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A response strategy predicts acquisition of schedule-induced polydipsia in rats

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ABSTRACT

Schedule-induced polydipsia (SIP) is excessive, non-regulatory drinking. We aimed to identify phenotypic learning traits representative of neural circuitry that underlies SIP and hypothesized that rats that are response-learners will be more susceptible in developing compulsive water drinking. Using the Y-maze, the rats were characterized as either place- or response-learners. They were exposed to the SIP protocol for a period of 21 days. Subsequent histological staining for FosB/ΔFosB examined neuronal activation associated with SIP in several brain regions. The rats with a preference for a response-learning strategy were more likely to develop SIP than the rats using a place-learning strategy. Furthermore amphetamine sensitization, observed to increase SIP, also shifted learning strategy to a response-learning strategy. No differences were observed in FosB/ΔFosB expression between SIP and non-SIP rats in the dorsolateral striatum (DLS) and CA1 region of the hippocampus. However, SIP rats had greater FosB/ΔFosB expression in prefrontal cortex regions. The rats that develop SIP have a preference for response-learning strategies and increased neuronal activation in frontal cortical regions associated with habit formation and compulsion.

1. Introduction

Habits develop if a behavior is performed frequently with an unchanging outcome. Moreover, habits render the behavior relatively inflexible to future changes in outcome (Gillan et al., 2014). Studies have shown that nucleus accumbens (NAc) is critical for outcome-sensitive behaviors and as habitual behavior develops, control appears to shift gradually to dorsomedial striatum (DMS) and then dorsolateral striatum (DLS; Yin et al., 2004, 2006). Furthermore evidence suggests that aberrant functioning of cortico-striatal loops involving the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) may facilitate habit behaviors to become compulsive (Robbins et al., 2012) — a pathology characterized by automatic and repetitive actions observed in a number of psychiatric conditions such as obsessive compulsive disorder (OCD; Moreno and Flores, 2012; Woods-Kettelberger et al., 1997), addiction (e.g., alcohol abuse; Tang and Falk, 1990), and primary polydipsia associated with schizophrenia (Hawken et al., 2011; Hawken and Beninger, 2014).

Schedule-induced polydipsia (SIP) has been identified as a useful animal model to study the underlying neurobiology of compulsivity (Moreno and Flores, 2012). SIP is excessive, non-regulatory drinking that develops in a hungry animal in association with the intermittent presentation of food (Falk, 1961). However, not all rats exposed to this protocol develop polydipsia. Moreover, the rats that develop high compared to low drinking in the SIP protocol show differences in the binding affinity of dopamine (DA) D1/D2 receptors in the amygdala, ventral tegmental area (VTA), NAcC and the mPFC (Pellón et al., 2011). Thus, there may be inter-individual differences in the vulnerability to acquisition of compulsivity in this model. Observed DA receptor changes following SIP training, however, may be the result of SIP behavior itself (i.e., a consequence of repeated water loading) and it is difficult to know if these neurobiological differences are inherent, preceding SIP, or neurological adaptations that follow SIP exposure (for a review see, Seger, 2010). Identifying phenotypic behaviors or traits associated with learning and memory in individuals that go on to exhibit compulsive behaviors may be a key to understanding the neurocircuitry that underlies aberrant behavior patterns.

Abbreviations: AMPH, Amphetamine; ANOVA, Analysis of variance; BSA, Bovine serum albumin; DAB, 3',3'-diaminobenzidine; DLS, Dorsolateral striatum; DA, Dopamine; DMS, Dorsomedial striatum; IEG, Immediate early gene; IL-PFC, Infralimbic prefrontal cortex; mPFC, Medial prefrontal cortex; NAc, Nucleus accumbens; NAcC, Nucleus accumbens core and shell (NAcS); NAcS, Nucleus accumbens shell; OCD, Obsessive compulsive disorder; OFC, Orbitofrontal cortex; PBS, Phosphate-buffered saline; SIP, Schedule-induced polydipsia; TBS, Tris-buffered saline; VLOFC, Ventral lateral orbitofronal; VTA, Ventral tegmental area.

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Multiple learning and memory systems operate simultaneously in the brain, each acquiring and storing its own specific information to influence behavior (McDonald and White, 1993; Bechara et al., 1995). One system may predominate at a given time as can be shown with appropriate behavioral tests (for a review see, White et al., 2013). For instance, with the use of a T-maze, Packard and McGaugh (1996) demonstrated that when learning to find a food pellet placed at the end of one arm of the T-maze, the rats initially rely on distal extra-maze cues to learn their spatial location, a process that is hippocampus-dependent and dubbed "place learning." Lesions to the hippocampus and DMS impair an animal's ability to use place learning strategies (Devan et al., 1999; Bartsch et al., 2010). Alternatively, the animals that rely on certain responses (i.e., on the motor action of turning to reach the baited arm) that are mediated by the DLS are dubbed "response learners". Packard and McGaugh (1996) demonstrated that place learning is acquired faster than response learning. Furthermore, extended training induces a shift to primarily using response-learning strategies; these strategies involve habit formation, consistent with their localization to the DLS (Packard and McGaugh, 1996; Yin et al., 2004).

