INTRODUCTION

Impulsivity is defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to themselves or others (Moeller et al., 2001). It is an action without foresight and is one of the main constituents of a number of psychiatric disorders such as mania, substance abuse and attention deficit hyperactivity disorder (ADHD) (Winstanley et al., 2006). In ADHD, increases in the different levels of impulsivity are suggested to determine its different subtypes (e.g. hyperactive-impulsive, predominantly inattentive and combined type) (Sonuga-Barke, 2002; Nigg, 2003). ADHD is the most common neuropsychiatric disorder of childhood and it has a worldwide prevalence rate of 3-18%, depending on age, gender and the definition and specific assessment methods used (Jensen, 2006).

Measuring impulsivity in the laboratory is a daunting task as it is a diverse behavior, covering a variety of phenomena that may have independent biological mechanisms (Evenden, 1999). Nevertheless, test methods to measure impulsiveness have been developed and they are of the following categories: punishment/extinction, reward-directed or rapid-decision paradigms. In punishment/extinction paradigm, impulsivity is shown by subjects that persevere with responding despite punishment or unrewarded responses. Exploiting this principle, we developed a new behavioral test that would evaluate impulsivity in the most validated animal model of ADHD of the Spontaneously Hypertensive rat (SHR) as compared with the normotensive “control” strain, the Wistar Kyoto rat (WKY). In this paradigm we call the Electro-Foot Shock aversive water Drinking test (EFSDT), water-deprived rats should pass over an electrified quadrant of the EFSDT apparatus to drink water. We reasoned that impulsive animals show increased frequency to drink water even with the presentation of an aversive consequence (electro-shock). Through this assay, we showed that the SHR was more impulsive than the WKY as it demonstrated more “drinking attempts” and drinking frequency. Methylphenidate, the most widely used ADHD medication, significantly reduced drinking frequency of both SHR and WKY in the EFSDT. Thus, the present assay may be considered as another behavioral tool to measure impulsivity in animal disease models, especially in the context of ADHD.

Key Words: Impulsivity, ADHD, SHR, WKY, Methylphenidate

A Simple Behavioral Paradigm to Measure Impulsive Behavior in an Animal Model of Attention Deficit Hyperactivity Disorder (ADHD) of the Spontaneously Hypertensive Rats

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Abstract

Impulsiveness is an important component of many psychiatric disorders including Attention-deficit/hyperactivity disorder (ADHD). Although the neurobiological basis of ADHD is unresolved, behavioral tests in animal models have become indispensable tools for improving our understanding of this disorder. In the punishment/extinction paradigm, impulsivity is shown by subjects that persevere with responding despite punishment or unrewarded responses. Exploiting this principle, we developed a new behavioral test that would evaluate impulsivity in the most validated animal model of ADHD of the Spontaneously Hypertensive rat (SHR) as compared with the normotensive “control” strain, the Wistar Kyoto rat (WKY). In this paradigm we call the Electro-Foot Shock aversive water Drinking test (EFSDT), water-deprived rats should pass over an electrified quadrant of the EFSDT apparatus to drink water. We reasoned that impulsive animals show increased frequency to drink water even with the presentation of an aversive consequence (electro-shock). Through this assay, we showed that the SHR was more impulsive than the WKY as it demonstrated more “drinking attempts” and drinking frequency. Methylphenidate, the most widely used ADHD medication, significantly reduced drinking frequency of both SHR and WKY in the EFSDT. Thus, the present assay may be considered as another behavioral tool to measure impulsivity in animal disease models, especially in the context of ADHD.

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Impulsivity is defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to themselves or others (Moeller et al., 2001). It is an action without foresight and is one of the main constituents of a number of psychiatric disorders such as mania, substance abuse and attention deficit hyperactivity disorder (ADHD) (Winstanley et al., 2006). In ADHD, increases in the different levels of impulsivity are suggested to determine its different subtypes (e.g. hyperactive-impulsive, predominantly inattentive and combined type) (Sonuga-Barke, 2002; Nigg, 2003). ADHD is the most common neuropsychiatric disorder of childhood and it has a worldwide prevalence rate of 3-18%, depending on age, gender and the definition and specific assessment methods used (Jensen, 2006).

Measuring impulsivity in the laboratory is a daunting task as it is a diverse behavior, covering a variety of phenomena that may have independent biological mechanisms (Evenden, 1999). Nevertheless, test methods to measure impulsiveness have been developed and they are of the following categories: punishment/extinction, reward-directed or rapid-decision paradigms. In punishment/extinction paradigm, impulsivity is shown by the subjects when they persevere with responding despite punishment or the unrewarded responses. Reward-directed paradigms demonstrate impulsiveness when subjects prefer a smaller-but sooner reward over a larger-later reward. In rapid-decision paradigms, impulsivity is assessed when subjects make premature or disinhibited responses (Dougherty et al., 2003). On the other hand, Winstanely et al. (2006) summarized these different behavioral paradigms into...
two groups: those that measure impulsive choice, and impulsive action. Impulsive choice is elucidated by the making of impulsive decisions, that is, impulsive subjects opt for smaller and immediate rewards more often than delayed but larger rewards while impulsive action refers to the inability to withhold from making a response. Delay discounting paradigms represent successfully the experiments that measure impulsive choice. Examples of behavioral paradigms that measure impulsive action are the stop-signal reaction time (SSRT) and the go/no-go tasks. In addition, the five-choice serial reaction time task (5-CSRT) also measures motoric impulsivity while concurrently gauging sustained or divided attention (Winstanley et al., 2006).

