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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