aversion focus mainly on subreceptors of the dopamine and serotonin system, inspired by the efficacy of psychostimulants in the treatment of impulsivity. The aim of the present article is to identify new drug targets for the treatment of impulsivity based on the relationship between impulsivity and other constructs. Research in our laboratory (Van den Bergh et al., 2006) uncovers a positive correlation between delay aversion impulsivity, persistence during conditioned extinction trials and aggressive behavior. In addition, several research papers demonstrate a positive relationship between delay aversion impulsivity and various substance abuse disorders (Coffey et al., 2003; Kirby et al., 1999; Mitchell et al., 2005; Reynolds et al., 2004). Therefore, we tested drugs with known effects on receptor systems involved in each of these related behaviors for effects in the delayed reward task. The following drugs were tested:

- The psychostimulant D-amphetamine was tested as a reference drug because of its efficacy both in patients suffering from impulsivity (Arnsten, 2006) as well as in the delayed reward task (e.g., Van Gaalen et al., 2006; Cardinal et al., 2000; Charrier and Thiebot, 1996).
- The dopamine D_3-receptor agonist 7-OH-DPAT is expected to increase delay aversion because of its involvement in substance abuse (e.g. Heidbreder et al., 2004, 2005; Thanos et al., 2005; Xi et al., 2005; Retz et al., 2003).
- Flesinoxan and eltoprazine, serotonin 5-HT_{1A}- and 5-HT_{1B}-receptor agonists, respectively, are expected to decrease delay aversion because of its anti-aggressive properties. (e.g. Olivier and van Oorschot, 2005).
- GR127935, a 5-HT_{1B}-receptor antagonist was also tested to investigate possible effects of eltoprazine and because of its attenuating effects on substance abuse (Fuchs et al., 2002).
- D-cycloserine was tested because of its decreasing effects on persistence during conditioned extinction trials (Falls et al., 1992; Richardson et al., 2004). D-cycloserine was expected to decrease delay aversion.

2. Methods

2.1. Subjects

Sixteen male Wistar rats (HsdCpb:WU) obtained from Harlan (The Netherlands) weighing 125 g on arrival

Table 1
Effects of various drugs on the area under the preference curve

	Mean±SEM
d-amphetamine	
Vehicle	6.3±1.5
0.125	7.2±1.8
0.25*	10.4±2.3
0.5*	11.7±2.6
Flesinoxan	
Vehicle	10.3±2.6
0.13*	9.8±2.0
0.25	8.9±2.1
0.5*	8.2±1.9
GR127935	
Vehicle	9.0±2.0
0.3	9.5±2.3
1	10.2±2.3
3	9.3±2.4
7-OH-DPAT	
Vehicle	9.5±2.8
0.03*	5.7±1.1
0.1	7.6±1.5
0.3	8.3±2.1
Eltoprazine	
Vehicle	7.5±1.8
0.25	7.3±1.9
0.5*	9.3±1.8
1	7.1±1.6
d-cycloserine	
Vehicle	9.1±2.2
3.25	9.1±2.3
15	10.1±2.7
30	8.1±2.1

Values represent means±SEM. Significant changes compared to vehicle are marked with *.

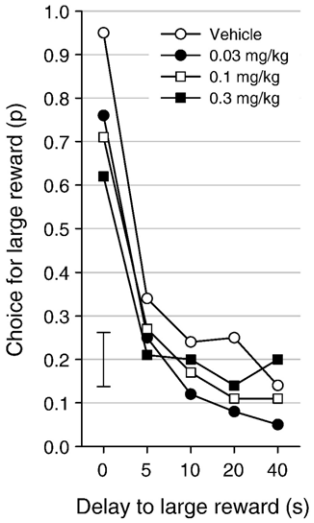

Fig. 2. Effects of 7-OH-DPAT on the preference curve. The *y*-axis represents the proportion (*p*) of choices for the large reward. The *x*-axis displays the delay to the large reward in seconds. A single error bar representing twice the standard error of the mean is shown.

