Atomoxetine Decreases Vulnerability to Develop Compulsivity in High Impulsive Rats

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Background: The factors contributing to the development and severity of obsessive-compulsive spectrum disorders such as obsessive-compulsive disorder, Tourette's syndrome, pathological gambling, and addictions remain poorly understood, limiting the development of therapeutic and preventive strategies. Recent evidence indicates that impulse-control deficits may contribute to the severity of compulsivity in several of these disorders. This suggests that impulsivity may be a transnosological endophenotype of vulnerability to compulsivity. However, the precise nature of the link between impulsivity and compulsivity in anxiety-related compulsive disorders remains unknown.

Methods: We investigated the relationship between impulsivity and the development of a compulsive behavior in rats, which captures the hallmarks of compulsivity as defined in the DSM-IV—namely, that it is maladaptive, excessive, repetitive, and anxiolytic.

Results: We demonstrate that a high-impulsivity trait, as measured in the five-choice serial reaction time task, predicts an increased propensity to develop compulsivity as measured in a schedule-induced polydipsia procedure. Trait impulsivity and compulsivity were nonlinearly related. This impulsivity–compulsivity relationship was lost after the development of compulsivity or under chronic treatment with atomoxetine, a noradrenergic reuptake inhibitor used to treat attention-deficit/hyperactivity disorder. Atomoxetine treatment both decreased impulsivity and prevented the development of compulsivity in high-impulsive animals.

Conclusions: These observations provide insight into the reciprocal influence of impulsivity and compulsivity in compulsive disorders and suggest that atomoxetine may be a useful treatment for patients suffering from obsessive-compulsive spectrum disorders with high impulsivity.

Key Words: Atomoxetine, compulsivity, five-choice serial reaction time task, impulsivity trait, obsessive-compulsive spectrum disorders, schedule-induced polydipsia, Tourette's syndrome

The factors contributing to the development and severity of obsessive-compulsive spectrum disorders (OCSDs) such as obsessive-compulsive disorder (OCD), Tourette's syndrome, pathological gambling, and addictions remain poorly understood, limiting the development of pathophysiologically based therapeutic and preventive strategies.

Increasing evidence suggests that impulse-control deficits, commonly observed in patients suffering from OCSDs (1–3), may be "transnosological" endophenotypes of the vulnerability to, and severity of, compulsive disorders rather than mere comorbid symptoms (2). For example, an impulsivity trait (4,5) and impulse control deficits in patients with attention-deficit/hyperactivity disorder (6,7) both predict vulnerability to developing compulsive drug use (8). Moreover, recent studies in rats have demonstrated that a high impulsivity trait, measured as the inability to withhold prepotent responses in the five-choice serial reaction time test (5-CSRTT) (9–11), contributes to an increased vulnerability to compulsive drug-seeking manifested as maintained drug self-administration despite punishment (11). Together with the demonstration that the "anti-impulsivity" drug atomoxetine, a noradrenergic reuptake inhibitor used to treat attention-deficit/hyperactivity disorder, reduces both impulsivity and subsequent relapse to compulsive drug seeking in rats (12–14), these data suggest that an impulsivity trait may predate and facilitate the development of compulsive behaviors (15).

However, impulsivity (16,17) and compulsivity are multifaceted constructs that may interact differently within various disorders. In particular, the precise nature of the relationship between waiting impulsivity and compulsivity characterized by repetitive, excessive, maladaptive, and anxiolytic behaviors observed in OCDs (18) remains to be established. The difficulty assessing premorbid personality characteristics such as trait impulsivity before the development of pathological compulsivity, including any potentially confounding alterations in impulse control, in human studies limits our understanding of the etiological contribution of impulsivity to OCSDs.

In this study, we tested the reciprocal influences of impulsivity and compulsivity in a preclinical model having heuristic value with regard to OCD as defined in the DSM-IV (18). Specifically, we implemented a longitudinal study in rats in which we combined a model of interindividual differences in impulse control, as measured in the 5-CSRTT (10), and the propensity to develop a

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compulsive behavior on a schedule-induced polydipsia (SIP) procedure (19–23).

SIP, an adjunctive compulsive drinking behavior in response to intermittent food delivery, recapitulates the hallmarks of the clinical definition of compulsivity in OCD (24–27)—namely, the expression of excessive, maladaptive, repetitive, and anxiolytic behaviors (19,28–30). The SIP model has been shown to have elements of face, construct, and predictive validity with respect to human compulsive disorders. SIP that allows for the investigation of interindividual differences in rats (20,31) has been shown not only to be dependent on the anterior insular cortex (32), a region repeatedly involved in the pathophysiology of OCD (33–35), but also to be sensitive to selective serotonin reuptake inhibitors (26,27), a common treatment for anxiety disorders and the symptoms of OCD.

We analyzed the contribution of a high-impulsivity trait on the propensity for the development of compulsive drinking, as well as how training on the SIP procedure affects subsequent expression of impulsive behavior. We further investigated whether the increased vulnerability of high-impulsive (HI) rats to develop compulsivity could be prevented by chronic treatment with the selective noradrenaline reuptake inhibitor atomoxetine, which has been shown to decrease impulsivity in rats (12).

