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The effects of juvenile capsaicin desensitization in rats: Behavioral impairments

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HIGHLIGHTS

- Juvenile capsaicin desensitization did not change pain thresholds.
- Treatment increased urinary bladder capacity and morphine-induced antinociception.
- Desensitization disturbed memory and motor but not sensorimotor gating functions.
- Desensitized animals showed impairment in thermoregulation.
- Capsaicin desensitization influenced several parameters related to schizophrenia.

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ABSTRACT

Capsaicin desensitization leads to behavioral changes, some of which are related to schizophrenia, but investigations into these effects have been scarce. The goal of this study was to characterize the consequences of juvenile capsaicin desensitization on different functions: acute and inflammation-induced thermal and mechanical sensitivity, urinary bladder capacity and thermoregulation, and also on the potentially schizophrenia-related impairments in sensory-motor gating, motor activity and cognitive functioning.

Male Wistar rats desensitized with increasing doses of subcutaneous capsaicin after weaning were investigated. Heat and mechanical pain sensitivity did not change significantly; however, morphine produced a prolonged decrease in the nociceptive response to inflammation in desensitized animals. Ultrasound examination of the bladder revealed enhanced bladder volume in treated animals.

Capsaicin-treated animals had higher body temperature at 22 °C in both dark and light periods, and they also showed prolonged hyperthermia in new environmental circumstances. Warm environment induced a profound impairment of thermoregulation in desensitized animals. The treated animals also showed higher levels of activity during the active phase and at both cool and warm temperatures.

The amplitude of the responses to auditory stimuli and prepulse inhibition did not differ between the two groups, but the desensitized animals showed learning impairments in the novel object recognition test.

These results suggest that juvenile capsaicin desensitization leads to sustained changes in several functions that may be related to schizophrenia. We propose that capsaicin desensitization, together with other interventions, may lead to an improved chronic animal model of schizophrenia.

1. Introduction

Vanilloids, such as capsaicin, exert complex pharmacological effects at transient receptor potential vanilloid-1 (TRPV1) receptors, producing an initial activation followed by a long-lasting desensitization of the channel [44,53]. The extensive distribution of TRPV1 receptors in the brain raised the possibility that this receptor could play a significant role in the central nervous system (CNS). It is suggested that TRPV1 receptors might take part in the pathogenesis of several disorders such as Parkinson's and Alzheimer's diseases, depression, anxiety and schizophrenia [7,14,40,45,51]. The dopaminergic dysfunction in schizophrenia is well-known, and TRPV1 receptors can regulate this system by striatal endocannabinoid neurotransmission [58]. It is also known that the cognitive and motor functions, and sensory-motor gating are disturbed in schizophrenia, however, only a few studies have investigated the effects of capsaicin desensitization on these processes [6,45].

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We applied capsaicin desensitization three weeks after birth, before the termination of the development of the central and peripheral nervous systems in the rat [50]. Earlier results suggested that capsaicin-induced neurodegeneration in specific brain sites declines progressively during maturation [48]. During postnatal development, sensory experiences play a critical role in the refinement of cortical connections. Therefore, degeneration of central axons and terminals of peripheral sensory neurons may lead to intrinsic somatosensory deprivation, which, in turn, could lead to functional and structural alterations in the CNS. Given that there is some evidence to suggest that schizophrenia might be connected with environmental and developmental disturbances at young age, we assumed that juvenile capsaicin desensitization might produce significant changes in behavioral profiles related to schizophrenia. However, as data are scarcely available about the effects of juvenile desensitization [25], the primary aim of this study was to characterize the influence of post-weaning high dose capsaicin treatment on various functions proven to be affected by TRPV1 receptor systems, such as pain sensitivity, inflammation, urinary bladder function and thermoregulation. The secondary aim was to investigate the effects of juvenile desensitization on behavioral parameters impaired in schizophrenia, such as sensory-motor gating, motor activity and memory function.

2. Materials and methods

2.1. Animals

All procedures were carried out with the approval of the Ethical Committee of the University of Szeged, Faculty of Medicine. Twenty-one-day-old male Wistar rats were injected with increasing doses (10, 20, 50 and 100 mg/kg subcutaneously) of capsaicin under ketamine and xylazine (72 and 8 mg/kg intraperitoneally, i.p. respectively) anesthesia through 4 days. Control animals received vehicle. The body weight of the animals was recorded on a weekly basis during the study.

