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The effects of lactation on impulsive behavior in vasopressin-deficient Brattleboro rats

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ABSTRACT

Vasopressin (AVP)-deficient Brattleboro rats develop a specific behavioral profile, which—among other things—include altered cognitive performance. This profile is markedly affected by alterations in neuroendocrine state of the animal such as during lactation. Given the links between AVP and cognition we hypothesized that AVP deficiency may lead to changes in impulsivity that is under cognitive control and the changes might be altered by lactation. Comparing virgin and lactating AVP-deficient female Brattleboro rats to their respective controls, we assessed the putative lactation-dependent effects of AVP deficiency on impulsivity in the delay discounting paradigm. Furthermore, to investigate the basis of such effects, we assessed possible interactions of AVP deficiency with GABAergic and serotonergic signaling and stress axis activity, systems playing important roles in impulse control. Our results showed that impulsivity was unaltered by AVP deficiency in virgin rats. In contrast a lactation-induced increase in impulsivity was abolished by AVP deficiency in lactating females. We also found that chlordiazepoxide-induced facilitation of GABAergic and imipramine-induced enhancement of serotonergic activity in virgins led to increased and decreased impulsivity, respectively. In contrast, during lactation these effects were visible only in AVP-deficient rats. These rats also exhibited increased stress axis activity compared to virgin animals, an effect that was abolished by AVP deficiency. Taken together, AVP appears to play a role in the regulation of impulsivity exclusively during lactation: it has an impulsivity increasing effect which is potentially mediated *via* stress axis-dependent mechanisms and fine-tuning of GABAergic and serotonergic function.

Introduction

Arginine-vasopressin (AVP) is a peptide hormone produced in the supraoptic and paraventricular nuclei of the hypothalamus (Rhodes et al., 1981; Sokol et al., 1976). Its primary physiological function is to stimulate water retention by increasing the water permeability of the distal tubules of the kidneys (Flamion and Spring, 1990; Wade et al., 1981). However, AVP also acts at vasopressin receptors at several brain areas (Buijs et al., 1978) to regulate a number of neuroendocrine and behavioral processes (Antoni, 1993).

The Brattleboro homozygous recessive rat does not synthesize AVP (Bohus and de Wied, 1998) and is thus a useful model for studying the role of AVP in behavioral processes. Brattleboro rats develop a unique physiological and behavioral profile as a result of lacking a functioning AVP system. Among other things, these rats show normal baseline hypothalamus–pituitary–adrenal (HPA) axis activity and decreased HPA axis reactivity to a variety of stressors (Zelena et al., 2009), slightly reduced anxiety (Fodor et al., 2012) and depression-like behavior (Fodor et al., 2012; Mlynarik et al., 2007). Additionally, they display social deficits (Engelmann and Landgraf, 1994; Feifel et al., 2009; Schank, 2009) and impairments in cognitive performance (Aarde and Jentsch, 2006; Colombo et al., 1992; Varga et al., 2013). The behavioral effects of AVP deficiency are thought to depend on the neuroendocrine state of the individual, e.g. in several cases on the specific physiological conditions during lactation. For example, AVP deficiency does not alter baseline HPA axis activity in virgin females, while it dampens chronic hyperactivity of the HPA axis in lactating female rats (Fodor et al., 2013), an effect that contributes to maternal neglect and mild anxiolysis (Fodor et al., 2012).

Prior work has shown that cognitive performance can be altered by changes in impulsivity (Bizot and Thiebot, 1996). Impulsivity is generally characterized by a failure to resist a drive to respond to environmental stimuli (motor impulsivity) and by responses without consideration of alternatives and/or future consequences (choice impulsivity) (Evenden and Ryan, 1996; Kim and Lee, 2011; Solanto et al., 2001). While it is possible that impulsivity impacts cognitive performance, it is also probable that cognitive and various physiological processes affect impulsivity (Aron, 2007). Thus, as cognitive functions are altered in AVP-deficient rats, one might assume that impulsive behavior is also affected.

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In the present study, firstly we aimed to identify the effects of AVP deficiency on impulsive behavior. As AVP deficiency can alter behavioral processes in a lactation-dependent manner, we also studied possible interactions between AVP activity and lactation in the regulation of impulsivity using virgin and lactating female AVP-deficient and control Brattleboro rats. Specifically, we used the delay discounting paradigm to study impulsive behavior. In this paradigm preference of a delayed, large reward over a smaller, immediate reward is tested with the employment of an operant conditioning procedure. Typically, impulsive individuals tend to choose the latter type of reinforcer in similar paradigms (Adriani and Laviola, 2003; Adriani et al., 2003b; Bizot et al., 1999; Evenden and Ryan, 1996, 1999; Thiebot et al., 1985). Prior to investigations of impulsive behavior, we also assessed cognitive performance of AVP-deficient rats during the training phase of the delay discounting paradigm.

