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Dopaminergic and serotonergic modulation of anterior insular and orbitofrontal cortex function in risky decision making

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ABSTRACT

Systemic manipulations have shown that dopamine and serotonin systems are involved in risky decision making. However, how they work within the regions that implement risky choices remains unclear. The present study investigated the role of dopamine and serotonin in the rat anterior insular cortex (AIC) and orbitofrontal cortex (OFC), which make different contributions to risky decision making. We examined the effects of local injection of the D_1 (SCH23390), D_2 (eticlopride), 5-HT_{1A} (WAY100635) and 5-HT_{2A} (M100907) receptor antagonists into the AIC or OFC on risk preference in a gambling task. We found that different dopamine and serotonin receptor subtypes in the AIC and OFC differentially influence risky decision making: intra-AIC injection of D_2R or 5-HT_{1A}R blockers increased risk preference whereas intra-OFC injection of the 5-HT_{1A}R blocker decreased it. Risk preference was not altered by intra-AIC injection of D_1R and 5-HT_{2A}R blockers or by intra-OFC injection of D_1R, D_2R, and 5-HT_{2A}R blockers. Furthermore, additional analyses revealed that dopamine and serotonin signaling in the AIC have outcome history-dependent effects on risk taking: intra-AIC injection of the D_2R blocker increased risk preference particularly after winning in a previous risky choice, whereas intra-AIC injection of the 5-HT_{1A}R blocker increased risk preference after losing.

1. Introduction

A risky choice is the selecting of an option that, like the toss of a coin, has an uncertain outcome. To obtain greater gains we sometimes need to choose a risky option rather than playing it safe, although excessive risk taking also can lead to ruin. The two neuromodulators, dopamine and serotonin, have been implicated in risky decision making (Cools et al., 2011; Rogers, 2011; Takahashi, 2012). For example, reducing dopamine levels impairs optimal performance in the Iowa gambling task (Sevy et al., 2006). Systemic administration of amphetamine increases risk taking of rats, an effect that is blocked by co-administration of either D_1 or D_2 receptor antagonists (St Onge and Floresco, 2009). Moreover, transgenic mice lacking $GABA_A$ receptors in dopamine neurons show a higher preference for risk than controls (Parker et al., 2011). People with the short variant allele of the serotonin transporter polymorphism gene (presumably resulting in more serotonin left in the synapse) are more averse to financial risk than people who have the long allele of the gene (Kuhnen and Chiao, 2009). Serotonin-depleted monkeys and rats (Long et al., 2009; Koot et al., 2012) show higher risk preference. Higher serotonin levels thus appear to be associated with higher risk aversion whereas at least some research suggests that higher dopamine levels are associated with higher risk preference.

Thus, global manipulations of dopaminergic and serotoninergic systems have provided evidence that these neuromodulators are involved in risky decision making. Recent studies have begun to investigate the function of these neuromodulators in some of their target regions during risky decision making. For example, St Onge and her colleagues found that local injection of a D_1R blocker into the medial PFC decreased risk preference, while local injection of a D_2R blocker increased it (St Onge et al., 2011; see also Mai and Hauber, 2012). However, dopaminergic and serotonergic neurons project to partly different target regions with different functions. Moreover, the distributions of receptor subtypes are largely different between target regions. Thus, the question arises "how dopamine and serotonin work within given target regions."

In the present study, we investigated the roles of dopamine and serotonin in the anterior insular cortex (AIC) and the orbitofrontal cortex (OFC). Human studies have shown these regions to be

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involved in risk processing (e.g., Tobler et al., 2007; Burke et al., 2013). In rats, inactivation of the AIC decreases risk preference and inactivation of the OFC increases it (Ishii et al., 2012), suggesting that the AIC and OFC make different contributions to risky decisions. These regions also differ in dopaminergic innervation: the AIC receives substantial dopaminergic projections, whereas the OFC receives little or none (Berger et al., 1976, 1991; Ohara et al., 2003; Van De Werd and Uylings, 2008). Accordingly, clear expression of D_1R and D_2R mRNA can be observed in the AIC but not the OFC (Santana et al., 2009). In contrast, both the AIC and the OFC receive serotonergic innervation (Linley et al., 2013). The major serotonin receptor subtypes, 5-HT_{1A}R and 5-HT_{2A}R, are expressed in both regions (Santana et al., 2004). Given these data, it is conceivable that blocking dopamine and serotonin in the AIC and OFC reveals distinct, target region-specific roles of the two neuromodulators in risky decision making.