2.2. Drugs

Drugs used in the study were: capsaicin (Plantakem Kft, Sándorfalva, Hungary), ketamine hydrochloride (Calypsol, Richter Gedeon Rt., Budapest, Hungary), xylazine hydrochloride (Rompun, Bayer, Leverkusen, Germany), gentamicin (Sanofi-Aventis, Budapest, Hungary), dexmedetomidine hydrochloride (Orion-Pharmos Pharmaceuticals Turku, Finland), λ-carrageenan (Sigma-Aldrich Kft., Budapest, Hungary) and morphine hydrochloride (Teva Zrt, Debrecen, Hungary). Capsaicin was dissolved in 10% Tween 80 and 10% ethanol. All the other substances were dissolved in saline.

2.3. Wiping test

To confirm the desensitization following capsaicin treatment, we assessed responses to corneally-applied capsaicin (1 drop of 0.001% capsaicin) into one of the eyes of the animals at least 5 weeks after the desensitization by recording the number of front paw eye wipes over a 30-second period.

2.4. Assessment of mechanical and thermal sensitivity

Mechanical sensitivity was assessed with a Dynamic Plantar Aesthesiometer (automatic von Frey test; Ugo Basile, Italy). Incremental force (from 0 to 50 g in 8 s) was applied to the plantar surface of both hindpaws through a mesh base.

To determine the heat pain threshold, the paw-withdrawal test (PWD) was used [20]. In this test, heat stimulation is applied to each hindpaw, and the time until the animal withdraws the tested paw is measured. At the age of 10 weeks baseline values of joint diameter, mechanical sensitivity and thermal sensitivity were recorded. Thereafter, unilateral inflammation was induced by intraarticular injection of carrageenan (300 μg/30 μl saline) into the right ankle joint [41]. The measurements were repeated 3 h after the injection, then the animals were treated with 3 mg/kg morphine, s.c., and the mechanical and thermal nociceptive thresholds were determined at 30-min intervals for 90 min. Joint diameter was also measured at the end of the experiment.

2.5. Ultrasound examination of the urinary bladder

The method was based on our earlier study [28]. At the age of 12 weeks, the rats were anesthetized with dexmedetomidine (150 μg/kg, s.c.), which has long-lasting hypnotic anesthetic effects; furthermore, it produces diuresis and overflow incontinence which allows for the ultrasound examination of the urinary bladder. We used sonography — 7.5 MHz linear passed array transducer (Hitachi EUB 405), and the bladder volume was estimated from a longitudinal and a transverse image section by substituting the diameters into the ellipsoid equation formula, and it was corrected for 100 g body weight (relative bladder volume: RV). Bladder volume was assessed when the first urine drop appeared, and two more times with 30-min intervals in each animal.

2.6. Prepulse inhibition (PPI)

At the age of 12 weeks, PPI of the acoustic startle response was measured, as described previously [2]. Rats were allowed to habituate to the background noise (70 dB) for 10 min, and immediately thereafter animals were exposed to three different types of trials: *pulse alone* (*PA*), in which a 40 ms white noise burst was applied at 95 dB to elicit the startle reflex; *prepulse alone* (*PPA*), 20 ms 76 dB; and *prepulse-pulse pair* (*PP*), that is a prepulse stimulus followed by the acoustic startle-eliciting stimulus with a latency of 150 ms. All conditions were presented 10 times. Interstimulus intervals ranged from 7 to 13 s. Between each trial, there was a 10 minute resting period. %PPI values were calculated as percentages using the following formula:

$$\%PPI = [1 - (\textit{startle response for PP trial}) / (\textit{startle response for PA trial})] \times 100\%.$$

2.7. Novel object recognition (NOR) test

NOR test was conducted in a Plexiglas box (60 × 34 × 33 cm) without bedding at the age of 7 weeks. Toy brick towers (Lego Group, Billund, Denmark) with similar size (8 × 2 × 3 cm) were used as test objects. The rats were habituated to the testing room for 60 min prior to the beginning of the experiments.

The following parameters were scored in each phase (habituation, sample and test phases): frequency of occurrence of stereotypic behaviors (such as rearing and self-grooming), and the time of exploratory activity and inactivity. *Habituation phase*: During a single 10 minute session, each rat was allowed to explore the open field without any objects. *Sample phase*: 1 min after the habituation, the sample phase began. Two identical objects were mounted in the open field. Rats were allowed to explore them for 5 min. *Test phase*: At the end of the sample phase, each rat was returned to their home cage for a 1 hour interphase interval. Thereafter, one of the objects was replaced with another visually non-identical one, and rats were placed back to the arena for a 5 minute test phase.

