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Research report

Antidepressant-like effects of buprenorphine in rats are strain dependent

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HIGHLIGHTS

- Buprenorphine produced antidepressant-like effects in the forced swim test in WKY rats.
- Buprenorphine produced anxiolytic effects in the emergence test in WKY rats.
- Wistar and Sprague-Dawley rats did not respond to buprenorphine.
- WKY rats from different suppliers varied in behavior and response to buprenorphine.

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ABSTRACT

The prevalence of major depressive disorder and the limited efficacy of conventional drug treatments provide significant impetus to develop novel and more rapidly acting antidepressants for individuals with treatment resistant forms of depression. The primary goal of these studies was to ascertain whether buprenorphine (BPN), a medically available drug with mixed effects at opioid receptors, was effective in behavioral tests using the Wistar Kyoto (WKY) rat strain, a rodent model of exaggerated depressive and anxiety behaviors that demonstrates resistance to certain antidepressants. As WKY rats are maintained by different sources, we assessed the behavioral effects of BPN using the modified rat forced swim test (FST) and the emergence test in WKY rat colonies obtained from different vendors. BPN dose-dependently reduced immobility and increased swimming behavior in the FST and reduced emergence latencies in two WKY lines (Charles River (WKY/NCrl) and Harlan laboratories (WKY/NHsd)) that also showed high baseline immobility in the FST. WKY rats from Taconic (WKY/NTac) did not show high baseline immobility in the FST or anxiety as had been previously reported, suggesting a drift in the phenotype of rats from this supplier. Furthermore, BPN did not reduce immobility in the FST or reduce latencies in the emergence test in WKY rats from Taconic. BPN also failed to produce antidepressant-like effects in Wistar and Sprague-Dawley rats. These results indicate a striking strain-selectivity for the effects of BPN, producing antidepressant and anxiolytic-like responses in WKY/NCrl and WKY/NHsd lines but not in the normosensitive control Wistar and Sprague-Dawley strains.

1. Introduction

Major depressive disorder (MDD) is a debilitating psychiatric disorder with a lifetime prevalence of ~17% in the United States [1]. Despite the wide range of therapies available to treat MDD, there are significant limitations associated with conventional antidepressants, including a delay in therapeutic efficacy of 3–4 weeks and successful remission in only 40–60% of patients [2]. Those that fail to respond to two or more antidepressant treatments are considered to have a form of treatment resistant depression (TRD) [3]. Individuals with TRD complain of suicidal ideation and comorbid anxiety more frequently than other MDD patients [4]. TRD generates a greater economic burden than MDD, primarily due to the

Abbreviations: WKY/NTac, Wistar Kyoto rats Taconic; WKY/NCrl, Wistar Kyoto rats Charles River; WKY/NHsd, Wistar Kyoto rats Harlan; Crl:SD, Sprague-Dawley rats Charles River; Crl:WI, Wistar rats Charles River; FST, forced swimming test; κ-OR, kappa opioid receptors; TRD, treatment resistant depression; BPN, buprenorphine.

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increasing medical costs associated with resistance to therapy [5]. Therefore, there is a pressing medical, social and economic need to develop novel antidepressants for the treatment of MDD.

Appropriate rodent models of depression are necessary to adequately evaluate the antidepressant potential and mechanism of action of novel therapeutics for MDD. One such model is the Wistar-Kyoto (WKY) rat strain. Originally developed as the normotensive control for the spontaneously hypertensive rat (SHR), WKY rats have consistently exhibited increased depressive-like behavior in the forced swim test (FST) and rapid development of learned helplessness [6–9]. WKY rats also displayed increased anxiety-like behavior in many behavioral tests, including the conditioned defensive burying test, open field, elevated plus maze and the novelty-induced hypophagia (NIH) test [9–14]. Furthermore, increased physiological responses to stress, as shown by prolonged activation of the hypothalamic–pituitary–adrenal (HPA) axis [15,16] and increased development of stress-induced ulcers [17], has been reported in WKY rats. Additionally, WKY rats recapitulate resistance to the suppression of corticosterone by dexamethasone [15] and abnormalities in sleep architecture [18], characteristics commonly observed in patients with severe depression. WKY rats fail to exhibit behavioral responses following acute and chronic treatment with the most commonly prescribed class of antidepressants, selective serotonin reuptake inhibitors (SSRIs) [8,19,20], a trait shared by certain cohorts of treatment resistant MDD patients. Similarly, WKY rats did not exhibit behavioral responses to 5-HT_{1A} receptor agonists and environmental enrichment in tests for behavioral domains relevant to depression and anxiety [8,21,22]. These traits mark WKY rats as a genetic and pathological model of depression and anxiety [23].