(corresponding to approximately 6–8 weeks of age), were housed in a light (lights on from 7:00 to 19:00), temperature (21±2 °C), and humidity (50±10%) controlled animal facility. Animals were housed in groups of four and received 15 g of standard laboratory chow per day and had free access to water. The ethical committee on animal experiments of the Faculties of Pharmaceutical Sciences, Chemistry and Biology of Utrecht University approved the experiments.

2.2. Apparatus

Sixteen operant cages (MED Associates) controlled by MED-PC IV software were used. The boxes (l×w×h: 30 cm×24 cm×21 cm) were equipped with a houselight and a central food magazine in which 45 mg Noyes precision pellets (formula P) were delivered. Retractable levers were located on the left and right of the food magazine, and signal lamps were located above the levers and the food magazine.

2.3. Procedure

The delayed reward task was adapted from Cardinal et al. (2000). In a session consisting of 5 blocks of 8 trials, rats had a choice between a lever that delivered a single food reward instantaneously, and a second lever that delivered four food rewards, but after a delay. In the first block, this delay was 0 s, but each block the delay was increased until it is 40 s in the final block (0 s, 5 s, 10 s, 20 s, 40 s). Total trial length was 10 s longer than the delay used in that block, even if the animal opted for the small reward. After a response, both levers were retracted, limiting the rats to a single response in each trial. To make sure that the rats had actually sampled both levers, the first two trials of each block were forced trials in which only one of the levers was present. Both levers were presented once in the forced trials, and the order of presentation was determined randomly. The remaining 6 choice trials were used to calculate a preference ratio for each delay. Training for the delayed reward task took approximately 2 months, as a result the animals were approximately 4 months old at the start of the pharmacological experiments.

The used procedure differs from the procedure used by Cardinal et al. (2000) upon which it was based in a number of important points. In the original procedure, trial length is based on the maximum delay used in the entire session instead of the delay for the block. In addition, we found in pilot studies that none of our animals chose the large reward at a delay of 60 s. We therefore used a maximum delay of 40 s. As a result of these changes, the duration of a session was approximately 25 min instead of 100 min. As a result, drug plasma concentrations are more likely to be the same throughout the entire session.

2.4. Statistics

Per experiment, two analyses were made. The first is a repeated measures ANOVA of the preference for the large reward per block, with the delay to the large reward and the dosage as within-subjects variables. Post-hoc tests of the different dosages were corrected for comparisons with vehicle only. Post-hoc test were also conducted to explore effects of several drugs on the first block of the test (0 s delay). These tests were also corrected for comparison to the vehicle only. In addition to analyzing the raw choice data, the data was also reduced to the area under the preference curve (AUPC). This area reflects a theory-neutral index of inhibition in the delayed reward task (Myerson et al., 2001), but is not sensitive to interactions between drug administration and the delay to the large reward. AUPCs were analyzed in a separate repeated measures ANOVA with dose as a within-subjects factor.

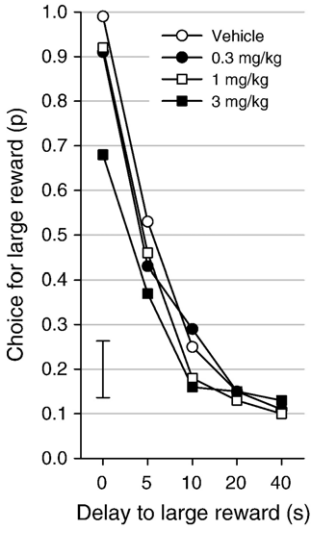

Fig. 3. Effects of flesinoxan on the preference curve. The *y*-axis represents the proportion (*p*) of choices for the large reward. The *x*-axis displays the delay to the large reward in seconds. A single error bar representing twice the standard error of the mean is shown.

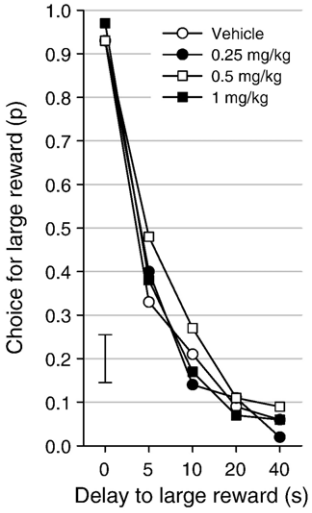

Fig. 4. Effects of eltoprazine on the preference curve. The *y*-axis represents the proportion (*p*) of choices for the large reward. The *x*-axis displays the delay to the large reward in seconds. A single error bar representing twice the standard error of the mean is shown.