2.8. Telemetry

This device is appropriate to monitor abdominal temperature and gross locomotor activity in freely moving animals (Respironics, Mini Mitter, Vitalview, Oregon, USA). Animals at the age of 9 weeks were peritoneally implanted with Mini Mitter transmitters and received gentamicin (10 mg/kg, s.c.) under ketamine–xylazine anesthesia. After a one-week recovery period the animals were housed individually, and their cages were placed in an isolated room maintained at 22 °C with a 6:00 a.m.-18:00 p.m. light cycle. Body temperature and motor activity

were monitored continuously for 5 days at normal room temperature (22 °C). For ambient temperature challenge, on the sixth day the animals were exposed to decreased room temperature (17 °C) for 4 h, while on the seventh day to 27 °C for 5 h starting at 8:00 a.m.

In the first series of experiments, the animals were involved in the pain tests and the ultrasound examination. Three additional groups of animals took part in prepulse inhibition, novel object recognition tests or telemetry.

2.9. Statistical analysis

Data are presented as means ± SEM. One- and two-way ANOVA with repeated measures and the Fisher-LSD post hoc test were used for the evaluation of the effects of capsaicin desensitization on the different parameters. A p-value of less than 0.05 was considered significant. Data were analyzed using STATISTICA 11 software (Statsoft Inc., Tulsa, OK, USA). In the case of the telemetric experiment, sampling frequency was set to 1 min.

3. Results

All of the animals survived capsaicin desensitization with this dose regimen, suggesting that this method is non-lethal for juvenile animals. The ANOVA of body weight revealed a significant effect of time but not for treatment, thus capsaicin-treated animals had similar body weight as the control animals (data are not shown). Regarding the effects of the capsaicin eye drop, it produced blepharospasm and violent wipes of the eye in control, but not in the capsaicin-treated animals, confirming desensitization (data are not shown).

3.1. Mechanical and thermal pain sensitivity

Before the inflammation no significant differences were observed between the two groups on acute pain sensitivity either on the PWD or von Frey tests (Fig. 1).

Regarding the inflammatory effects of carrageenan, ANOVA with repeated measures revealed a significant effect of side ($F_{1,34} = 593$; $p < 0.001$), time ($F_{2,68} = 274$; $p < 0.001$) and their interaction ($F_{2,68} = 245$; $p < 0.001$). Thus, carrageenan caused a significant increase in the cross-section are of both groups; however, the degree of the edema was significantly larger in the capsaicin-treated animals (data are not shown).

Regarding the threshold for mechanical allodynia, significant effects of treatment ($F_{1,35} = 11.0$, $p < 0.005$), side ($F_{1,35} = 90.2$; $p < 0.001$), time ($F_{4,140} = 50.6$; $p < 0.001$) and their interactions were observed. Post-hoc comparison revealed that juvenile capsaicin desensitization resulted in a slightly decreased mechanical allodynia ($p = 0.13$), while the anti-allodynic effect of morphine was significantly prolonged in desensitized animals (Fig. 1a). On the non-inflamed side, significant increases in the withdrawal threshold were observed in both groups after morphine administration (Fig. 1b).

In the case of thermal hyperalgesia, significant effect of treatment ($F_{1,35} = 19.0$, $p < 0.001$), side ($F_{1,35} = 14.8$; $p < 0.001$), time ($F_{4,130} = 31.4$; $p < 0.001$) and their interactions were observed. Carrageenan resulted in a similar degree of thermal hyperalgesia in both

