

The prepulse inhibition deficit appearance is largely independent on the circadian cycle, body weight, and the gender of vasopressin deficient Brattleboro rat

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Objective. A disturbance of sensorimotor gating measured by prepulse inhibition of acoustic startle (PPI) is one of the best tests of the schizophrenia-like behavior. Vasopressin was implicated in the development of schizophrenia; therefore, the naturally occurring vasopressin-deficient Brattleboro rat has been suggested to be a reliable non-pharmacological animal model. However, previous studies focusing on PPI deficit did not use proper control and despite clear gender differences in the development of the disorder, the effect of gender has been mostly neglected.

Methods. First, we compared the „noise” and „tone” type prepulse at 73-77-81 dB intensity during the light or dark phase using small (~150 g) or big (~500 g) Wistar rats. The test parameters were validated by a pharmacological schizophrenia model (30 mg/kg ketamine i.p.). Then male, female, and lactating vasopressin-deficient animals were compared with +/+ ones.

Results. We established that the prepulse “noise” type is not optimal for PPI testing. The cycle of the day as well as the body weight had no effect on PPI. Even if we compared vasopressin-deficient animals with their closely related +/+ controls, the PPI deficiency was visible with more pronounced effect at 77 dB prepulse intensity similarly to pharmacological schizophrenia model. Despite our expectation, the gender as well as lactation had no effect on the vasopressin-deficiency induced PPI deficit.

Conclusions. The present data confirmed and extended our previous studies that vasopressin-deficient rat is a good model of schizophrenia. It seems that female as well as lactating Brattleboro rats are useful tools for testing putative novel antipsychotics in line with special attention required for schizophrenic women.

Key words: schizophrenia, ketamine, male, female, lactation, acoustic startle response

Attention deficit is one of the key symptoms in schizophrenia (Geyer et al. 2001), but it is characteristic for other mental disorders as well, like obsessive compulsive disorder and Gilles de la Tourette’s syndrome (Kohl et al. 2013). One of the widely used diagnostic tools for assessment of attention deficit is the prepulsed inhibition of acoustic startle (PPI). PPI is the reduction of the acoustic startle response

(ASR) when the startle-eliciting stimulus is immediately preceded by a weak, not ASR-inducing stimulus (Swerdlow and Geyer 1998). The advantage of this test is that it can be used both in patients and animal models (Kumari and Sharma 2002).

PPI deficit measurable in pharmacological schizophrenia models are less likely to identify novel mechanisms, therefore other behavioral models are need-

ed (Feifel *et al.* 2011). A nonpharmacological animal model of schizophrenia is the vasopressin (AVP)-deficient Brattleboro rat (*di/di*), the naturally occurring model of genetic AVP deficiency. AVP, beside its well known role in salt-water homeostasis (Decaux *et al.* 2008), is a key player in the regulation of complex social behaviors in mammals (e.g. aggression, pair bonding and parental behavior, memory, social recognition) (Caldwell *et al.* 2008; Fodor *et al.* 2014). The AVP-deficient Brattleboro rats have a number of social and cognitive abnormalities (Engelmann and Landgraf 1994) resembling a schizophrenic-like behavior.

Indeed, alterations in AVP gene or its receptors have already been linked to the development of schizophrenia (Levin *et al.* 2009; Teltsh *et al.* 2012; Golimbet *et al.* 2015). Moreover, previous studies have reported lower AVP release in schizophrenic patients (Frederiksen *et al.* 1991; Mai *et al.* 1993; Ohsawa *et al.* 1993; Elman *et al.* 2003; Jobst *et al.* 2014; Rubin *et al.* 2014); however, others have found enhanced AVP levels (Linkowski *et al.* 1984; Goldman *et al.* 1997). The results with AVP agonist treatments were also contradictory with significant improvement in some (Forizs 1952a,b; Bakharev *et al.* 1984; Brambilla *et al.* 1986; Brambilla *et al.* 1989; Hosseini *et al.* 2014), while questionable results in other cases (Korsgaard *et al.* 1981; Iager *et al.* 1986).

Nevertheless, the PPI deficit, the most studied characteristic of schizophrenia-like behavior of Brattleboro rat, was consequently present (Feifel and Priebe 2007), and restored by a wide range of antipsychotics, e.g. haloperidol (Feifel and Priebe 2001), clozapine (Feifel *et al.* 2004; Cilia *et al.* 2010), risperidone (Feifel *et al.* 2007) or chlorpromazine (Feifel *et al.* 2011). However, the results should be taken with caution, as AVP-deficient animals were compared with Long Evans rats, although the mutation in this strain occurred more than 50 years ago. Thus, the strain differences may confound the effect of AVP and *di/di* rats should be compared to their close relative *+/+* animals (Bohus *et al.* 1998).

