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Effects of Injection of Gamma-Aminobutyric Acid Agonists into the Nucleus Accumbens on Naloxone-Induced Morphine Withdrawal

Betilay Topkara Hasan R. Yananli Eren Sakallı Mahluga Jafarova Demirkapu

Department of Pharmacology, Marmara University School of Medicine, Istanbul, Turkey

Keywords
Gamma-aminobutyric acid · Nucleus accumbens · Sprague-Dawley rats

Abstract
Aims: This study was to investigate the effects of local administration of gamma-aminobutyric acid (GABA) agonists into the nucleus accumbens (NAc) on naloxone-induced morphine withdrawal symptoms. ***Methods:*** Bilateral guide cannulas were stereotaxically implanted in the shell or core regions of the NAc of Sprague-Dawley rats. After a recovery period, 3 morphine pellets, each consisting of 75 mg morphine base, were placed subcutaneously on the first and third days of the study with the rats under mild ether anaesthesia. The GABA agonists, baclofen hydrochloride or muscimol hydrobromide, were injected into the NAc, and morphine withdrawal was induced by naloxone on the fifth day. ***Results:*** Administration of baclofen to the shell or core regions of the NAc of Sprague-Dawley rats led to statistically significant decreases in both behavioural and locomotor activity parameters during the morphine withdrawal period, compared to the control group. However, there were no statistically significant changes in locomotor activity or withdrawal behavioural parameters, with the exception of wet dog shakes, between control and muscimol-treated groups. ***Conclusion:*** These findings show that GABAergic conduction in the NAc is effective on the morphine withdrawal symptoms, and that both the shell and core regions of the NAc are associated with this effect.

Introduction

Both the shell (NAcSh) and core (NAcC) regions of the nucleus accumbens (NAc) are known to play important roles in reward and motivation behaviours [1] and cognitive function [2]. Mesolimbic dopaminergic pathways, which have projections from the ventral tegmental area (VTA), are also of critical importance in opioid addiction [3]. Studies have demonstrated the possible roles of GABAergic, nitridergic and glutamatergic systems in the modulation of this pathway [4–7]. Opioids have been shown to disinhibit dopaminergic neurones in the VTA, bringing about increased dopamine release in the NAc, resulting from a decrease in gamma-aminobutyric acid (GABA) release from the GABAergic neurones of the VTA [8, 9]. In addition, the administration of muscimol, a $GABA_A$ agonist, and baclofen, a $GABA_B$ agonist, was reported to decrease the reinforcing effects of morphine in rats in a dose-dependent manner, effects which were regained by the GABA antagonists SCH 50911 and bicuculline [10]. Systemic administration of baclofen was shown to de-

E-Mail karger@karger.com
www.karger.com/pha

Hasan R. Yananli
Department of Pharmacology
Marmara University School of Medicine, Instanbul (Turkey)
Eastern Mediterranean University, School of Medicine, Famagusta (Cyprus)
E-Mail hasanyananli@yahoo.com

crease the naloxone-induced withdrawal jumping response in mice [11], and it also significantly decreased withdrawal symptoms such as stereotypic head nodding, chewing, ptosis and teeth chattering [12]. A preclinical study reported that baclofen exerts its effect in cocaine-, nicotine-, and alcohol-dependence via regulation of mesolimbic dopaminergic signalling [13]. In a clinical study, the systemic administration of baclofen significantly decreased morphine withdrawal symptoms and depressive symptoms compared to a control group [14]. The NAc is thought to be responsible for purposive behaviours, such as escape or orientation, by acting as an interface between the limbic and motor regions [15]. It is anatomically and functionally divided into 2 regions, the NAcSh and the NAcC [16], which have distinct projections [17] and different roles in drug addiction behaviour [18, 19].

In this study, we first aimed to investigate the effects of local administration of the GABA agonists, baclofen and muscimol, into the NAcSh, on morphine withdrawal symptoms and locomotor activity during naloxone-induced morphine withdrawal. Thus, we could determine the effect of targeted GABAergic stimulation in the NAc during morphine withdrawal without the confounding effects of other brain regions, especially the VTA. Following this, the effect of baclofen on morphine withdrawal symptoms, which was found to be more profound than that of muscimol, was investigated by microinjection into the NAcSh or NAcC.