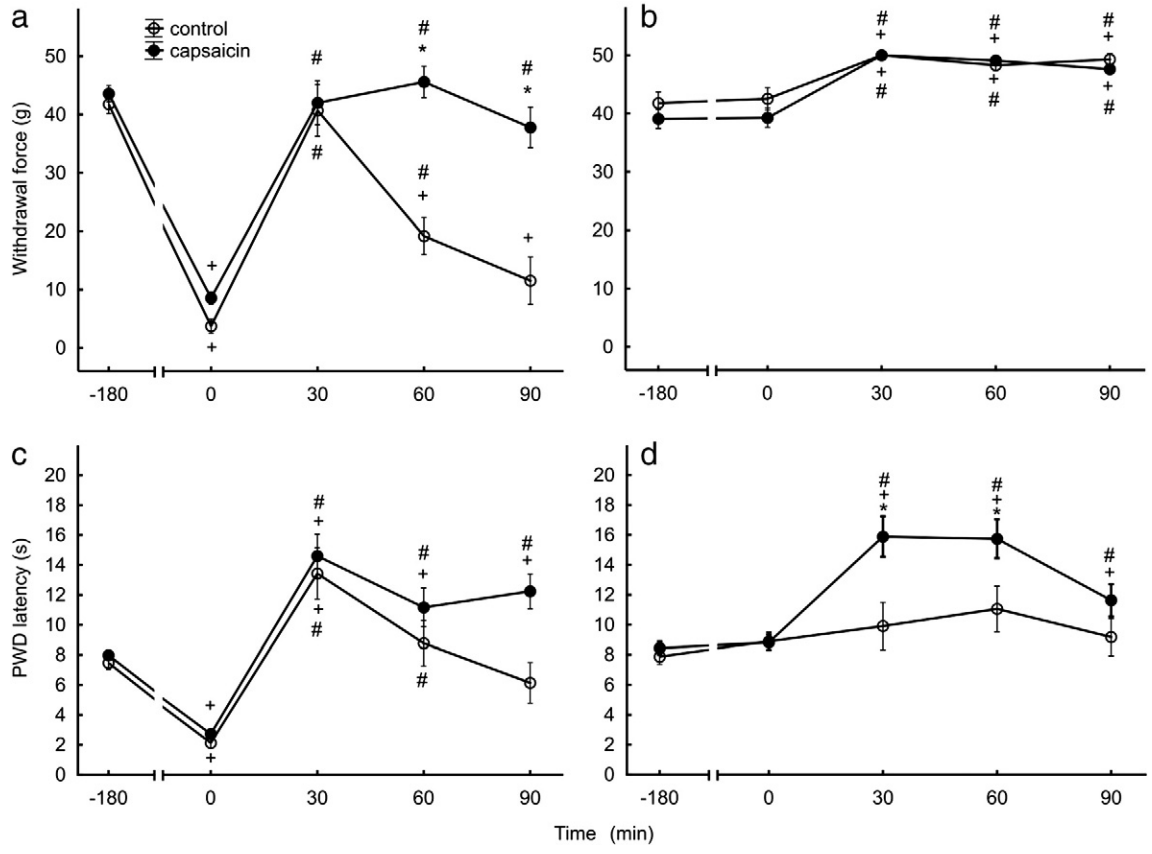

Fig. 1. Mechanical (a, b) and thermal (c, d) pain thresholds before (−180 min) and after (0 min) carrageenan administration, and the effect of morphine (3 mg/kg, s.c.) on the inflamed (a, c) and non-inflamed (b, d) sides. Data are presented as means ± SEM; n = 8–11. The symbols denote significant differences: * from control group, + from pre- and # from post-carrageenan values.

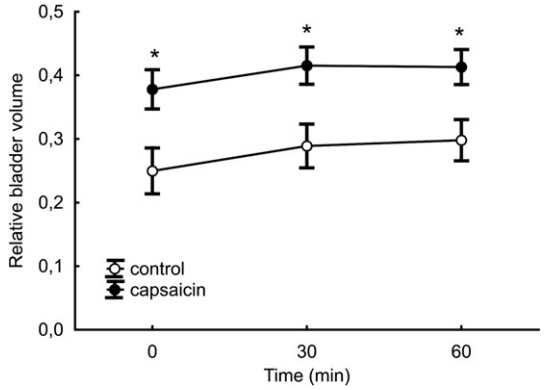

Fig. 2. Relative urinary bladder volume determined by ultrasound examination at the beginning of urine dribbling (0 min), 30 and 60 min later. Data are presented as means ± SEM; n = 8–11. The symbol * denotes significant differences from control group.

groups. Morphine caused a significant increase in PWD latency on the inflamed side with a more prolonged effect in the desensitized group (Fig. 1c). Furthermore, morphine caused a significant increase in the nociceptive threshold on the non-inflamed paw in the capsaicin-pretreated animals (Fig. 1d).

3.2. Urinary bladder volume

The first urine drop appeared about 20 min after the dexmedetomidine administration. Urine dribbling was observed almost continuously, suggesting a continuous overfilling of the bladder. As for the effect of capsaicin desensitization on bladder capacity, ANOVA with repeated measures revealed a significant effect of treatment ($F_{1,17} = 8.8$; $p < 0.01$) and time ($F_{2,34} = 4.6$; $p < 0.05$), thus capsaicin treated animals had larger bladder volumes compared to the control group (Fig. 2).