Again, post-hoc tests of dose effects were corrected for the comparisons to the vehicle only. Significance levels for all tests were set at 5%. Huyn–Feldt corrections were applied to the degrees of freedom if data did not meet sphericity demands.

2.5. Drugs

Drugs and dosages (in mg/kg) were selected based on their efficacy in constructs related to impulsivity as described in the Introduction. Citations for each drug indicate the source of the dose-range. D-amphetamine HCl (0.25, 0.5, 1; Van Gaalen et al., 2006, delayed reward task), 7-OH-DPAT HBr (0.03, 0.1, 0.3; Fuchs et al., 2002, cocaine seeking), flesinoxan HCl (0.3, 1, 3; Olivier and van Oorschot, 2005, aggressive behavior), eltoprazine HCl (0.25, 0.5, 1; Olivier and van Oorschot, 2005, aggressive behavior), GR127935 (0.3, 1, 3; Acosta et al., 2005, cocaine seeking behavior), D-cycloserine (3.25, 15, 30; Richardson et al., 2004, fear extinction). All drugs were dissolved in saline and administered subcutaneously 2 ml/kg, 30 min before testing. Dosages were based on the salt weights. Drug dosages were tested in balanced Latin square designs. Between drug test days, animals had a 3-day break.

3. Results

The number of completed trials was statistically similar across all testing conditions.

3.1. D-amphetamine

D-amphetamine (Fig. 1) significantly increased choice for the large reward (F[3, 42]=5.8; p=0.002). This impulsivity attenuating effect was present at 0.25 and 0.5 mg/kg (p=0.003 and p=0.03 respectively). Analysis of the AUPC (Table 1) yielded similar results (F[3, 42]=4.4; p=0.009; 0.25 mg/kg: p=0.036; 0.5 mg/kg: p=0.03).

3.2 7-OH-DPAT

The dopamine D_3-receptor agonist 7-OH-DPAT (Fig. 2) had no overall effects on choice (F[2.2, 27.2]=2.3, NS), and an analysis of the AUPC (Table 1) yielded similar results (F[3, 39]= 1.1, NS). Closer inspection of Fig. 2 reveals that effects of the higher dosages of 7-OH-DPAT may obscure the effects of the lowest (0.03 mg/kg) dose in the analysis. To explore this effect of 7-OH-DPAT, a separate analysis was conducted comparing this dose against vehicle only. The results show that animals pre-treated with 0.03 mg/kg 7-OH-DPAT selected the smaller reward more often compared to animals that received a vehicle injection (F[1, 14]=6.2, p=0.026).

3.3. Flesinoxan

The 5-HT_{1A}-receptor agonist flesinoxan increased the choice for the small reward, but only if the delays were short (reflected in a delay×dose interaction: F[9.3, 84]=2.4, p=0.013; Fig. 3). To further explore this effect, the 0 s delay block was analyzed separately. The results showed that 1 and 3 mg/kg flesinoxan significantly decreased choice for the large reward, even without a delay (F[1.4, 19.7]=8.4, p=0.005; 1 mg/kg: p=0.042; 3 mg/kg: p=0.012). The AUPC (Table 1) was not sensitive to this effect of flesinoxan (F[1.4, 21.1]=0.9, NS).