Moreover, most of these tests have been performed in male subjects, although a clear gender difference exists in the prevalence, development, and progression of schizophrenia (Mendrek 2015). Among others, female patients with schizophrenia tend to have a more benign course and better outcomes than males (da Silva and Ravindran 2015). Previous reports have indicated gender difference in ASR (Reilly *et al.* 2009) and PPI (Lehmann *et al.* 1999) also in rats. Most schizophrenia research forgot about women altogether, possibly because of the greater prevalence

of schizophrenia in men than women during the first half of life. However, there is a second peak of new cases in women around the age of menopause. Moreover, the prime age of onset for schizophrenia in women is during the childbearing years from ages 25–35 and indeed, 50–60% of these women will become pregnant (Robinson 2012). Thus, schizophrenic women require special attention (Seeman 2013). Therefore, we aimed to compare PPI deficit in male, female, and lactating Brattleboro rats using *di/di* and *+/+* animals of the Brattleboro strain.

Before starting the investigation, we had to choose a proper protocol as differences in the test parameters may lead to discrepancies between studies (Feifel *et al.* 2011). Based upon extensive literary search, we established that in all cases the test starts with a 5 min habituation period. The startle inducing pulse was mostly a 40 ms (may vary between 20–50 ms) noise type 120 dB (sometimes 105, 110 or 115 dB) pulse and was repeated 3–5 times to get a stable response. Then, a random block was introduced with no stimulus, 120 dB pulse alone and different prepulse intensity preceding by 100 ms the pulse (interstimulus interval-ISI). Most authors used not only one, but also more prepulse intensity varying between 68–89 dB (or 3–24 dB above a 65 dB background). Therefore, we have chosen to test three prepulse intensities throughout as the most studied and effective ones (73, 77 and 81 dB). In case it was reported, the type of prepulse was mostly also “noise”; however, it had to be tested whether the type has an influence on the startle response *per se*. The intertrial interval (ITI) varied between 10 and 20 s not only between authors, but also mostly within a single section with an average of 15 s.

Rodent are nocturnal animals, therefore most of the behavioral test should be preferably done during the dark, i.e. active phase. Indeed, in rats several reports have indicated a robust increase in acoustic startle amplitude during the dark vs. the light phase (Horlington 1970; Chabot and Taylor 1992; Frankland and Ralph 1995), although subsequent studies did not confirm this assumption (Weiss *et al.* 1999a,b). Little is known about the circadian modulation of PPI, despite the fact that changes in the locomotion influenced by the circadian cycle may substantially contribute to PPI (Weiss *et al.* 1999a,b). Some authors have reported that at higher prepulse intensities rats tested during the dark phase elicited higher PPI (Adams *et al.* 2008). Interestingly, in human, melatonin administration, mimicking the dark inactive phase, has been found to reduce the startle magnitude without influencing the PPI (Lehtinen *et al.* 2014).

One further important issue is the weight of the animals, as di/di rats at the same age are smaller than their counterparts (Mlynarik et al. 2007) and many manipulations may induce weight differences, which may confound the outcome of the PPI test (Pulliam et al. 2010; Jiang et al. 2011; Le et al. 2014).

Thus, we started our examination with testing the effect of prepulse type “noise”–“tone” followed by studying the effect of circadian cycle and body weight on acoustic startle and PPI, than confirmed the chosen parameters with a known pharmacological schizophrenia model (ketamine, Yang et al. 2010) and finally examined male, female, and lactating Brattleboro rats.