3.3. Prepulse inhibition

Repeated measures ANOVA of the relative startle reaction (referred to the body weight) revealed a significant effect of prepulse stimuli ($F_{1,16} = 68.95$, $p = 0.001$), but not of treatment. Capsaicin-treated animals (n = 10) showed similar startle reflex amplitude elicited by PA or PP compared to the control group (n = 8); the response amplitude significantly decreased in both groups with PP; therefore, the %PPI did not show significant differences between the two groups (data are not shown).

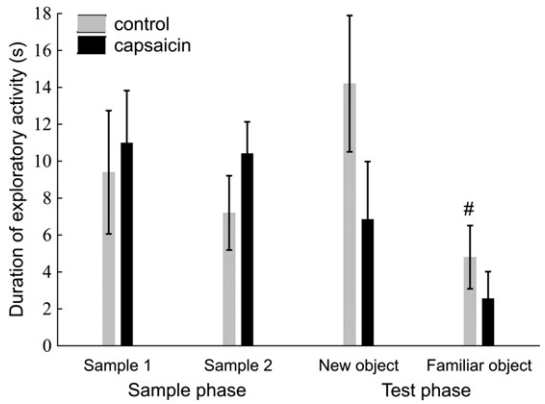

Fig. 3. Object exploratory activity in the sample and test phases of NOR test. Data are presented as means ± SEM; n = 5–7. The symbol # indicates significant differences in the exploration time between the familiar and novel objects.

3.4. Novel object recognition test

No significant difference was observed in the rearing and grooming behaviors and inactivity in any phases between the two groups (data are not shown). In the sample phase, no significant differences were observed in the time spent exploring the two identical objects between the groups (Fig. 3). In the test phase, the time of the novel object exploration was significantly longer than that of the familiar one in control animals ($p < 0.01$), while this difference was not significant in the desensitized group.

3.5. Thermoregulation and motor activity

Abdominal core temperature, independently of treatment, showed a clear-cut daily rhythm with night maxima and day minima. The analysis of the mean values of dark and light phases showed a significant effect of phase ($F_{1,62} = 9.00$, $p < 0.005$) and treatment ($F_{1,62} = 22.00$,

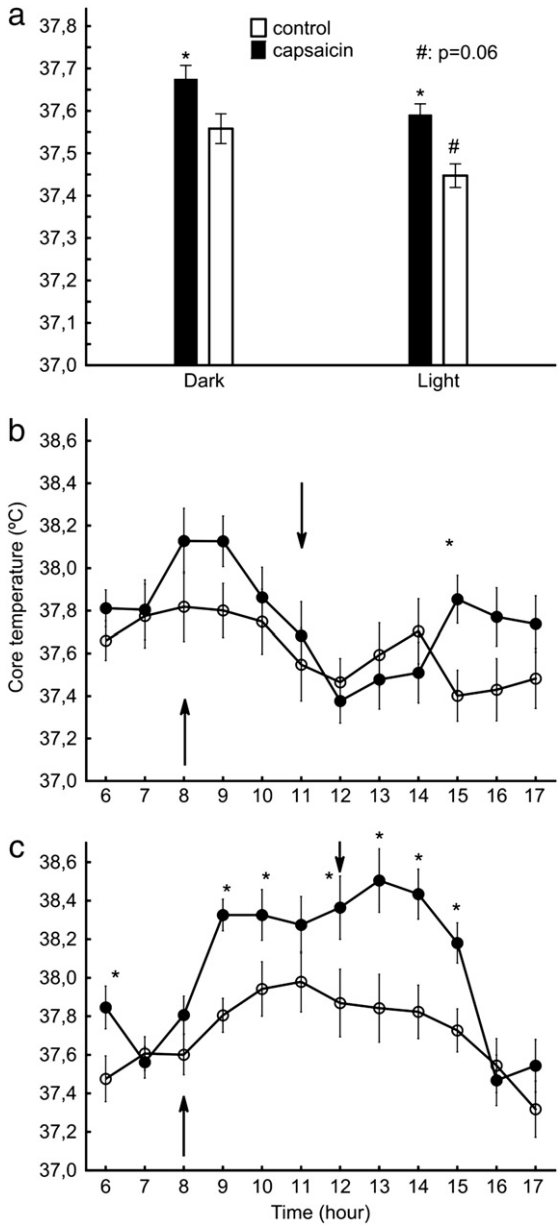

Fig. 4. Mean body temperature during dark and light periods (a). Core temperature changes in the cold (b) and warm (c) conditions. Data are presented as means ± SEM; n = 7–8. The symbols denote significant differences between the two groups (*) and day cycles (#). The arrows denote the starting (↑) and ending (↓) of the temperature changes.