Emerging evidence suggests that opioid receptors, particularly kappa (κ-ORs) and their endogenous κ-OR ligand dynorphin (DYN), may play a key role in the etiology of anxiety and depression [24,25]. The κ-OR/DYN system is critical in the production of stress-induced aversion; this system is significantly upregulated by the release of corticotrophin-releasing factor following stress exposure [26]. Increased κ-OR/DYN signaling has been shown to induce depressive-like behavior, dysphoria and increased drug seeking in rodents [27–30]. Furthermore, WKY rats exhibit increased κ-OR expression in the locus coeruleus, piriform cortex and nucleus accumbens compared to Sprague-Dawley rats [14,31]. Although not consistently apparent in non-stressed rodents, our laboratory has shown that the κ-OR antagonists, nor-BNI and DIPPA, effectively reduced immobility and increase swimming behavior in the FST in WKY rats [14,32]. Critically these antidepressant-like effects of κ-OR antagonists persisted for 24 h after a single injection, a time frame longer than conventional antidepressants. Furthermore, these κ-OR antagonists effectively reduced anxiety-like behavior, as measured by a lower latency to approach and eat food in the NIH test and reduced defensive burying behavior in rats [14]. The κ-OR antagonists produced their effects more rapidly than conventional antidepressants, which require chronic administration for weeks to reduce approach latencies in the NIH test [33,34].

Buprenorphine (BPN) is a relatively short-acting κ-OR antagonist [35] that is medically available and currently used to treat opiate addiction and chronic pain. The first suggestion that BPN may be of benefit in treating depression was in the early 1980s [36]. Subsequently, two small studies conducted in TRD patients, indicated that BPN rapidly reduced depressive symptoms [37,38]. Recent clinical evidence has outlined a significant benefit of BPN in TRD patients following chronic administration at low doses [39]. Recently, our lab has shown that BPN reduced immobility time in the FST and reduced anxiety-like behavior in the novelty-induced hyponeophagia test in C57BL/6J mice [40]. The purpose of these studies was to examine the potential behavioral effects of BPN in a rodent model of pathological anxiety and depression, namely the WKY rat. As WKY rats can be sourced from a number of suppliers, we compared baseline depressive-like and anxiety-like behavior and the response to BPN in WKY rats obtained from Taconic (WKY/NTac), Charles River (WKY/NCrl) and Harlan laboratories (WKY/NHsd). Following these studies, we examined BPN-induced antidepressant and anxiolytic-like effects in Wistar and Sprague-Dawley rats as non-stressed control strains. The results highlight the potential of BPN as a novel antidepressant in a model of depression in which conventional therapies have previously failed, and also indicate a striking disparity between rat strains in their sensitivity to the behavioral effects of BPN.

2. Materials and methods

2.1. Animals

Male WKY rats were obtained at age 6–7 weeks from three different sources, Taconic, (WKY/NTac, Cambridge City Facility, IN), Harlan laboratories (WKY/NHsd, Indianapolis, IN), and Charles River Laboratories (WKY/NCrl, Kingston, NY). Male Wistar (Crl:WI, Charles River Laboratories, Raleigh, NC) and Sprague-Dawley rats (Crl:SD, Charles River Laboratories, Kingston NY) were obtained at age 7 weeks. Rats were housed 3 per cage upon arrival and allowed at least 1 week to acclimate to the facility. All animals were maintained under a 12-h light cycle (lights on at 07:00 h) with room temperature of 22 ± 1 °C and food and water were provided ad libitum. All procedures were carried out in accordance the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drug preparation

Buprenorphine (BPN) hydrochloride was obtained from the National Institute on Drug Abuse and was freshly prepared on the morning of each experimental day. The compound was dissolved in sterile molecular grade deionized water and administered at a volume of 2 ml/kg subcutaneously. Doses were calculated according to the base weight. Vehicle groups received distilled water in an equivalent volume. All experiments were conducted during the light phase.

2.3. Study design

2.3.1. Experiment 1

This experiment compared behavioral responses of WKY rats obtained from different suppliers. At the time of testing, all rats were 8 weeks old. WKY/NTac weighed approximately 280 g, WKY/NHsd weighed approximately 215 g, and WKY/NCrl rats weighed approximately 220 g. Two weight-matched groups of WKY rats per substrain were assigned to the vehicle ($N = 12$) or 2.25 mg/kg BPN ($N = 12$) condition. This dose was selected based on pilot data. All rats were transported to the experimental room 1 h prior to testing. The effects of BPN were measured 24 h following injection because of previous reports that the behavioral effects of BPN and KOR antagonists are long-lasting [32,40]. The emergence test was studied first. After a rest period of one week, the effects of BPN were determined in the FST.

2.3.2. Experiment 2

This experiment examined the effects of different doses of BPN in the FST and emergence test in WKY/NCrl and in two control strains, Wistar rats and Sprague-Dawley rats. At the time of testing all rats were 8 weeks old, WKY/NCrl weighed approximately 220 g; Crl:WI weighted approximately 275 g, and Crl:SD rats weighed approximately 265 g. Four sets of male WKY/NCrl rats ($N = 32$), male