Materials and Methods

Animals. Male Wistar rats (Exp. 1–4) were bought from Charles River Laboratory (Budapest, Hungary). Brattleboro rats (Exp. 5–6) were maintained in the Institute of Experimental Medicine (Budapest, Hungary) in a colony originating from commercially available breeder rats (Harlan, Indianapolis, IN, USA). They were kept under a light/dark cycle of 12 h with the lights on at 07:00 h (except Exp. 2: half of the animals were kept in reversed cycle with lights off at 10:00 for at least 10 days prior experimentation) and temperature and humidity were kept at $23\pm 2^\circ\text{C}$ and $60\pm 10\%$, respectively. For Exp. 5–6 we compared AVP-deficient homozygous (di/di) with homozygous (+/+) control rats. The control line was bred out from the Brattleboro line. After mating heterozygous (di/+) males and females and separating the homozygous di/di animals from the offspring, the remaining +/+ or di/+ animals were bred with di/di males and females. The parents used for the +/+ and di/+ line are closely related to each other (di/+ mothers are the daughters of +/+ mothers), keeping the genetic background of the two lines as close as possible (Zelena et al. 2009). Male and female virgin rats (Exp. 5) were isolated one week before starting the experimentation and kept individually until the end of the experiments. As it has been previously reported that estrous cycle does not influence the PPI, we did not check the cycle of the animals (Adams et al. 2008). Female rats, which were studied during lactation (Exp. 6), were mated at the age of 75–115 days and were isolated approximately 1 week before delivery. One day after delivery, the pups were reduced to 3 male and 3 female individuals that were kept with their mother throughout the experiments (except experimentation in the prepulse inhibition boxes at day 19–21 of lactation). Tap water and rat chow were

available *ad libitum*. Pups were also daily measured to monitor their development. All manipulations of the animals were approved by the local committee for animal health and care and performed according to the European Communities Council Directive recommendations for the care and use of laboratory animals (2010/63/EU).

Prepulse inhibition apparatus and procedure. The Colbourne Instruments Acoustic Startle setup was used in our experiments. After a weight calibration, the subjects were placed in a test cage on the instrument measuring the startle response (by recording small changes in weight) inside a sound attenuated chamber. Following 5 min of habituation, the subjects were presented a 40 ms long, 120 dB acoustic stimuli (“noise”, referred as pulse) for five times in every 20 s to standardize startle. Five trial types were then presented during testing: pulse alone, pulse preceded 80 ms by a 20 ms prepulse (“tone” type) of varying intensity (73, 77 or 81 dB), and a trial with no prepulse and 0 dB pulse. Trials were repeated until every type of trials was presented five times. Different animals received different trial types in a different, randomized order. The program automatically recorded the startle response. Response to the 0 dB pulse was the weight of the subject and was subtracted from subsequent startle response data. Mean of the startle response to the 120 dB pulse without prepulse was calculated for every subjects and served as ASR. Moreover, it was considered 100%, from which prepulse inhibition (PPI) was calculated by the following formula: $\text{PPI} = 100 - (\text{startle after prepulse} / \text{startle without prepulse} * 100)$. Mean PPI values were given for different prepulse intensities.

Experiment 1. Characteristic of the prepulse. Additional three trials were included in the above described PPI test (prepulse without pulse, 73, 77 or 81 dB), and the prepulse was either “noise” type (similar to pulse) or “tone” type.

Experiment 2. Lighting. The animals were kept under standard condition or in reversed cycle. Thus, the test was conducted during the early hours of the light or dark phase.

Experiment 3. Weight. Animals weighing 161.8 ± 9.4 g (small) were compared to 520.5 ± 9.55 g (big) rats.

Experiment 4. Pharmacological treatment. An NMDA antagonist (ketamine 30mg/kg i.p.) was used right before the beginning of the test.

Experiment 5. Male and female Brattleboro rats were compared.

Experiment 6. Lactating Brattleboro mothers were also tested.

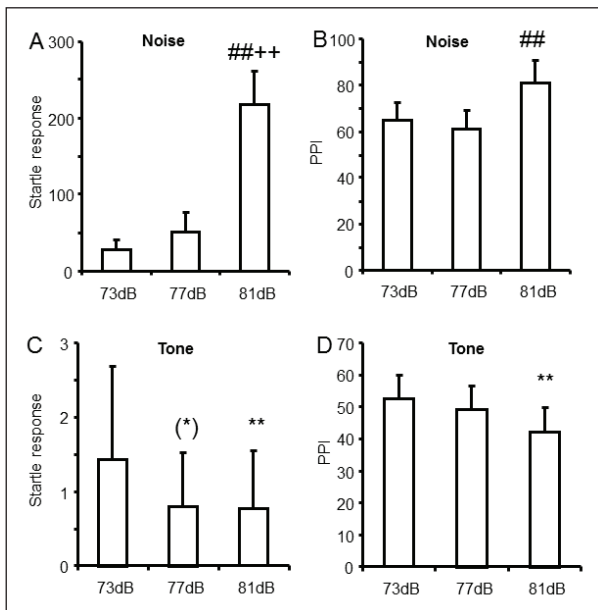


Figure 1. The effect of different type prepulse on acoustic startle response (ASR) and prepulse inhibition (PPI). A-B: “noise” type prepulse; C-D: “tone” type prepulse (n=12). *p<0.05, **p<0.01 vs. “noise”; ##p<0.01 vs. 73 dB and 77 dB; +++p<0.01 difference from 0 according to single sample t-test

