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α4β2* AND α7 NICOTINIC ACETYLCHOLINE RECEPTOR BINDING PREDICTS CHOICE PREFERENCE IN TWO COST BENEFIT DECISION-MAKING TASKS

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Abstract—Nicotinic receptors have been linked to a wide range of cognitive and behavioral functions, but surprisingly little is known about their involvement in cost benefit decision making. The goal of these experiments was to determine how nicotinic acetylcholine receptor (nAChR) expression is related to two forms of cost benefit decision making. Male Long Evans rats were tested in probability- and delay-discounting tasks, which required discrete trial choices between a small reward and a large reward associated with varying probabilities of omission and varying delays to reward delivery, respectively. Following testing, radioligand binding to α4β2* and α7 nAChR subtypes in brain regions implicated in cost benefit decision making was examined. Significant linear relationships were observed between choice of the large delayed reward in the delay discounting task and α4β2* receptor binding in both the dorsal and ventral hippocampus. Additionally, trends were found suggesting that choice of the large costly reward in both discounting tasks was inversely related to α4β2* receptor binding in the medial prefrontal cortex and nucleus accumbens shell. Similar trends suggested that choice of the large delayed reward in the delay discounting task was inversely related to α4β2* receptor binding in the orbitofrontal cortex, nucleus accumbens core, and basolateral amygdala, as well as to α7 receptor binding in the basolateral amygdala. These data suggest that nAChRs (particularly α4β2*) play both unique and common roles in decisions that require consideration of different types of reward costs.

Key words: delay discounting, probability discounting, nicotinic receptor, acetylcholine, rat, impulsivity.

INTRODUCTION

Cost benefit decision making is characterized by the ability to make choices among reward options for which the outcomes differ in both reward magnitudes and costs, the latter of which can include such variables as delay to reward delivery and probability of reward omission. Optimal cost benefit decision making yields maximum rewards with minimum costs, whereas poor cost benefit decision making (termed ''impulsive'' in the case of suboptimal delay-based decision making and ''risky'' in the case of suboptimal probability-based decision making) results in larger costs and/or smaller rewards. Over the last 15 years, much has been learned about the pharmacological basis of cost benefit decision making (see Cardinal, 2006; Floresco et al., 2008; Pattij and Vanderschuren, 2008 for reviews). Largely absent from this literature, however, is information concerning the involvement of cholinergic systems.

The lack of knowledge about the role of cholinergic systems in cost benefit decision making is surprising given that cholinergic signaling has been implicated in psychological processes necessary for cost benefit decision making, including attention, learning and memory, and motivation, particularly for rewards and reward-related cues (Hoebel et al., 2007; Robbins and Roberts, 2007; Kenney and Gould, 2008; Hasselmo and Sarter, 2011). Additionally, there is limited evidence from studies in rodents and humans that pharmacological modulation of nicotinic acetylcholine receptors (nAChRs) can shift choice preference in tasks that assess cost benefit decision making (Mitchell, 2004; Reynolds et al., 2004; Dallery and Locey, 2005; Kolokotroni et al., 2011; Mendez et al., 2012; Xie et al., 2012). Finally, cholinergic signaling has been implicated in the etiology and/or treatment of numerous neuropsychiatric conditions in which cost benefit decision making is altered, including schizophrenia, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, and addiction (Clark and Robbins, 2002; Kalivas and Volkow, 2005; Karlawish et al., 2005; Thompson et al., 2007; Williams and Adinoff, 2008; Euteneuer et al., 2009; Weiler et al., 2009; Gleichgerrcht et al., 2010). These relationships are complemented by human studies using radioligand binding to assess nAChR density in patients with schizophrenia and Alzheimer's disease. Patients with these disorders show decreased post-mortem levels of the heteromeric α4β2* nAChR subtype in both striatum and cortex when compared to controls (Flynn and Mash, 1986; Warpman

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Abbreviations: ADHD, attention deficit hyperactivity disorder; ITI, intertrial interval; nAChR, nicotinic acetylcholine receptor.

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and Nordberg, 1995; Breese et al., 2000; Durany et al., 2000). Similarly, post-mortem analysis of individuals diagnosed with schizophrenia shows decreased levels of the homomeric α7 nAChR subtype within the prefrontal cortex (Guan et al., 1999).

The current study was designed to address this gap in the literature, by determining the relationships between cost benefit decision making and radioligand binding to α4β2* and α7 nAChRs across multiple brain regions in adult male rats. These analyses took advantage of the reliable and stable individual differences in cost benefit decision making that are observed in rats, which allow correlations between neurobiological and behavioral measures to be conducted (Loos et al., 2010; Simon et al., 2011). In addition, two forms of cost benefit decision making were examined: ''impulsive'' decision making, as assessed using a delay-discounting task, and ''risky'' decision making, as assessed using a probability-discounting task (Evenden and Ryan, 1996; Cardinal and Howes, 2005; Floresco et al., 2008; Mendez et al., 2010).