3.4. Eltoprazine

The 5-$HT_{1A/1B}$-receptor agonist eltoprazine (Fig. 4) had no effects on choice for the large reward (F[3, 42]=2.4, p=0.077). The AUPC seemed mildly more sensitive to the effects of

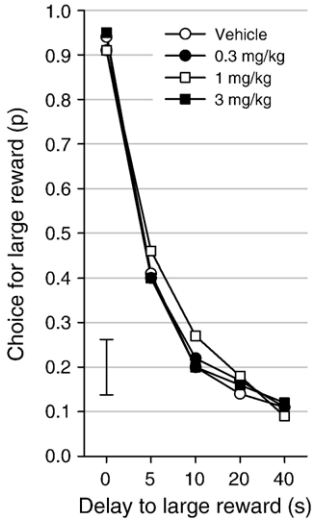

Fig. 5. Effects of GR127935 on the preference curve. The *y*-axis represents the proportion (*p*) of choices for the large reward. The *x*-axis displays the delay to the large reward in seconds. A single error bar representing twice the standard error of the mean is shown.

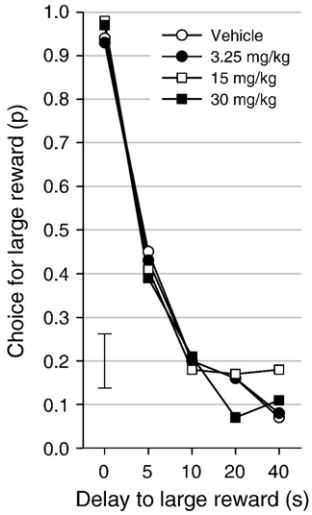

Fig. 6. Effects of D-cycloserine on the preference curve. The *y*-axis represents the proportion (*p*) of choices for the large reward. The *x*-axis displays the delay to the large reward in seconds. A single error bar representing twice the standard error of the mean is shown.

eltoprazine, but the effects also did not reach significance (F[3, 42]=2.7, p=0.059). Closer examination of the preference curve revealed that the highest and lowest dosages of eltoprazine were not effective, but at 0.5 mg/kg, choice for the large reward was increased (F[1, 14]=5.1, p=0.04).

3.5. GR127935

The effects of the 5-HT_{1B}-receptor antagonist GR127935 are shown in Fig. 5. GR127936 had no effects on the preference curve (F[3, 45]=0.4, NS) or the AUPC (F[3, 45]=0.4, NS).

3.6. D-cycloserine

As seen in Fig. 6, the NMDA-receptor agonist D-cycloserine had no effects on choice (F[3, 45]=0.8, NS). Analysis of the AUPC (see Table 1) led to the same conclusion (F[3, 45]=1.5, NS).

4. Discussion

In the present study, we assessed the effects of a variety of different psychoactive drugs on delay aversion using a delayed reward task. D-amphetamine was selected as a reference drug, as psychostimulants have been demonstrated to be effective in this task before (e.g., Van Gaalen et al., 2006; Cardinal et al., 2000; Charrier and Thiebot, 1996). Indeed, D-amphetamine dose-dependently increased choice for the large reward.

The dopamine D_3-receptor is an interesting drug target for the modulation of delay aversion. Substance abuse and delay aversion are intimately linked (Mitchell et al., 2005; Petry, 2001a; Ohmura et al., 2005; Reynolds et al., 2004; Coffey et al., 2003; Kirby et al., 1999; Alessi and Petry, 2003; Petry, 2001b), and the D_3-receptor plays an important role in addiction (Heidbreder et al., 2005). In the present study, administration of the dopamine D_3-receptor agonist 7-OH-DPAT decreased choice for the large reward at a low dose, and this effect disappeared at higher dosages. Interestingly, the direction of this effect is the same as for the dopamine D_1-antagonist SCH23390 reported by Van Gaalen et al. (2006) (although SCH23390 had no effects in an adjusting amount procedure, see Wade et al., 2000). The D_3-receptor is primarily found in the limbic system, in particular in the (shell of the) nucleus accumbens and the islands of Calleja (Bouthenet et al., 1991; Sokoloff et al., 1992b). Many (63% in the nucleus accumbens and up to 79% in other areas) neurons containing D_3-receptors also express D_1-receptors, and stimulation of the two receptors by selective agonists have been demonstrated to have opposite effects on c-fos expression (Ridray et al., 1998; Schwartz et al., 1998). The opposite role of these two receptors is also reflected in the similar effects of D_1-receptor antagonists and D_3-receptor agonists in delay aversion, as both have been found to increase choice for the large reward (Van Gaalen et al., 2006, and the present data, respectively). At this moment, it is unclear why the impulsivity-lowering effect of 7-OH-DPAT disappears at higher dosages, although in the elevated plus maze, the effects of 7-OH-DPAT have also been reported to display a similar u-shaped curve (Rogoz et al., 2004). Perhaps these effects may be attributed to binding of 7-OH-DPAT to the D_2-receptor at higher dosages (Damsma et al., 1993; Sokoloff et al., 1992a).