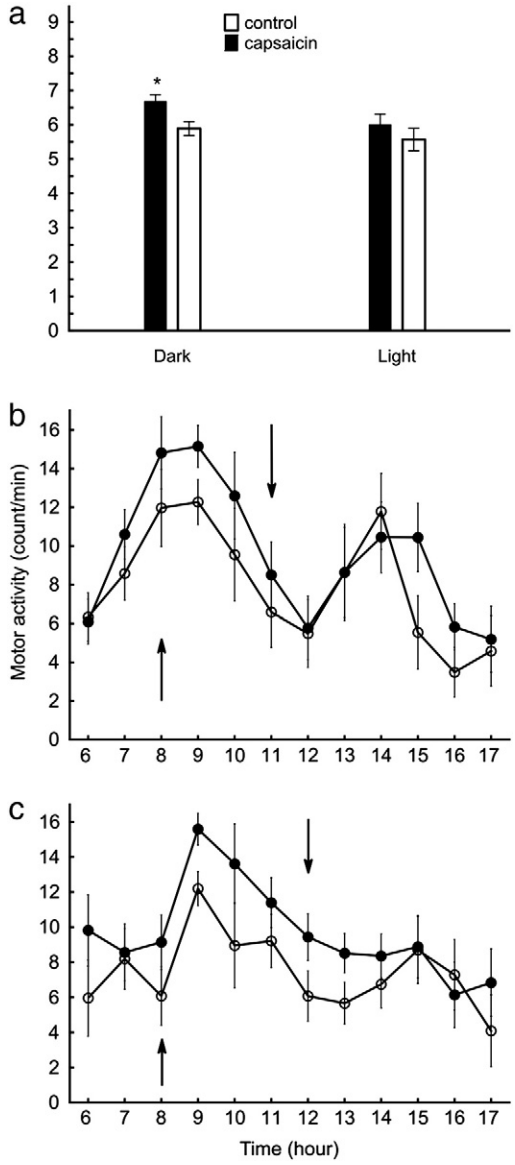

Fig. 5. Mean motor activity during dark and light periods (a). Motor activity changes in the cold (b) and warm (c) conditions. N = 7–8 rats/group. The symbol * indicates significant differences between the two groups. The arrows denote the starting (↑) and ending (↓) of the temperature changes.

$p < 0.001$), i.e. capsaicin-treated animals had significantly higher core temperature during both phases (Fig. 4a).

Motor activity also showed a daily rhythm with night maxima and day minima. The separate analysis of dark and light phases showed a significant effect of treatment ($F_{1,62} = 5.87, p < 0.05$) and a close to significant effect of period ($F_{1,62} = 3.56, p = 0.06$), which is to say that the desensitized animals exhibited enhanced motor activity during the active phase compared to control rats (Fig. 5a).

ANOVA with repeated measures revealed a significant effect of treatment ($F_{1,13} = 5.0, p < 0.05$) and time ($F_{11,143} = 3.0, p < 0.001$) in cold ambient. Cooling caused a slightly more intensive decrease of core temperature in the capsaicin-treated group, and after reheating they showed minor overcompensation (Fig. 4b). Regarding the motor activity, the ANOVA revealed a significant effect of treatment ($F_{1,13} = 6.03$, $p < 0.05$) and time ($F_{11,143} = 6.26, p < 0.001$), i.e. capsaicin-treated animals showed higher activity (Fig. 5b).

ANOVA with repeated measures revealed a significant effect of treatment ($F_{1,13} = 5.2, p < 0.01$), time ($F_{11,143} = 11.3, p < 0.001$) and interaction ($F_{11,143} = 2.0$, $p < 0.05$) at 27 °C temperature. Warming significantly enhanced the body temperature in both groups; however, the desensitized animals showed higher core temperature compared to controls (Fig. 4c). As for motor activity, the ANOVA showed a significant effect of time ($F_{11,143} = 3.54, p < 0.001$) and treatment ($F_{1,13} = 14.49$, $p < 0.01$), signifying a slight hyperactivity in the capsaicin-treated group (Fig. 5c).