EXPERIMENTAL PROCEDURES

Subjects

The subjects were male Long Evans rats (n = 16) weighing 250–275 g upon arrival (Charles River Laboratories, Wilmington, NC, USA). Rats were housed individually in a climate-controlled vivarium (25 °C) at Texas A&M University. Rats had food and water freely available except as noted below. Testing took place during the light cycle of a 12-h light/dark schedule (lights on 08:00–20:00 h), and was conducted according to the ''Principles of Laboratory Animal Care'' (National Academy of Sciences, USA) and NIH and institutional animal care and use guidelines. Rats were allowed to acclimate to vivarium conditions for at least 1 week before the start of experiments. Prior to testing in the discounting tasks, rats were food restricted to 85% of their free-feeding weight over the course of 5 days. In order to maintain the rats at this weight during behavioral testing, food was limited to 15 g per day (in addition to food rewards earned during the tasks), with allowances for growth. Upon completion of behavioral testing, rats were returned to a free-feeding schedule.

Behavioral apparatus

Decision making was assessed in eight identical standard rat behavioral test chambers (31 × 25 × 31 cm) located in sound-attenuating cubicles (Coulbourn Instruments, Whitehall, PA, USA). Each chamber had aluminum front and back walls, acrylic side walls, and a floor composed of steel rods (0.4 cm diameter, spaced 1.1 cm apart). A recessed food trough (4.1 × 3.2 cm) into which grain-based food pellet rewards (PJAI, Test Diet, 45 mg) were delivered was equipped with a photobeam to detect head entries and a 1.12 W trough light, and was located in the center of the front wall of each chamber (2.2 cm above the floor). Retractable response levers were located on each side of the food trough (11 cm above the floor), and they were extended and withdrawn as described in the task protocols below. Locomotor activity was detected by activity monitors with infrared detectors mounted on the ceilings of the test chambers. The chambers were interfaced with a computer running Graphic State 3.01 software (Coulbourn Instruments) to control stimulus deliveries and record data.

Behavioral protocols

Probability-discounting task. The day before training in the task began rats were given five 45-mg food pellets in their home cages to reduce neophobia to the food rewards used in the task. Shaping began with a 64-min session of magazine training consisting of 38 deliveries of a single food pellet with an intertrial interval (ITI) of 100 ± 40 s. On the following day, rats were shaped to press a single lever (either left or right, balanced across rats; the other was retracted during this phase of training) in order to receive a single food pellet. Once they reached a criterion of 50 lever presses during a 30-min session, they were shaped to press the opposite lever using the same schedule and criterion. Following completion of lever press shaping, both levers were retracted, and rats were shaped to nose poke into the food trough during simultaneous illumination of the trough light and a 1.12 W house light mounted on the rear wall of the isolation cubicle. When a nose poke occurred, a single lever was extended, and a lever press resulted in immediate delivery of a single food pellet. Immediately following the lever press, the house and trough lights were extinguished and the lever was retracted. The left and right levers were presented an equal number of times, with no more than two consecutive presentations of the same lever. Rats were trained to a criterion of at least 60 successful trials in 1 h with an ITI of 40 ± 10 s, after which testing on the probability-discounting task began.

Test sessions in the probability-discounting task were conducted once per day. Each session was 60-min long and consisted of five blocks of 18 trials each. Each 40-s trial began with a 10-s illumination of the food trough and house lights. A nose poke into the food trough during this time extinguished the food trough light and triggered the extension of either a single lever (forced choice trials) or both levers simultaneously (free choice trials) for 10 s. Trials on which rats failed to nose poke during this time window were scored as omissions. A press on one lever (either left or right, balanced across rats) resulted in immediate delivery of a single food pellet (the small reward). A press on the other lever resulted in immediate delivery of four food pellets (the large reward). Failures to press either lever were scored as omissions. During the first block of trials, the large reward was delivered with 100% probability following selection of the large reward lever. During each of the four subsequent blocks, the probability of large reward delivery was systematically decreased (50%, 25%, 12.5% and 0%). Each 18 trial block began with eight forced choice trials (four for each lever) used to expose the rats to the reward probabilities in effect for that block, followed by 10 free choice trials (Cardinal and Howes, 2005; Simon et al., 2009). Once either lever was pressed, both levers were immediately retracted. Food delivery was accompanied by illumination of both the food trough and house lights, which were extinguished upon entry to the food trough to collect the food or after 10 s, whichever occurred first. Rats were tested in the probability-discounting task until stable performance (as described in the section 'Statistical analysis') was achieved, at which point they were switched to the delay-discounting task.

Delay-discounting task. This task was similar in design to the probability-discounting task, and hence no further shaping sessions were required. Each 60-min session consisted of five blocks of 12 trials each. Each 60-s trial began with a 10-s illumination of the food trough and house lights. A nose poke into the food trough during this time extinguished the food trough light and triggered the extension of either a single lever (forced choice trials) or of both levers simultaneously (free choice trials). Each block consisted of two forced choice trials used to expose the rats to the delays in effect for that block, followed by 10 free choice trials. A press on one lever (either left or right, balanced across rats) resulted in one food pellet (the small reward) delivered immediately. A press on the other