Several lines of evidence support the link between delay aversion and substance abuse disorders. First, delay aversion in rats predicts acquisition of cocaine self-administration (Perry et al., 2004). Second, people addicted to alcohol (Mitchell et al., 2005; Petry, 2001a), nicotine (Ohmura et al., 2005; Reynolds et al., 2004), cocaine (Coffey et al., 2003), heroine (Kirby et al., 1999), and gambling (Alessi and Petry, 2003; Petry, 2001b) all display delay aversion, and discount delayed rewards faster than controls. Blockade of dopamine D_3-receptors has been demonstrated to attenuate acquisition and expression of addictive behavior to many of the mentioned substances in various behavioral tests (Andreoli et al., 2003; Ashby et al., 2003; Gilbert et al., 2005; Thanos et al., 2005; Xi et al., 2004; Xi et al., 2005). Dopamine D_3-receptors may also be involved in violent behavior as demonstrated in a linkage study (Retz et al., 2003). We demonstrated that aggressive rats are impulsive in the delayed reward task (Van den Bergh et al., 2006), lending further credibility to the dopamine D_3-receptor as a potential target for the treatment of pathological delay aversion.

As stated above, aggressive behavior is linked to delay aversion. Although no drugs developed specifically for the treatment of aggression are commercially available, a class of serotonin agonists called serenics has anti-aggressive properties (Olivier et al., 1994; Ratey and Gordon, 1993). These drugs target 5-HT_{1B}-receptors, and to a lesser degree 5-HT_{1A}-receptors, although the latter are less specific to aggressive behavior (Olivier and van Oorschot, 2005). The 5-HT_{1B}-receptor is of particular interest for delay aversion, as stimulation of that receptor also decreases reinstatement of cocaine seeking behavior after extinction (Acosta et al., 2005). In the present article, we tested the 5-HT_{1A}-receptor agonist flesinoxan, the mixed 5-$HT_{1B/1A}$-agonist eltoprazine and the 5-HT_{1B}-receptor

antagonist GR127936. Flesinoxan lowered choice for the large reward in the first block where the delay to the large reward was 0 s, but this effect disappeared at longer intervals. This effect of flesinoxan is very similar to the effects of 8-OH-DPAT, another 5-HT_{1A}-receptor agonist, as reported by Evenden and Ryan (1999), although Charrier and Thiebot (1996) failed to find any effects of 8-OH-DPAT. This discrepancy may be due to procedural differences, as our procedure more closely resembled the procedure used by Evenden and Ryan. The change in the 0-delay preference point of the preference curve as observed after administration of the highest dose of flesinoxan reflects a problem in the execution of the task rather than an increase in delay aversion. While the effects of flesinoxan in the present study and the effects of 8-OH-DPAT found by Evenden and Ryan are very similar, the effects of buspirone, a third (partial) 5-HT_{1A}-receptor agonist (with additional agonism at the α_1-adrenoreceptor and the dopamine D_2-receptor) on delay aversion are very different (Liu et al., 2004). A single dose of buspirone increases delay aversion (at all delays, not just at 0 s), while delay aversion decreases after chronic administration. These effects of buspirone can be blocked using WAY-100,635, indicating the 5-HT_{1A}-receptor is responsible for these effects. It is unclear why the effects of acute buspirone differ from the effects of flesinoxan or 8-OH-DPAT, and if chronic administration of these drugs lead to anti-impulsive effects.