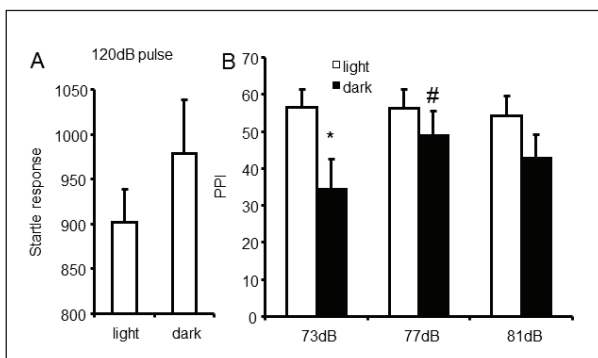


Figure 2. The effect of the circadian cycle on acoustic startle response (ASR) and prepulse inhibition (PPI). (n=10) *p<0.05 vs. light; #p<0.05 vs. 73 dB

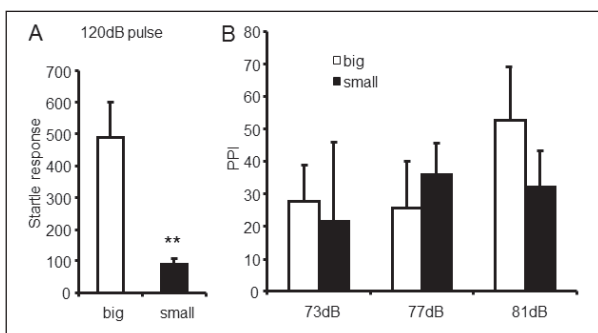


Figure 3. The effect of body weight on acoustic startle response (ASR) and prepulse inhibition (PPI). (n=10) **p<0.01 vs. big

Statistical analyses. Data were presented as mean \pm standard error of the mean. Behavioral variables were analyzed with one-way (factor: character, light, weight, treatment or genotype), two-way (factors: gender, genotype) or repeated measure (different prepulse intensity) ANOVA. The Newman Keuls test was performed for post-hoc analysis when main effect was significant. Characteristic of the prepulse was analyzed by t-test (prepulse only, difference from 0). The p-values lower than 0.05 were considered statistically significant.

Results

Experiment 1. Specificity of the prepulse type.

The “noise” type prepulse induced significant ASR per se ($F_{(2,22)}=34.5, p<0.01$) (Figure 1A), which elevated with increasing prepulse intensity similarly to the PPI response ($F_{(2,22)}=6.29, p<0.01$) (Figure 1B). Indeed, single sample t-test revealed marginally significant effect of “noise” type prepulse at intensity of 73 dB ($p=0.07$) and 77 dB ($p=0.05$), while at 81 dB, the effect became significant ($p<0.01$). The highest levels were detectable after 81 dB prepulse compared both to 70 and 77 dB. On the other hand, “tone” type prepulse intensity had no effect either on ASR or PPI (Figure 1C,D). The difference between „noise” and „tone” ASR was significant ($F_{(2,21)}=7.67, p<0.01$), which became bigger with increasing intensity (prepulse intensity: $F_{(2,42)}=12.52, p<0.01$; type and intensity interaction: $F_{(2,42)}=18.2, p<0.01$) being marginally significant at 77 dB prepulse ($p=0.08$), significant at 77 dB ($p=0.05$) and highly significant at 81 dB ($p<0.01$). For PPI, there was an interaction between prepulse intensity and the type of the prepulse ($F_{(4,42)}=3.15, p<0.05$) with significant difference only at 81 dB prepulse ($p<0.01$). According to definition, prepulse alone does not induce ASR; therefore, for all subsequent studies we used a “tone” type prepulse.

