Introduction

Impulsivity is currently thought to be a heterogeneous construct that is comprised of two subcomponents: impulsive action and impulsive choice (see Whitaker et al., 2006 for a review of animal models of impulsivity). There is increasing evidence for dissociable neurocognitive substrates underlying these constructs.

Premature responding in the 5-choice serial reaction time task (5-CSRRT), which has been described in detail elsewhere (e.g., van der Weele, 2010), is hypothesized to provide a measure of impulsive action, i.e., a failure to withhold an inappropriate response. The 5-CSRRT is a pre-clinical analogue of the continuous performance test (CPT).

The delay discounting task (DDT) is a cross-species task used to assess impulsive choice, defined as intolerance of reward delay (Whitaker et al., 2006). High impulsivity in the delayed task is thought to be a trait of attention deficit/hyperactivity disorder (ADHD) patients and other patient populations. In the DDT a group of ADHD medications, and additional neuroimaging substrates of impulsivity.

Methods

Animals

Male Long-Evans rats (250-300g) were obtained from Harlan Laboratories (Indianapolis, IN). Upon arrival, the rats were assigned unique identification numbers (ID) and were transferred to 10 cages and allocated for 7 days prior to commencing a food-restriction regimen: rats were held at 85% of approximated free-feeding body weights, receiving 0.32 g/daily. Water was provided ad libitum except during testing. Animals were maintained in a L:12 h light:dark cycle (lights on (10:00 EST) with room temperature maintained at 22 ± 2°C and the relative humidity maintained at approximately 50%. All animals were examined, handled and weighed prior to initiation of the study (during the week of habitation) to ensure adequate health and suitability and to minimize non-specific stress associated with testing. All operant procedures were conducted during the animal’s light cycle. All experiments were approved by the Institutional Animal Care and Use Committee (IACUC), Tufts University, in accordance with the Guide for the Care and Use of Laboratory Animals (NIH, 2010).

Apparatus

The apparatus consisted of 10 aluminum and Plexiglas chambers with grid floors (95 cm long x 20 cm wide, 30 cm high) located in sound-attenuating cabinets (Med Associates, St Albans, VT). Each chamber was equipped with two equally spaced, located approximately 2.5 cm from the floor. Each apparatus contained a standard 20 LED to serve as the stimulus. The LED stimulus configuration was set to be a centrally located circled stimulus, which provided the operant response (i.e., lever press). The inter-trial interval (ITI) was randomly varied from 20 to 40 s. The lever to the right was designated as the lever for immediate reward, while the lever to the left was designated as the lever for delayed reward. The right lever was the preferred lever (approximately 2 cm long) was positioned on either side of the food magazine (approximately, 2 cm from the grid floor). Each chamber was illuminated with a 1,000 lux bright white incandescent bulb mounted 1 cm from the chamber ceiling. After each lever press the apparatus was cleared with 70% ethanol; at least 20 minutes elapsed before the next lever press. Responses were recorded by a computer using Nici-Stim software (Nici-Sim, Hut, Switzerland) and were captured by a computer using nStim software (Nici-Stim, Hut, Switzerland).

Drugs

Methylphenidate hydrochloride was obtained from Sigma-Aldrich, Missouri, USA. Tomoxetine hydrochloride, ketanserin and SB242084 were obtained from Tocris (Bristol, UK). Methylphenidate hydrochloride was dissolved in saline mixture and administered in IP volume of 1 ml/kg (expressed as salt form). Atomoxetine, ketanserin and SB242084 were administered with permanent times of 20 minutes. In the co-administration studies (Experiment 5), test compounds were administered immediately after each other in two dose regimens. In all studies, at all rats received drugs at treatment according to a randomized schedule, the first drug was administered in the left chamber, the second drug was administered in the right chamber, and the third drug was administered in the left chamber. Following administration, the animals were returned to their home cages and allowed to recover for 24 hours prior to the next trials. At baseline, the animals were housed, when subjects met pre-determined performance criteria.

Statistical Analysis

Data were analyzed via one-way analysis of variance (ANOVA) followed by the Newman-Keuls multiple comparison tests. The probability level was set at 0.05 for all analyses. Data that failed to pass ANOVA, were fitted with appropriate, when subjects met pre-determined performance criteria.

Results

Administration of atomoxetine (Panel a) decreased tolerance for reward delay (significant main effect of Dose, *p<0.05). By contrast, administration of ketanserin (Panel b) compared to vehicle (Panel a), increased tolerance for reward delay, and the effect was more pronounced at the 20 mg/kg dose of atomoxetine. The treatment effect was significant at each dose of ketanserin. Although administration of atomoxetine or ketanserin (Panel c) did not affect the tolerance for reward delay, administration of SB242084 (Panel d) increased tolerance for reward delay (significant main effect of Dose, *p<0.05). Data are expressed as mean ± SEM.

Co-administration of methylphenidate and atomoxetine or ketanserin attenuated impulsive action in the DDT.

Co-administration of methylphenidate and atomoxetine or ketanserin attenuated impulsive action in the DDT.

Study 1: Atomoxetine and Ketanserin, but not methylphenidate or SB242084, attenuated impulsive action, as measured in the 5-CSRRT.

Procedure

Animals were trained to perform the five-azpeira for stimulus light: illumination a response into the illuminated stimulus resulted in delivery of a food pellet. Three blocks of 20 trials each were performed, with inter-trial interval (ITI) trials as defined in the 5-CSRRT task results in increased premature responding at longer ITI values.

Other measures obtained during the test session were: (1) percent correct (number of correct trials / total trials), (2) percent omission (number of total trials / 200), (3) perseverative responding (addictional responses emitted after the initial non-poke within a single trial) (trials), and (4) incorrect and correct responses latency (time-to-make a correct/incorrect response after the illumination of the stimulus). (5) premature responses (time taken to enter the food magazine after a correct response).

Additional measures obtained were: (1) percent omission: failures to respond when magazine is illuminated or lever is presented, (2) latency data are expressed as mean ± SEM. Asterisks indicate significant differences compared to vehicle at mean ± SEM intervals values.

References


References


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Study 2: Methylphenidate and atomoxetine, but not Methylphenidate or Ketanserin, attenuated impulsive choice, as measured in the DDT.

Procedure

When tested to respond on one lever for a large (2 pellets) reward delivered on variable delays (5, 10, 20 and 40 s) after pressing the lever, and is as a response to different a lever for a small 1 pellet reward delivered immediately, after the lever press. Trials were presented in four distinct blocks of 12 trials, with lever order counterbalanced across blocks. The first four trials within each block were free choice trials (i.e., both levers were presented). The designation of the left/right lever as delayed/immediate reward was counterbalanced across blocks. Percent preference for the large reward was calculated as the number of choices for the large reward/total number of choices for both (large/small) rewards * 100, calculated for each specific delay.

Results

Additional measures obtained were: (1) percent omission: failures to respond when magazine is illuminated or lever is presented, (2) latency data are expressed as mean ± SEM. Asterisks indicate significant differences compared to vehicle at mean ± SEM intervals values.

Co-administration of methylphenidate and atomoxetine, ketanserin, or SB242084 enhanced reward delay tolerance in the DDT. Percent correct for delayed reward data are expressed as mean ± SEM. Asterisks indicate significant differences compared to vehicle at mean ± SEM intervals values.

Co-administration of methylphenidate and atomoxetine, ketanserin, or SB242084 enhanced reward delay tolerance in the DDT. Percent correct for delayed reward data are expressed as mean ± SEM. Asterisks indicate significant differences compared to vehicle at mean ± SEM intervals values.