Showing that AVP deficiency decreases impulsivity in lactating rats, our second aim was to assess the basis of such effects. GABAergic and serotonergic signaling play important roles in the regulation of impulsive behavior; pharmacological manipulation of these systems leads to changes in impulsivity (Bizot et al., 1999; Evenden and Ko, 2005). As AVP activity was shown to alter both GABAergic and serotonergic function (Auerbach and Lipton, 1982; Hermes et al., 2000; Ramanathan et al., 2012; Schwarzberg et al., 1981; Wang et al., 2002), we studied whether AVP deficiency exerts its impulsivity altering effects *via* possible GABAergic and serotonergic interactions. To assess such interactions, we investigated impulsive behavior in AVP-deficient virgin and lactating female Brattleboro rats following treatment with a benzodiazepine, which has been reported to increase impulsivity (Evenden and Ko, 2005; Thiebot et al., 1985; Wolff and Leander, 2002), or a selective serotonin reuptake inhibitor, which has been reported to decrease impulsivity in several studies (Bizot et al., 1988; Miyazaki et al., 2011). In addition to measurements of impulsive behavior, HPA axis activity (i.e. corticosterone levels) was also assessed, as the HPA axis has been reported to be altered by AVP deficiency (Fodor et al., 2013; Makara et al., 2012) and to play a role in impulsivity (Torregrossa et al., 2012).

Material and methods

Subjects

We compared AVP-deficient homozygous female rats with homozygous control (+/+) rats. AVP-deficient and control Brattleboro rats came from a colony maintained in our Institute. The breeding stock was started from breeder rats provided by Harlan Laboratories (Indianapolis, USA). The parents of control rats were homozygous for the non-mutated gene, while AVP-deficient subjects originated from breeding pairs composed of AVP-deficient fathers and heterozygous mothers. Heterozygous mothers always derived from control and AVP-deficient parents, to keep the genetic background of the two lines close. Animals were kept on a light/dark cycle of 12 h with the lights on at 0700 h. The temperature and humidity were kept at 23 ± 2 °C and 60 ± 10%, respectively. Virgin female rats were isolated one week before the start of experimentation and housed individually until the end of all experiments. Female rats that were studied during lactation were mated at the age of 75–115 days and were isolated approximately one week before delivery. Female subjects mated with males of different homozygous genotype, i.e. AVP-deficient females mated with control males, while control females mated with AVP-deficient males. With this design the genotype of all pups was heterozygous; therefore, litter genotype did not differ between subjects and it could not alter maternal behavior. Virgin and lactating females were the same age at the time of experimentation. One day after delivery litters were culled to three males and three females to control for the behavioral effects of quantity and quality of pups. Pups were housed with their dam throughout the experiments (except for during experimentation in the delay discounting boxes). Tap water was available ad libitum. Rat chow was limited to 6 pellets a day (approximately 20 g total) to increase exploration during the delay discounting experiments. Food was provided immediately after the daily training/testing sessions. The weight of each rat was measured daily. Food restriction was adjusted where necessary to maintain the rats at a minimum of 80% of their starting weight. Pups were also evaluated daily to monitor their development. All animals survived experimentation and showed no sign of pain or discomfort throughout our studies. All experiments were conducted in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) and were reviewed and approved by the Animal Welfare Committee of the Institute of Experimental Medicine, Budapest, Hungary.

Drugs and doses

The benzodiazepine, chlordiazepoxide (CDP), and the tryciclic antidepressant, imipramine (IMI), were dissolved in saline. These drugs were administered intraperitoneally 15 min (CDP) or 60 min (IMI) before the start of the experiment at a dose of 0 (vehicle) or 10 mg/kg in a volume of 1 ml/kg. The doses, volume, injection routes and pretreatment time were determined based on previous studies (Evenden and Ko, 2005; Evenden, 1998).

Delay discounting apparatus and procedure

Experiments assessing impulsive behavior were conducted using automated operant chambers equipped with two nose-poke holes with infrared sensors and LED lights, a chamber light and a feeder device with a magazine into which food pellets were dropped (Med Associates, St. Albans, VT, USA). Chambers were placed inside sound-attenuated wooden cubicles and were controlled via computers running Med-PC IV software (Med Associates, St. Albans, VT, USA).

During the training phase, animals were placed inside a chamber for 30 min daily for 5 days. A response on one of the nose-poke holes was rewarded with one 45 mg food pellet (small reward), while a response on the other hole resulted in five 45 mg food pellets (large reward). Both types of reward were presented immediately after the response and were followed by a 25 s timeout with the chamber light switched on. Chamber light was used as a cue which could be associated with the reward after responding on one of the nose-poke holes. It is a common practice to associate visual or auditory cues with the feedback to accelerate learning in operant conditioning procedures (Panlilio et al., 2012). During the timeout period, responses were not rewarded but were registered. To avoid side preference, the nose-poke hole on which responding was rewarded with five food pellets was randomly assigned to either the left or the right side between animals. Animals were placed in the same chamber with the same nose-poke hole side assignment throughout the experiment. After each session ended, the chambers were cleaned with 70% ethanol and were dried with paper towels. All experiments were conducted in the early hours of the light phase. At the end of the training phase, the animals were expected to respond on the nose-poke hole that was paired with the large reward in approximately 90% of all trials (Adriani et al., 2003a).

After two days of rest, the animals underwent the test phase. During this phase, each animal was placed in a chamber for 30 min daily for 8 days. The procedure was similar to that described for the training phase, but a delay was inserted before the large reward. The delay was fixed for each daily session and was increased progressively over subsequent days (10, 20, 30, 45, 60, 80, 100 and 120 s). Responses during these delays were not rewarded, but they were recorded by the software. Sessions of the test phase were conducted at the same time as sessions of the training phase. During the test phase, subjects were expected to shift their preference from the nose-poke hole rewarded by the delayed large reward to the nose-poke hole rewarded by the immediate small reward (Adriani and Laviola, 2003; Adriani et al., 2003b).