Animal models help to simplify and promote the understanding of disorders. Much of the understanding in ADHD due to animal models. A number of animal models have been developed for ADHD and the most validated are the Spontaneously Hypertensive rats (SHR). The SHR, derived from the main progenitor Wistar-Kyoto rats (WKY) and originally developed as animal models of hypertension, also display the salient features of ADHD (e.g. hyperactivity, inattention and impulsiveness) (Sagvolden, 2000). The SHR were readily shown to be impulsive in various delay discounting paradigms (Bizot et al., 2007; Fox et al., 2008). SHR are more active than WKY (Hard et al., 1985; Hendley et al., 1985; Wultz et al., 1990; Mook and Neuringer, 1994; Berger et al., 1998; Sagvolden et al., 1998), and tend to prefer immediate smaller rewards rather than delayed larger rewards (Mill et al., 2005). However, there is a difficulty in demonstrating impulsive actions in SHR using the 5-CSRT thus the SHR have been criticized to not fully represent the symptoms of ADHD (Van der Bergh et al., 2006). It also remains to be known if SHR show impulsiveness in two other tasks, the go/no-go and the SSRT. It could be that the complexity. If this indeed is true, there is a need to develop relatively easier behavioral models that could measure impulsiveness with ease, without sacrificing good results.

In the present study, we present a simple but effective behavioral paradigm that measures impulsivity in an animal model of ADHD of the SHR (as compared with WKY). We call this the Electro-Foot Shock water Drinking aversive test (EFSDT) and this operates according to the concepts exploited in punishment/reinforcement paradigms. We report the results of a pilot experiment and conducted pharmacological validation to ensure reliability of the present assay to measure impulsivity, at least in an animal model of ADHD.

MATERIALS AND METHODS

Subjects

We used 4-week old male SHR and WKY rats supplied by Charles River, Japan via Orient Co. (Korea). Rats were housed in cob containing plastic cages placed in a temperature-controlled room (21 ± 1°C) under a reverse light/dark cycle (lights on at 07:00 until 19:00). They were allowed free access to water and standard laboratory food except during the experiments. Test sessions were performed during the light cycle, 3 days per week, one session per day. Animal treatment and maintenance were carried out in accordance with the Principles of Laboratory Animal Care (NIH publication No. 85-23 revised 1985) and the Animal Care and Use Guidelines of Konkuk University, Korea.

Methods for baseline factors

Locomotor activity in open-field and the EFSDT box: Open-field test experiment was conducted in apparatus made of Plexiglas (42×42×50 cm). Rats were placed in the center of the apparatus and allowed to move freely. Behavioral data in the open-field test was recorded for 20 minute and analyzed using Noldus EthoVision software. Those data were analyzed as indicator of hyperactive properties. We also measured the basal locomotor activity levels of rats during the first two days of the training phase. Rats were placed in the EFSDT box and the distance travelled for 10 minute were recorded via the EthoVision system.

Water consumption: We evaluated the total water consumption levels during the first two days of the test. For 3 consecutive days of the phase the basal water intake was observed in the two groups after water deprivation. Each day, subjects were weighed and given water for 1 hour through 100 ml calibrated water bottle. At the end of an hour, the consumption of water was measured nearest milliliter. Food was available during each of testing phase. Water intake was calculated at ml consumption.

Pain sensitivity: Separate groups of rats were tested for electroshock sensitivity. This test was performed by examining the ability of an automated Freeze Monitor system to reliably record immobility behavior displayed by rats subjected to a variety of experimental manipulations. A footshock (2 mA, 1 second) was delivered through the grid floor of the chamber for 10 minute (1 second duration/20 second inter-shock-interval). Behavioral responses in an automated Freeze Monitor system are measured manually.

Elevated plus maze test: We conducted elevated plus maze test as an assay of anxiety-related behavior. Rats are placed in the intersection of the four arms of the elevated plus maze and their behavior is typically recorded for 8 minute. The time spent on the open and closed arms were measured and the percentage of time spent (duration) in the each arms [100 × each arms/(open+enclosed)] was calculated.

Cognitive ability: We measured number of drinking attempts in both strains during each training phase for cognitive ability. Rats were placed in the EFSDT box and the drinking attempts for 10 minute were recorded.

Apparatus

The Electro-foot shock aversive water drinking test (EFSDT) box: Experiments were conducted in an EFSDT box measuring 60×60×30 cm. The box is made of wood, painted black, and divided into three compartments (start area, water area and a free area, Fig. 1). With the exception of the start area, the floor of the EFSDT box was made of grid electrified wire (Fig. 1). In the water area, a water bottle with a stainless steel nozzle was fitted from outside of the box so that the nozzle extended 4 cm into the box at a height of 6 cm above the floor. The Noldus EthoVision system (Noldus information technology, Wageningen, The Netherlands) was used to track movement of rats and frequency in each of the compartments of the EFSDT box.

Procedures

The EFSDT consisted of two phases; the training phase which lasted for two days and a testing phase which lasted for a day (Fig. 2). The procedures of each of the phases are described below.

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