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Marked inbred mouse strain difference in the expression of quinpirole induced compulsive like behavior based on behavioral pattern analysis

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Abstract

Obsessive–compulsive disorder (OCD) is a chronic and complex psychiatric disorder with a lifetime prevalence of 2–3%. Recent work has shown that OCD rituals were not only characterized by a high rate of repetition but also by an increased behavioral repertoire due to additional non-functional unique acts. These two behavioral characteristics may provide an ethological basis for studying compulsive behavior in an animal model of OCD. Here, quinpirole induced behavior (so far only investigated in rats) has been studied in A/J and C57BL/6J mice by using behavioral pattern analysis. The aim of this study is to investigate whether genetic background is mediating this behavior. Results showed that open field motor activity levels of saline treated C57BL/6J mice was significantly higher compared to A/J treated saline mice. Long-term quinpirole treatment increased open field motor activity levels in A/J, but not in C57BL/6J. Quinpirole treatment induced a strain dependent difference in behavioral repertoire. There was a dose dependent increase in the number of different behavioral patterns in A/J, whereas, in C57BL/6J there was a dose dependent decrease. This data suggest that genetic background is important in expressing quinpirole induced compulsive like behavior. Following quinpirole treatment, A/J mice express a greater behavioral repertoire with a high rate of repetition. This phenotype resembles that of OCD rituals in patients and indicates that this strain is very interesting to further validate for studying neurobiological mechanisms of compulsive behavior.

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1. Introduction

Obsessive–compulsive disorder (OCD) is a chronic and complex psychiatric disorder with a lifetime prevalence of 2–3%. This disorder is accompanied by intrusive, unwanted and recurrent thoughts or images (obsessions) and/or repetitive ritualistic behaviors (compulsions). Obsessions can be related with the fear of being contaminated, with symmetry or ordering. Compulsions can be hand washing, checking of objects or locations or counting. These thoughts and ritualistic behaviors become excessive, distressing and significantly interfere with every day functioning. Recent work has shown that behavior in OCD patients was characterized not only by a high rate of repetition but also by addition of non-functional unique acts, together referred to as pessimal behavior (Eilam et al., 2011; Zor et al., 2009a, 2009b). The observed larger behavioral repertoire and higher rate of repetition of behaviors may provide an ethological basis for studying compulsive behavior in an animal model of OCD (Eilam et al., 2011).

The underlying mechanism of OCD is still unknown. Successful treatment in OCD patients with selective serotonin re-uptake inhibitors (SSRI's) alone or in combination with an atypical antipsychotic drug indicates a role of serotonin and dopamine in the pathophysiology of OCD (Abudy et al., 2011). Direct support for a role of dopamine also stems from neuroimaging studies showing higher densities of the dopamine transporter in tandem with a down regulation of the D2 receptors in the basal ganglia of OCD patients. These findings suggest a higher dopaminergic tone in this brain circuitry (Westenberg et al., 2007).

Twin and family studies have provided convincing evidence for the importance of genetic factors for the expression of OCD. There is limited knowledge about pathophysiological pathways and networks of interacting genes in OCD also non-significant results from linkage and association studies suggest it is too early to focus on specific candidate genes associated with OCD. A genome wide association study with a sufficient sized sample should be performed to identify genomic regions containing promising candidate genes (Pauls, 2010).

Animal models may be useful in unraveling genetic and neurochemical underlying mechanisms of OCD; however they are inappropriate to investigate the entire OCD spectrum (obsessions) but seem more than adequate for studying forms of compulsivity.

The most studied animal models for OCD are; 8-OHDPAT (8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide) induced decreased alternation (Yadin et al., 1991), quinpirole-induced compulsive checking (Szechtman et al., 1998), marble burying (Gyertyan, 1995), signal attenuation (Joel and Avisar, 2001) and spontaneous stereotypy in deer mice (Korff et al., 2008; Powell et al., 1999).

Previously we have reported that long-term quinpirole treatment induced behavior in rats mimicking only part of the compulsive behavior as shown in OCD patients (de Haas et al., 2011). Behavioral pattern analysis revealed that quinpirole-induced behavior consisted, unlike OCD rituals, of a smaller behavioral repertoire. However, similar as in OCD patients, quinpirole treated rats performed these behaviors with a high rate of repetition.

In this study the effect of long-term quinpirole treatment on behavior will be investigated in two different inbred strains of mice. Mouse strains are widely used to study genetic background effects due to the great variety and availability of resources. Previously, it has been reported that there is a marked strain difference between C57BL/6J and A/J mouse strains in expressing compulsive wheel running during daily scheduled limited food access (Kas et al., 2010). This behavior is assumed to be compulsive because of the continuous and repetitive wheel running during the 2 h of food availability indicating the inability to stop this activity despite the more appealing food (Altemus et al., 1993). C57BL/6J developed high wheel running activity prior to food access and when scheduled food restriction prolonged they showed a strong suppression of wheel running during food availability. In contrast, A/J showed no food anticipatory activity but did show high wheel running levels during food availability. Thus, A/J seemed to be more sensitive to develop compulsive-like behavior compared to C57BL/6J.

The aim of this study is to investigate quinpirole-induced behavior in A/J and C57BL/6J mice using behavioral pattern analysis and specifically to investigate whether genetic background is mediating this behavior. The hypothesis is that after long-term quinpirole treatment A/J mice will be more sensitive to develop compulsive-like behavior compared to C57Bl/6J.

2. Experimental procedures

2.1. Animals

In this study female mice from two inbred mouse strains A/J and C57BL/6J were used. Initial breeding pairs were obtained from The Jackson Laboratory (Bar Harbor, ME, USA) and sustained in our breeding facility. All female mice were socially housed under controlled conditions (temperature 20–21 °C and humidity 50–70%) with a 12-hour light–dark cycle. Food and water were given freely. All mice were 3–4 months old at the start of the experiment. All experiments were conducted during the light hours. The experimental procedure was approved by the Animal Ethical Committee of Utrecht University.

2.2. Experimental setup

At the arrival in the test room mice were injected with either quinpirole or saline. Immediately after the injection the animal was placed in the middle of the open field. Quinpirole injections were given twice a week for 4 consecutive weeks instead of 5 weeks previously used in rats. The behavior of mice was tracked for 50 min and analyzed by EthoVison version 3.1 and Theme version 5.0 (Noldus Information Technology B.V., Netherlands).

Each inbred mouse strain was divided in four treatment groups of 8 animals per group. The four treatment groups were; saline, quinpirole 1 mg/kg, quinpirole 3 mg/kg and quinpirole 6 mg/kg. Hereafter referred to as saline, QNP 1, QNP 3 and QNP 6 respectively.

2.3. Open field

In this study small adjustments were made concerning the experimental procedure previously used for rats (de Haas et al., 2011). The dimensions of the open field and its objects were adapted to the size of the mice. The open field (80×80 cm) was constructed of PVC without walls and was placed 60 cm above the floor. The