Finally, behaviorally inert dosages of 8-OH-DPAT may attenuate the anti-impulsive effects of D-amphetamine in the delayed reward task (Winstanley et al., 2005), indicating that serotonin may be involved in response modulation rather than in the actual preference. Agonists of the 5-HT_{1A}-receptor have a dual effect: binding to the autoreceptor causes inhibition of serotonin release, while binding to the postsynaptic receptor mimics released serotonin (de Boer and Koolhaas, 2005; De Groote et al., 2002). Since a serotonin depletion by 5,7-DHT also attenuates the anti-impulsive effects of D-amphetamine (Winstanley et al., 2003), the effects of 5-HT_{1A}-receptor agonists may be due to binding to the autoreceptor and a resulting decrease in serotonin availability.

The 5-$HT_{1A/1B}$-receptor agonist eltoprazine slightly increased choice for the large reward and at one dose, an expected effect considering eltoprazine's effectiveness as an anti-aggressive drug (Olivier et al., 1995; Olivier and van Oorschot, 2005). The effect was rather modest, however, and more research should be directed at the exact circumstances under which eltoprazine can lower delay aversion. Another explanation for the effects of eltoprazine on delay aversion lies in the inhibitory effect 5-HT_{1B}-receptor stimulation has on food intake (Liu et al., 2004), however, whether satiety leads to an increase or decrease in delay aversion is unclear. Like the 5-HT_{1A}-receptor described above, the 5-HT_{1B}-receptor is also expressed pre-and post-synaptically (de Boer and Koolhaas, 2005). Multiple lines of evidence suggest that the 5-HT_{1B}-autoreceptor is responsible for eltoprazine's efficacy in aggression (Olivier and van Oorschot, 2005), but if the mechanism of eltoprazine is the same in the delayed reward task remains speculative. Like 7-OH-DPAT, the effects of eltoprazine are strongly dependent on the used dosage, with higher dosages being less effective. In aggression tests, De Boer et al. (1999) report a similarly shaped curve, especially for exploratory behavior. To expand on the role of 5-HT_{1B}-receptors, we tested the antagonist GR127936. In the present study, GR127935 had no effect on choice behavior. Evenden and Ryan (1999) used several serotonin receptor antagonists (for 5-HT_{1A}, 5-HT_2, and 5-HT_3-receptors), and also report no alterations on delay aversion. They conclude that serotonin does not exert tonic control over the execution of the delayed reward task. Talpos et al. (2006), however, show that SER-082, a 5-$HT_{2A/2C}$-receptor antagonist decreased impulsivity in the delayed reward task. We conclude that the serotonin system does exert tonic control over the processes governing delay aversion, but not all serotonin subreceptors are involved in this type of control.

Finally, in addition to the relationships discussed above, delay aversion and extinction are also correlated (Van den Bergh et al., 2006). In extinction tests, conditioned behavior is no longer reinforced, and the occurrence of the conditioned response is taken as an index of extinction. Several manipulations have effects on extinction of conditioned behavior, including serotonin depletion by the serotonin synthesis inhibitor PCPA (Beninger and Phillips, 1979). The links between serotonin and delay aversion are discussed extensively in the previous paragraphs. In addition to serotonin, the glutamate system is also important in extinction, as has been shown in various extinction tasks. Blockade of NMDA-receptors by local infusion of AP5 into the amygdala slows fear extinction (Falls et al., 1992). Extinction may also be facilitated by stimulation of NMDA-receptors by D-cycloserine (Ledgerwood et al., 2005; Walker et al., 2002), a drug now used in combination with exposure therapy to facilitate extinction of fear (Ressler et al., 2004; Richardson et al., 2004). In the present study, D-cycloserine had no effects on delay aversion. Perhaps the effects of D-cycloserine are specific to extinction of fear, although Port and Seybold (1998) reported effects of D-cycloserine on extinction of lever-pressing for food.

The present study investigated several drug targets inspired by the correlation between delay aversion and aggressive behavior, substance abuse and extinction. In addition, the data demonstrate a multitude of different effects drugs can have on choice behavior in the delayed reward task, including increased and decreased choice for the large reward, and interactions between the drugs and the delays to the large reward. Potential new drug targets identified in this study were the dopamine D_3-receptor and the 5-HT_{1B}-receptor, both new targets that have not been investigated in the context of delay aversion before.

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