Experiment 2. Circadian changes. There was no significant difference between the ASR in rats tested during the light or dark phase (Figure 2A). There were no significant difference between the PPIs after different prepulse intensities in animals tested during the light phase (Figure 2B). Interestingly, animals during the dark phase responded to 77 dB stimulation with the highest PPI (effect of intensity: $F_{(2,18)}=4.10, p<0.05$, significant difference between 73 dB and 77 dB). On the other hand, at the lowest intensity (73 dB), the animals from the light phase showed significantly higher PPI levels than rats from the dark phase ($p=0.03$). As higher PPI can be more easily manipulated, testing PPI during the light phase (as we did in subsequent studies) seems to be beneficial.

Experiment 3. Effect of body weight. In line with a significant difference in the body weight ($F_{(1,18)}=517.4$, $p<0.01$), the startle response of the smaller animals were significantly lower ($F_{(1,18)}=12.93$, $p<0.01$) (Figure 3A). On the other hand, body weight did not influence the PPI responses (Figure 3B).

Experiment 4. Pharmacological schizophrenia model. Ketamine (30 mg/kg) administration before the test had no effect on ASR (Figure 4A). On

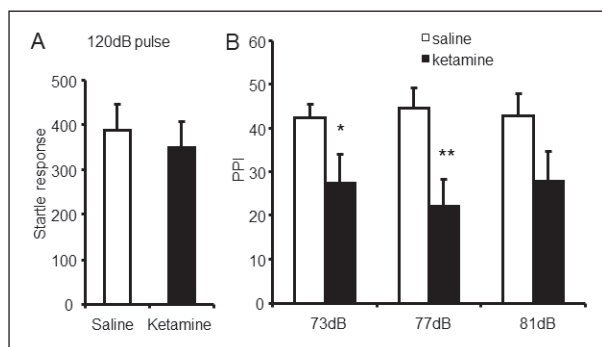


Figure 4. The effect of ketamine (30 mg/kg in saline i.p. right before the test) on acoustic startle response (ASR) and prepulse inhibition (PPI). (n=10) * $p<0.05$, ** $p<0.01$ vs. saline

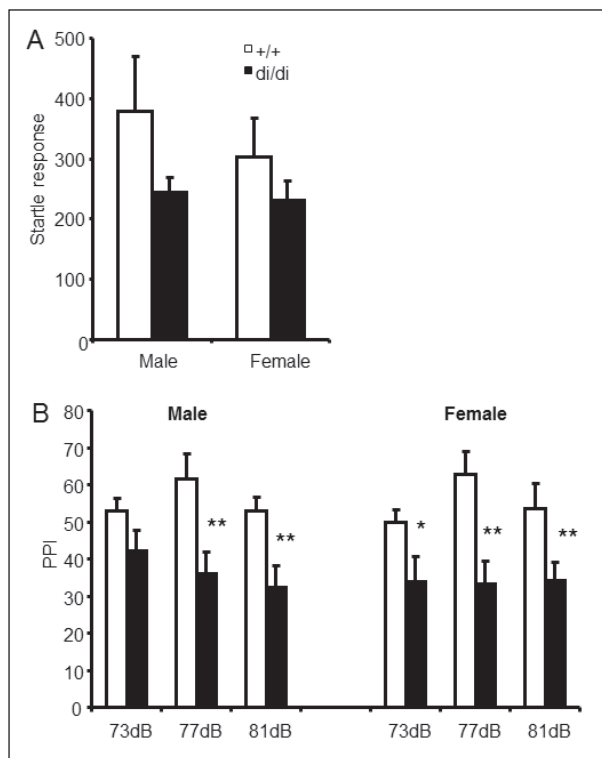


Figure 5. The effect of gender on acoustic startle response (ASR) and prepulse inhibition (PPI) in vasopressin (AVP)-deficient (di/di) Brattleboro rat. (n=10) * $p<0.05$, ** $p<0.01$ vs. +/+

the other hand, there was a significant reduction of the PPI ($F_{(1,18)}=7.59$, $p=0.01$) (Figure 4B). Specifically, at 73 dB prepulse intensity the effect was significant ($p<0.05$), at 77 dB highly significant ($p<0.01$), while at 81 dB prepulse intensity there was only a marginal effect ($p=0.09$).

Experiment 5. Male and female Brattleboro rats. AVP-deficient di/di animals tend to react to pulse with smaller ASR amplitude, however, the difference did not reach the level of significance ($F_{(1,36)}=3.03$, $p=0.08$) (Figure 5A). On the other hand, PPI deficit was clearly present in both gender ($F_{(1,36)}=25.47$, $p<0.01$) (Figure 5B). The highest difference between +/+ and di/di animals was detectable after 77 dB prepulse, while in the case of 73 dB prepulse – despite significant main effect of genotype ($F_{(1,36)}=7.25$, $p=0.01$) – in males the posthoc comparison did not show significant alterations. Neither of the studied parameters showed any gender related changes.