4. Discussion

Juvenile capsaicin desensitization caused long-lasting disturbances in different physiological parameters; i.e. increased carrageenan-induced edema, morphine sensitivity and urinary bladder capacity were observed. It also caused significant deterioration in memory function, thermoregulation and motor activity under freely moving conditions, but no disturbances of the sensory gating were observed.

The persistent changes in wiping behavior of rats treated with the described protocol provide behavioral verification of the efficiency of capsaicin treatment in juvenile rats. We did not observe significant alterations in acute and inflammatory pain sensitivities in these animals, which is in agreement with earlier data obtained in neonatal or adult desensitized rats [6,47]. It is assumed that alterations in capsaicin-insensitive neurons and/or reorganization of the CNS may contribute to the normal pain sensitivities in capsaicin-treated animals [23,47]. However, the antinociceptive effect of morphine was enhanced and prolonged during joint inflammation in both mechanical and thermal tests. Only one study investigated the antinociceptive action of morphine in inflammatory pain, which found that morphine causes a greater effect in the inflamed than in the non-inflamed paw in control rats, and this difference is absent in capsaicin-treated animals [3]. We found a similar phenomenon in our model, as well as a prolonged effect of morphine. Opioid receptor binding studies showed that the number of binding sites and binding affinity in the dorsal horn remained unaltered after adult capsaicin treatment, but were decreased by neonatal capsaicin exposure [9,24]. The paradoxical finding that desensitization enhances the effects of morphine might be due to the decreased nociceptive input to dorsal horn neurons because of the absence of TRPV1-expressing afferent fibers. Regarding the increased vascular permeability after capsaicin desensitization, our data are in agreement with those of Helyes et al. [21], and these results may be explained by a lack of somatostatin release from primary sensory neurons.

A considerable amount of evidence indicates that capsaicin-sensitive mechanisms regulate the micturition threshold by relaying information to the CNS about the volume of fluid present in the bladder [5,24,30,37]. Both neonatal and adult capsaicin treatments lead to an impairment of urinary bladder function, such as an increased threshold for micturition or a reduced frequency of micturition contractions [26,37]. Neonatal and adult capsaicin desensitization leads to increased bladder capacity detected by the cystometrographic method [5,37]. Almost 20 years ago, we described a simple, noninvasive and reliable ultrasonographic method for the determination of urinary bladder capacity in anesthetized rats [28]. Our in vivo results revealed that the bladder capacity is significantly larger in juvenile desensitized rats compared to the control animals. Additionally, increased bladder volume was also observed 5 weeks after adult capsaicin desensitization in rats (RV: 0.25 ± 0.012 and 0.33 ± 0.014, control vs desensitized animals). Thus, capsaicin desensitization applied at any age results in enhanced bladder capacity, suggesting that sensory transmission from the bladder in the micturition reflex depends on TRPV1 receptors at all stages of development.

Ample data are available on the effects of activation or desensitization of TRPV1 receptors on various CNS structures and functions, but the results are inconsistent. The majority of the neurons may be spared by the protective effects of exogenous nerve growth factor, and also markers that are associated with CNS neurons are unchanged after neonatal capsaicin administration [29,42]. It seems that TRPV1 receptors comprise a neuromodulatory system in the brain, operated by endovanilloids [13,34]. Their activation appears to be anxiogenic,

while their pharmacological blockade seem to bring about an anxiolytic effect [14,36].

Prepulse inhibition is impaired in several neuropsychiatric disorders, including schizophrenia [52]. Only a few studies investigated the role of TRPV1 receptors in sensory gating. It has been shown that neither capsazepine, a TRPV1 receptor antagonist, nor cannabidiol (a TRPV1 receptor agonist) affected PPI by themselves, but cannabidiol reversed the NMDA-receptor antagonist-induced (MK-801) disruption of PPI and capsazepine prevented this effect [35]. In contrast, a more recent study found disrupted PPI after cannabidiol administration in rats, but it had no effect on the MK-801-induced disruption of PPI [19]. The only available study that investigated the effect of neonatal capsaicin desensitization supports our finding that desensitization has no effect on PPI [8]. These data suggest that TRPV1 receptors do not directly interfere with normal sensory-motor gating, but further studies are required to reveal the effects of capsaicin desensitization on PPI in different conditions.