2. Materials and methods

2.1. Animals

Thirty-four male Wistar rats initially weighing 200–250 g were used for the experiments. Training of the behavioral task took over 2 months, leading to final weights at test of 250–310 g. During behavioral and pharmacological tests, individual body weight was stable. Rats were individually housed under 12-h light/dark cycles with light onset at 8:00 P.M. Training and testing took place during the dark phase. They had ad libitum access to food for the duration of the experiments but limited access to drinking water in their home-cage. Usually, the rats received all the water needed in a day through the behavioral experiments. To prevent weight loss, their body weights were monitored daily, and if necessary, they were given additional water after the daily experiment. The experimental plan of the present study was approved and licensed (2013LSA-006-1) by the Institutional Animal Care and Use Committee of Tohoku University. Throughout the experiments, animals were treated in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and Tohoku University *Guidelines for Animal Care and Use*.

2.2. Overall structure of the experiment

We tested the effects of blocking four representative receptor subtypes—D_1R, D_2R, 5-HT_{1A}R, and 5-HT_{2A}R—in either the AIC or OFC on rats' risky decision making in the gambling task we had used in a previous study (for details, see Ishii et al., 2012). All procedures were the same as those used in that study; only the drugs were different. The basic task for the rat was to get water by choosing one of two levers associated with different outcomes. After the rats were trained to discriminate the different reward amounts provided by the two levers, their behavioral performance was tested in a gambling task. Guide cannulae for drug injections were then implanted and, after a recovery period of 7 days, pharmacological tests in the gambling task and reward-amount-discrimination task as a control were conducted.

2.3. Apparatus

Experiments were conducted in dimly lit sound-attenuated boxes (60 cm × 45 cm × 35 cm) (Fig. 1A). On one wall of each box was a nose-poke hole at the center and two protruding levers, one on each side of the hole and each with a white LED above it. A nozzle delivering water was on the opposite wall. Nose-poke responses were detected by a horizontal infrared beam (OMRON). Each device was connected to a computer via a Digital I/O card (PCI-7248, ADLINK technology) and controlled by an in-house software program (based on C++).

2.4. Training: reward-amount-discrimination task

The rats were first trained to discriminate differences in the number of water drops. A trial consisted of three events: a nose-poke into the central hole to start a trial, a press of one of the available levers (availability was indicated by the LED-ON), and delivery of drops of water from the nozzle on the opposite wall of the box. One drop of water was 50 μl, the interval between each drop was 700 ms, and water was given 3 s after lever press. If the rat did not press either lever within 10 s after nose-poke, the trial was aborted and the LED was turned off until the next trial. Rats first learned in 40 forced-choice trials that the high-amount option (lever) provided 4 drops of water and the low-amount option provided 2 drops. In subsequent discrimination trials, rats were given 100 free choices between the high- and low-amount options. Assignment of outcomes to levers was counterbalanced between sessions. Sessions were conducted up to three times a day and lasted over 3 h. A rat was moved to the next step (the gambling task) when it had performed 10 or more consecutive sessions in which it had chosen the high-amount option in more than 65% of the trials. In most sessions the rats chose the better option in over 85% of the trials.

2.5. Gambling task

The task was modified from previously described procedures (Logan, 1965). The rats were required to choose between a risky option (variable amount: either 4 drops or no water, 50–50 chance, random order) and a sure option (fixed amount: x drops of water; $x = 1, 2, 3, 4$; with x fixed in a session). The session and trial structures were the same as in the amount-discrimination task. Before we conducted pharmacological experiments, we investigated behavioral performance without drug injections at each x in the gambling task. More than 10 sessions were conducted at each level of x, and for each rat the percent choice of the risky option was the average of the last 10 consecutive sessions. Subjective equivalence points between risky and sure options (percent choice of the risky option = 50%) were based on logistic sigmoid functions [$f(x) = a + b/(1 + \exp(-(x - c)/d))$, where a, b, c, and d were free parameters] which were fitted to the observed choices using the least-square method. Drug tests were performed only at the x closest to the subjective equivalence point.

2.6. Surgery

The rats were surgically implanted with four stainless steel guide cannulae (0.6 mm in diameter) targeting 1 mm above bilateral AIC (AP +3.0, ML ±4.2, DV −5.6 mm) and OFC (AP +4.4, ML ±2.2, DV −5.0 mm). Under ketamine (80.0 mg/kg) and xylazine (0.8 mg/kg) anesthesia, the scalp was retracted, craniotomies were made bilaterally above the target sites, and four guide cannulae were inserted and fixed with dental cement. To prevent clogging by blood clots, dummy injection cannulae (0.3 mm in diameter) were inserted into the guide cannulae. Rats were given 1 week of recovery from the surgery.

2.7. Drugs

The following drugs were used: the D_1R antagonist *R*-(+)-SCH23390 hydrochloride (2.0 and 4.0 μg/μl), the D_2R antagonist eticlopride hydrochloride (2.0 and 4.0 μg/μl), the 5-HT_{1A}R antagonist WAY100635 (2.0 and 4.0 μg/μl), and the 5-HT_{2A}R antagonist M100907 (0.2 and 2.0 μg/μl). Moreover, 0.9% saline served as a