Methods and Materials

Two independent experiments were carried out in this study. The first was performed on 23 male Sprague-Dawley rats from Charles River (Arbresle, France), which are known to display high rates of premature responding in the 5-CSRTT akin to Lister Hooded rats used in previous experiments (11,36–38). This experiment was aimed at identifying the nature of the reciprocal influences of impulsivity and compulsivity. The second experiment was performed on a cohort of 48 male Sprague-Dawley rats from Janvier (Saint Berthevin, France), which are known to display robust, but moderate levels of premature responses in the 5-CSRTT. This experiment was aimed at 1) reproducing the results obtained in experiment 1 controlling for any potential rate-dependency or cohort-specific contribution on the dimensional relationships observed, 2) measuring the influence of chronic atomoxetine treatment on the propensity of HI rats to develop SIP, and 3) identifying whether atomoxetine alters the relationships between impulsivity and compulsivity.

Subjects

Rats were housed two per cage under a reversed 12-hour light–dark cycle (lights on at 7:00 PM) at controlled room temperature (22°C). At the start of the experiments, rats weighed 270 g and were maintained at 85% of their free-feeding weight, starting 1 week before the beginning of the experiments by restricting the amount of standard rodent lab chow to 15 g per rat. Water was available ad libitum throughout the experiment, and food was given 1 hour after daily testing. All experiments were conducted between 8:00 AM and 6:00 PM in agreement with the European Community Council Directives (86/609/EEC).

Apparatus

For the 5-CSRTT, 5-hole boxes have been previously described (76). A detailed description is provided in Supplement 1.

For SIP, 24 operant chambers (24 × 24 × 26 cm, MedAssociates, St. Albans, Vermont) were equipped with stainless-steel grid floors, a house light (3 watts), and a food tray installed at the center of the front wall, 2 cm from the grid floor. Front and back panels of the test chambers were aluminium, and right and left walls and the roof were transparent acrylic plastic. Each chamber was equipped with a water bottle fitted with a stainless steel sipper tube that delivered water to the rats within the chamber 3 cm from the front plastic panel and 3.5 cm above the grid floor on the wall opposite the wall on which the food tray was placed centrally. For Experiment 1, the 12 cages were also equipped with lickometers (MedAssociates), allowing for the measure of licks on the bottle spout.

Behavioral Procedures

The 5-CSRTT procedure has been extensively described (9,36–39). Detailed methods are provided in Supplement 1.

SIP is a compulsive adjunctive behavior resulting in an anxiolytic excessive intake of freely available water in the face of predictable intermittent food delivery that has been suggested to generate distress in animals [for review, see Platt *et al.* (19)]. We used an SIP procedure based on a fixed-interval 60-second schedule of food delivery that has previously been shown to induce both high levels of compulsive drinking and marked interindividual differences in the propensity to develop this behavior (22,40). Detailed methods are provided in Supplement 1.

Timeline of the Experiments

Experiment 1. Rats were trained in the 5-CSRTT and identified as either HI or low impulsive (LI) from the upper and lower quartile of the population, respectively, based on their premature responding in the last two long intertrial interval (lITI) probe sessions. Twenty-four hours after the last 5-CSRTT session, rats were placed in the SIP boxes for the baseline session, followed 24 hours later by the magazine training session and the subsequent 23 daily sessions of SIP. To measure the influence of SIP on impulsivity, behavioral performance in the 5CSRTT was assessed again 2 weeks after the end of the SIP procedure. One week after the end of the last SIP session, rats were subjected to six training sessions before being tested again on two lITI sessions in the 5-CSRTT.

Experiment 2. Rats were trained in the 5-CSRTT and identified as either HI ($n = 11$) or LI ($n = 11$) from the upper and lower quartile of the population, respectively, on the basis of their premature responding in the last two LITI probe sessions. Four rats did not acquire the task and were discarded from the experiment. After the last baseline session following the third LITI challenge, the HI, LI, and intermediate animals were each distributed in vehicle (HI $n = 5$, LI $n = 5$) or atomoxetine groups (HI $n = 6$, LI $n = 6$) matched for their level of impulsivity. Rats received daily intraperitoneal injections of either atomoxetine or vehicle. Twenty-four hours after the initiation of the differential treatment, rats were subjected to five baseline sessions in the 5-CSRTT before being challenged with two LITI sessions separated by three baseline sessions.

Twenty-four hours after the final 5-CSRTT baseline session, rats were placed in the SIP boxes in which they were subjected to a baseline session. The next day, rats were subjected to a magazine training session followed by 23 daily sessions of SIP. During this period, three vehicle-treated rats lost too much weight over 2 weeks despite intensive care and nursing and were excluded from the procedure, and thus the final number of animals included in the experiment was HI-vehicle: $n = 5$, LI-vehicle: $n = 5$, Int-vehicle: $n = 8$, HI-atomoxetine: $n = 6$, LI-atomoxetine: $n = 6$, Int-atomoxetine: $n = 12$.

Drugs

Atomoxetine (Sequoia Research Products, Pangbourne, United Kingdom) was freshly prepared each morning, formulated at 1 mg/kg/rat/day, dissolved in .01 mol/L phosphate-buffered saline

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