We found that the capsaicin-desensitized animals showed increased activity under different conditions as observed with continuous telemetry, while no activity changes were observed during the NOR test in the open field when observed for short periods only. Impairment of motor behavior is also an important sign of schizophrenia: motor agitation and reduced motor activity are both observed [56]. Both the dopaminergic and the glutamatergic systems in the prefrontal and subcortical areas are involved in these abnormalities [12]. Many dopaminergic cells in the mesencephalon are TRPV1-immunopositive [32,38,42], and the activation of TRPV1 receptors in the midbrain ventral tegmentum transiently increased dopamine release in the nucleus accumbens [39]. There are studies indicating that motor activity can be suppressed by the activation of TRPV1 receptors, and these effects were reversed by capsazepine [15,46]. Findings about the effect of capsaicin desensitization on motor activity are inconsistent. No major differences were observed between capsaicin- or vehicle-treated animals in spontaneous and novelty-induced grooming, or in open-field exploration after either neonatal or adult capsaicin desensitization observed during a short period [11,36]. Since we did not find significant differences in the activity in NOR test paradigm either, we suppose that brief investigation in these tests are not enough to reveal the fine disturbance in motor activity. A recent study found that TRPV1 knockout animals showed slightly increased motor activity, as measured with the Mini Mitter method [17]. Our results also showed an enhanced motor activity in juvenile desensitized animals during their active phase, similarly to the pattern seen in schizophrenia. These data, together with earlier results, suggest that capsaicin desensitization disturbs the motor behavior for a long period, and as a putative explanation it is proposed that a tonic activation of TRPV1 channels suppresses the general locomotor activity.

The effect of capsaicin desensitization on thermoregulation was investigated by several groups in anesthetized or restrained animals, but only scarce data are available on measurements under freely moving conditions [33,51,54]. Changes in this parameter can be also important since impairment in thermoregulation was observed in schizophrenic patients [10,14,22,49]. Activation of the TRPV1 receptors in the preoptic area caused hypothermia and enhanced frequency of both glutamatergic and GABAergic postsynaptic currents [1,24,31]. However, it has to be kept in mind that investigation of the effect of capsaicin on thermoregulation is complicated by the fact that both peripheral C-fiber warmth receptors and central thermosensitive neurons are affected by the drug. Plenty of studies are available on the changes of thermoregulation after neonatal or adult capsaicin desensitization in restrained animals — with inconsistent results [14,27,51,55]. Two studies in adult desensitized mice or rats with telemetry showed that capsaicin desensitization significantly increases the core temperature and results in a marked deficit in heat tolerance [43,54]. We also found more pronounced changes in the warm than in the cold condition. Since motor activity increases body temperature, we suggest that body temperature increase in different conditions might be due to, at least partially, hyperactivity resulting from capsaicin desensitization.

Learning impairment was found in the desensitized group with the NOR test, a test which assesses what is a possible analog of declarative memory in humans [16,59]. Cognitive impairment is a well-known symptom of schizophrenia, and the extensive reduction of afferentation, together with the damage to the areas involved in memory processes should consequently bring about cognitive impairment after capsaicin desensitization. Several earlier studies suggested that TRPV1 receptors might play an important role in memory functions, mainly at the hippocampal level, but the results are controversial [14,40,57]. TRPV1 receptor activation can modify long term potentiation, and it is damaged in TRPV1-deficient mice [4,18,40]. Rats treated with capsaicin as neonates had reduced hippocampal volume and cortical thickness and they exhibited signs of learning impairment [6,40,45]. To our knowledge, this study is the first to investigate the effects of capsaicin desensitization on NOR test, and the results obviously support the role of TRPV1 receptors in memory functions.

5. Conclusion

The significant changes in sensory functions (e.g. wiping response, morphine efficiency, urinary bladder capacity) in juvenile desensitized animals proved that this treatment protocol may provide an appropriate model for the investigation of the effects of capsaicin desensitization before the completion of development. Our study described the effects of capsaicin desensitization on some parameters associated with schizophrenia, such as thermoregulation, memory functions and motor activity. In agreement with Chahl [7], it can be concluded that this animal model can simulate some symptoms of schizophrenia. We suppose that juvenile capsaicin desensitization together with other treatments (e.g. social isolation or NMDA receptor antagonist treatment) could further improve this model. Clearly, more work is needed to fully appreciate the role of TRPPV1 receptors in the CNS and, hence, the potential central consequence of the pharmacological targeting of this channel with either agonists or antagonists with therapeutic activity.

Acknowledgments

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