Using a Y-maze similar to the T-maze employed by Packard and McGaugh (1996), we aimed to identify phenotypic learning strategies that might predict subsequent acquisition of SIP. We hypothesized that response learners will acquire SIP more readily than place learners. We further hypothesized that amphetamine-sensitized rats, shown previously to be prone to SIP acquisition, will also predominately use response learning strategies. Immediate early gene (IEG) expression is widely used to map brain areas that have recently responded to behavioral stimuli (Herrera and Robertson, 1996; McClung et al., 2004). Specific IEGs like FosB/ΔFosB, are particularly long-lived, can accumulate, and thus are more responsive to chronic behavioral perturbations (Chen et al., 1997). Thus, in FosB/ΔFosB immunohistochemical studies we hypothesized greater activity in the DLS or in cortical regions that project to the striatum in the animals that acquire SIP.

2. Methods

2.1. Animals

Fifty-five male Sprague Dawley rats weighing 200–225 g (Charles River, QC) were housed separately in clear Plexiglas cages (45 × 23 × 20 cm deep). The floors were lined with bedding (Beta Chip, NEPCO, Warrenburg, NY) and the cages were located in a climate-controlled colony room (21 ± 1 °C; humidity 40–70%) on a reversed 12-h light/dark schedule (lights off at 0700 h). The rats initially had free access to food (LabDiet rodent feed #5001, PMI Nutrition International, Brentwood, MO) and water but were later food-restricted (see Section 2.4). Twenty-four of the 55 rats went on to SIP testing and those results are reported in a previous paper (Hawken and Beninger, 2014) (see Section 2.4). The rats were treated in accordance with the guidelines of the Canadian Council on Animal Care and the Queen's University Animal Care Committee approved the behavioral protocol.

2.2. Apparatus

2.2.1. Learning

A wooden Y-maze painted flat gray was used to test place- and response-learning strategies. The maze consisted of three arms each at 120° to the next. Each arm measured 17 × 35 × 26 cm deep with steel grid flooring and a triangular Plexiglas floor was in the center. A small plastic cup was fixed at the end of each arm to hold food pellets. Each arm of the Y-maze was randomly assigned a static identity for the duration of the experiment: training arm (start arm during training sessions), testing arm (start arm during testing sessions), and goal arm (location of pellet). The maze was located in a testing room that contained many extra-maze cues including high contrast wall decorations, animal cage rack and the experimenter always standing in the same location.

2.2.2. Drinking

Four commercially built (Med Associate Inc., St. Albans, VT) operant chambers (30.5 × 24.1 × 21 cm) were housed inside sound-attenuating cabinets that contained an electric fan for ventilation that ran throughout the experiment. The boxes were made of polycarbonate with aluminum panels and steel grid flooring. A house light remained on in the box for the duration of the session. Each reward consisted of one 45 mg dustless precision food pellet (Bio-serv, Frenchtown, NJ), released into the recessed dispenser tray (5 × 8 × 4 cm). On the opposite wall of the pellet dispenser and sitting between two inactive levers was a metal drinking spout containing a ball bearing. The drinking spout was freely available the entire session. A photo beam sensor was positioned across the mouth of the water spout inside the drinking compartment to measure head entries. The operant chambers were controlled by a computer running MED-PC IV (Med Associates Inc., St. Albans, VT).

2.3. Drug treatment

One week following arrival in the facility, 14 animals were randomly assigned to receive once daily amphetamine (AMPH; dissolved in saline, 1.5 mg/kg i.p.; Sigma, Oakville ON) and 14 animals were randomly assigned to receive saline injections (1 ml/kg) for five consecutive days. A 5-day washout period followed the injection cycle.

2.4. Behavioral procedures

Each day following arrival at the facility, the rats were handled daily in both the colony and testing rooms. After one week, food restriction began by providing access to food for 2 h each day. Once the animals had adjusted to the food restriction protocol (i.e., their weight drop stabilized), the animals were expected to gain small amounts of weight despite food restriction. The rats were weighed twice weekly. For the rats receiving AMPH and saline injections, food restriction began following the injection schedule.

The 55 rats were included in experiments as follows. Twenty-eight rats received injections (14 AMPH, 14 saline) and were evaluated for learning strategy in the Y-maze as described below. Twenty-four of these 28 rats went on to SIP testing and their SIP results are reported in Hawken and Beninger (2014); only the Y-maze (learning-strategy) data of these 28 rats are reported here. An additional 16 rats were evaluated for learning strategy in the Y-maze and then underwent SIP training as described below. The final 11 rats were used for FosB/ΔFosB immunohistochemistry following an abbreviated SIP training (three consecutive days of drinking at least 15 ml of water or a time-matched control that had not reached the SIP criterion).

2.4.1. Learning strategy

This protocol was adapted from that used by Packard and McGaugh (1996). On 2 consecutive habituation days, the rats were placed into the 'start arm' of the Y maze and allowed to explore the maze for 5 min. No food was present in the maze but the animals received 10 food pellets upon returning to their home cages. Food (training) trials began on day three. On each food trial, the rats were placed in the start arm and allowed to search the maze and consume a single food pellet located in a food cup at the end of the 'goal arm.' On the first food trial only, four food pellets along the length of the goal arm led the animal to the food cup. On each training day, the animals completed four food-rewarded trials. During training, entries into the unbaited (testing) arm were scored as incorrect responses and entries into the baited (goal) arm were scored as correct. When the rats made an incorrect response during training, they remained in the maze until they crossed the center and entered the goal arm where they consumed the food. If the rats failed to consume the food within 2 min, the trial was