Experiment 6. Lactating Brattleboro rats. In lactating animals, the lack of AVP did not influence the ASR (Figure 6A), but the PPI was significantly lower in di/di animals ($F_{(1,18)}=8.54$, $p<0.01$) (Figure 6B). More specifically, at 77 dB prepulse intensity the difference between genotypes was highly significant ($p=0.01$), with lower difference at 73 dB prepulse intensity ($p=0.03$), while with 81 dB prepulse intensity the difference was at the border of being significant ($p=0.05$). Although both the ASR amplitude (female +/+: 303.5 ± 64 ; lactation: 454.9 ± 65) and PPI deficit (73 dB prepulse: female +/+: 49.8 ± 3.4 ; lactation: 65.2 ± 6.2 ; 77 dB prepulse: female +/+: 62.9 ± 5.9 ; lactation: 69.2 ± 4.5 ; 81 dB prepulse: female +/+: 53.6 ± 6.6 ; lactation: 67.1 ± 6.3) was somewhat higher in lactating than female rats, direct statistical comparison cannot be made as these measures were done in separate experiments.

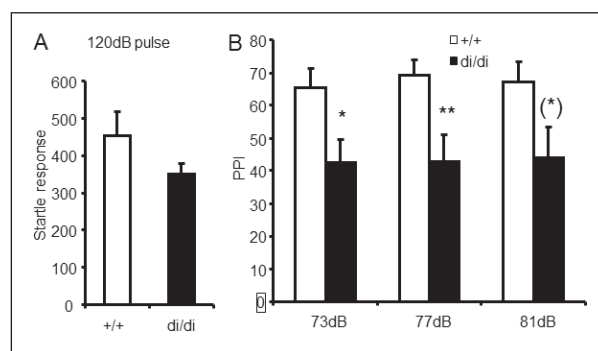


Figure 6. The effect of lactation on acoustic startle response (ASR) and prepulse inhibition (PPI) in vasopressin (AVP)-deficient (di/di) Brattleboro rat. (n=10) (*) $p=0.05$, * $p<0.05$, ** $p<0.01$ vs. +/+

Discussion

Regarding the PPI parameters, we established that 1) “noise” type prepulse is not optimal for PPI testing; 2) the cycle of the day had no effect on ASR and influenced the PPI only at lower prepulse intensity (73 dB) with lower level during the dark phase; 3) the smaller body weight reduced the ASR only, without any effect on PPI. Thus, our results roughly confirm the work of Weiss and collaborators (1999a,b), indicating that the circadian cycle has no effect on ASR as well as on PPI. Despite differences in ASR among animals with different weight, their PPI deficit was similar, thus the schizophrenia-like measure, PPI can be studied even after interventions inducing changes in body weight. 4) Indeed, the schizophrenia-like nature of PPI-deficit (Kumari and Sharma 2002) was further confirmed in a widely used pharmacological animal model, the N-methyl-D-aspartate antagonist administration (ketamine) with most robust effect at 77 dB prepulse intensity.

In respect to the AVP-deficiency, we can conclude that even if *di/di* animals were compared with their closely related *+/+* controls, the PPI deficiency was

clearly visible without any effect on ASR. This effect was more pronounced at 77 dB prepulse intensity similarly to the most robust effect seen in the pharmacological schizophrenia model (ketamine). Thus, our results confirmed the data of previous studies that AVP-deficient Brattleboro rat is a good non-pharmacological model of schizophrenia and is useful for testing of novel antipsychotics (Feifel and Priebe 2001; Feifel *et al.* 2004; Shilling *et al.* 2006; Feifel *et al.* 2007; Cilia *et al.* 2010). Despite our expectation, the gender as well as lactation had no effect on AVP-deficiency-induced PPI deficit. In line with enhanced impulsivity (Aliczki *et al.* 2014) in comparison to virgins, lactating rat tended to react to an acoustic stimulus with enhanced ASR. Our results are in agreement with Feifel and collaborators (2011), who have compared male and female animals and found that the AVP-deficiency-induced schizophrenia-like behavior was similarly present in both gender. Thus, it seems that female as well as lactating Brattleboro rats are useful models for testing the putative antipsychotics in line with special attention required for schizophrenic women (Seeman 2013).

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