**Abstract**

This study examined the analgesic effect of cocaine in Spontaneously Hypertensive Rats (SHR), which are considered a suitable model for the study of attention deficit hyperactivity disorder (ADHD), and in Wistar (WIS) rats of both sexes using the hot-plate test. In addition, we tested whether habituation to the unheated hot-plate apparatus, that "normalizes" the basal hypoalgesic phenotype of SHR, alters the subsequent cocaine-induced analgesia (CIA) in this strain. SHR of both sexes were hypoalgesic compared to WIS rats in the hot-plate test and showed higher sensitivity to CIA. Habituation to the unheated hot-plate reduced the basal nociceptive latency of SHR, suggesting cognitive/emotional modulation of pain in this strain, but did not alter the magnitude of CIA. The present study shows increased sensitivity to CIA in SHR, which may be related to abnormalities in the mesocorticolimbic dopaminergic system. Further studies using SHR strain may reveal new information on the neurobiological mechanisms underlying ADHD and its co-morbidity with drug addiction.

**Findings**

Pain is a complex and subjective experience that involves the transduction of noxious stimuli by nociceptive fibers, but also cognitive and emotional aspects [1]. For instance, human studies indicate that pain is perceived as less intense when individuals are distracted from the pain [2]. Gender and genetic differences also influence the pain perception and a number of animal models have been used to study the influence of these factors on nociception [3]. The Spontaneously Hypertensive Rats (SHR) show abnormal nociceptive reactivity in several nociceptive tests [4-8]. In the hot-plate test, SHR are hypoalgesic when compared to rats of other strains [4,5,7,8], but they show normal properties of nociceptive fibers [9]. We have recently reported that hypoalgesia was no longer observed in SHR rats after habituation to the unheated hot-plate apparatus, suggesting that their hypoalgesic phenotype may involve cognitive processes (e.g. distraction) [8]. This is consistent with the fact that SHR have been considered an animal model for the study of attention deficit hyperactivity disorder (ADHD), since they show inattention and impulsivity/hyperactivity [10,11]. It remains to be clarified whether this characteristic of SHR interferes with the analgesic properties of drugs.

Alterations in the dopaminergic system in ADHD patients as well as in SHR have been identified [10,11]. Methylphenidate, the first-choice treatment for ADHD, is known to block dopamine (DA) uptake by brain DA transporters in a similar way to potent psychostimulants like cocaine and amphetamine [12]. In addition, the mesocorticolimbic dopaminergic system is one of the main neurochemi-
cal pathways involved in the interface between pain, cognition and emotionality [13]. Systemic administration of DA re-uptake blockers induces analgesia in rodents, probably by acting on brain dopaminergic pathways [14,15].

The first aim of this study was to examine the effects of cocaine on nociceptive responses in the SHR and in the outbred Wistar (WIS) rat strain (representing a "normal" genetically heterogenic population) using the hot-plate test. In order to evaluate the contribution of cognitive/emotional processes in the analgesic effect of cocaine, another objective of our study was to evaluate whether habituation to the unheated hot-plate apparatus, that "normalizes" the basal nociception of SHR, alters the subsequent cocaine-induced analgesia (CIA) in this strain. Animals of both sexes were included in this study because there is a considerable amount of evidence for quantitative and qualitative sex differences in nociceptive-related behaviors [3].

Adult (12 weeks old) SHR and WIS rats from our own colonies were used [8]. The weight of the animals was 230–310 g for males and 150–210 g for females. They were housed collectively in plastic cages (5–6/cage), under controlled temperature (23 ± 2°C) with a 12-h light/dark cycle (lights on at 07:00) with free access to rat chow and tap water. All experiments were carried out during the light phase of the cycle.

The animals were injected with cocaine (20 mg/kg, Merck®) dissolved in physiological solution or an equivalent amount of vehicle (2 ml/kg) via intraperitoneal (i.p.) route 15 min before the nociceptive tests. The dose of cocaine was selected based on a pilot study and a previous report [14]. All procedures performed complied with the "Principles of laboratory animal care" from NIH.

The hot-plate (Ugo Basile, model-DS37) was maintained at 52.2 ± 0.5°C following a previously reported procedure [8]. Briefly, the animals were placed in a glass cylinder of 24-cm diameter on the heated metal surface, and the time between placement and hind paw licking or jumping (whichever occurred first) was recorded as nociceptive latency. A 70-s cut-off was established to prevent tissue damage. The procedure of the habituation to the hot-plate apparatus has been described elsewhere [8]. SHR were submitted to five sessions of 90-s exposure (at 10-min inter-trial intervals) to the unheated hot-plate apparatus. Another group of rats remained undisturbed in their home cages and served as non-habituated animals (test naive rats). One hour after the last habituation session, habituated and non-habituated rats were injected with cocaine as previously described and tested on the hot-plate. Because cocaine-induced analgesia was of similar intensity in both genders, this experiment was carried out only with female rats due to their greater availability in our laboratory.

The results were expressed as the latency (s) to nociception or the percentage of maximum possible effects (%MPE) defined by the following equation:

\[
%MPE = \frac{\text{post-drug latency} - \text{basal latency}}{\text{cut-off} - \text{basal latency}} \times 100
\]

Statistical analysis was performed using one-, two- or three-way ANOVA with condition (habituated and non-
study: N = 12 per group, bilateral tail-free incision for sham vs CIA, repeated measures ANOVA (condition) for the % MPE revealed an overall effect of condition [F(1,11) = 18.18; p < 0.005]. Habituated and nonhabituated rats displayed analgesic effects of cocaine [F(1,11) = 27.46; p < 0.001]. However, one-way ANOVA (condition) for the % MPE indicated that CIA was similar in these groups [F(1,11) = 0.63; p = 0.44].

This study provides evidence of increased sensitivity to cocaine in terms of analgesia in the SHR strain when compared to the WIS strain in the hot-plate test. Moreover, habituation to the unheated hot-plate reduced the basal nociceptive latency of SHR without altering the magnitude of the analgesic effect of cocaine.

SHR are hypoalgesic compared to Wistar, Wistar-Kyoto, Sprague-Dawley and Lewis rats [4-8,16]. Thus, the results here presented for basal nociception are in agreement with the aforementioned findings. As pointed out by Taylor et al., the exaggerated fight-or-flight stress responses and sympathetic activation in SHR may be related to their abnormal nociceptive phenotype [7]. Several studies have shown that stress can cause intense analgesia [8,17]; however, we have reported that when a more severe stressor was employed (forced swimming in cold water), SHR were less vulnerable to stress-induced analgesia compared to Lewis and WIS rats [8]. This apparent discrepancy regarding an “analgesic” effect produced by exposure in a novel environment and the reduced impact of stressful situ-

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in summary, SHR have increased sensitivity to behavioral and neurochemical effects of psychostimulants, which may be related to abnormalities in the mesocorticolimbic dopaminergic system. Because hyperlocomotion and analgesia share a common neural substrate with the rewarding effects of drugs of abuse [13], it is possible to suggest that the enhanced behavioral effects of cocaine in SHR could reflect the higher preference of SHR for drugs of abuse [27]. Thus, further studies using SHR strain may reveal new information on the neurobiological mechanisms underlying ADHD and its co-morbidity with drug addiction.

Competing interests
The author(s) declare that they have no competing interests.

Authors’ contributions
FAP carried out the data collection, designed the study and wrote the manuscript. LFV and RNT participated in the data analyses, interpretation of data and elaboration of the study.
of the manuscript. All authors read and approved the final manuscript.

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