Materials and Methods

Subjects

Adult male Sprague-Dawley rats (4–6 months, 250–290 g, n = 54) were obtained from the Marmara University Experimental Animal Research Centre (Ethics approval; 08.2012.mar). Animals were housed separately in a temperature-controlled room (21 ± 3°C) with a 12-h light/dark cycle with unlimited access to food and water.

Cannula and Morphine Pellet Implantation

Animals were anaesthetised with ketamine (75 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and their heads were placed in a stereotaxic frame (Stoelting Model 51600, USA). The scalp was incised longitudinally and the skull was exposed between lambda and bregma. Bilateral cannulas were stereotaxically implanted into the subregions of the NAc of the rats. The coordinates for the NAcSh (with a 10-degree angle, anteroposterior, AP: +1.7 mm, lateral, L: ±2.0 mm, ventral, V: 7.1 mm, from bregma) and NAcC (AP: +1.2 mm, L: ±2.2 mm, V: 7.3 mm, from bregma) were calculated according to the Rat Brain Atlas [20]. The animals were allowed to recover from surgery for ≥7 days before the first day of morphine pellet implantation. The experimental modelling of morphine dependence was established by implantation of 3 slow-releasing morphine pellets containing 75 mg morphine base under mild ether anaesthesia. On the first day, one of the morphine pellets was placed subcutaneously, and on the third day, 2 of the morphine pellets were placed subcutaneously. Rats were considered to be morphine-dependent on the fifth day.

Rats were released into this cage and the system automatically recorded their locomotor movement in the vertical and horizontal axes.

Experimental Design

Rats were allowed a 1-week recovery period following the implantation of cannulas into the NAcSh or NAcC regions via stereotaxic surgery. On the first day of the experiment after the recovery period, the basal locomotor activity of the rats was measured (AMS 9701, Commat Ltd., Turkey) and the first slow-release morphine pellet was placed subcutaneously when the rats were under mild ether anaesthesia. The rats were allowed to rest on the second day. Their locomotor activity was re-measured on the third day and the effect of morphine on this parameter was evaluated. Following the measurement of locomotor activity, the experimental modelling of morphine dependence was completed by placement of 2 of the slow-release morphine pellets subcutaneously the rats being under mild ether anaesthesia. The rats were allowed to rest on the fourth day. Following body weight measurement, bilateral microinjection of baclofen into the NAcSh or NAcC was carried out in morphine-dependent rats on the fifth day of the experiment. A control group of animals received only aCSF by microinjection into the NAcSh or NAcC. Morphine withdrawal was induced in dependent rats by an injection of naloxone (2 mg/kg, i.p.) 2 min after bilateral baclofen or muscimol microinjection. Following naloxone administration, rats were placed into the locomotor activity cage and morphine withdrawal symptoms and locomotor activity were simultaneously observed for 15 min. Symptoms of withdrawal such as jumping, wet dog shakes and teeth chattering were recorded during the 15-min period. Other withdrawal symptoms, which we have not included here, such as head and hand tremors, the number of fecal pellets, ptosis and diarrhoea, were also observed. Locomotor activity measurement and withdrawal symptoms were simultaneously evaluated for the same duration.

Drugs

Baclofen hydrochloride (G013), muscimol hydrobromide (G019) and naloxone hydrochloride (N7758) were obtained from Sigma-Aldrich, St Louis, MO, USA. Baclofen hydrochloride and muscimol hydrobromide were dissolved in aCSF (2.5 mmol/L KCl, 125 mmol/L NaCl, 1.26 mmol/L $CaCl_2$ [$2H_2O$], 1.18 mmol/L $MgCl_2$ [$6H_2O$] and 0.2 mmol/L NaH_2PO4 [$2H_2O$]; pH: 7.0) and diluted to the final concentrations with aCSF. Serum physiological solution was used for dissolution and dilution of naloxone. Morphine base was obtained from the Solid Products Office of the Turkish Ministry of Agriculture. Morphine pellets, each containing 75 mg of morphine base, or placebo control pellets were prepared by Marmara University, Faculty of Pharmacy, Department of Pharmaceutical Technology.

Histological Verification and Data Analysis

Rats were included in the analysis if the cannulas were located within NAc region (see included cannula placements in Figure 1). Data are represented as the mean ± SEM. GraphPad Prism 5.03

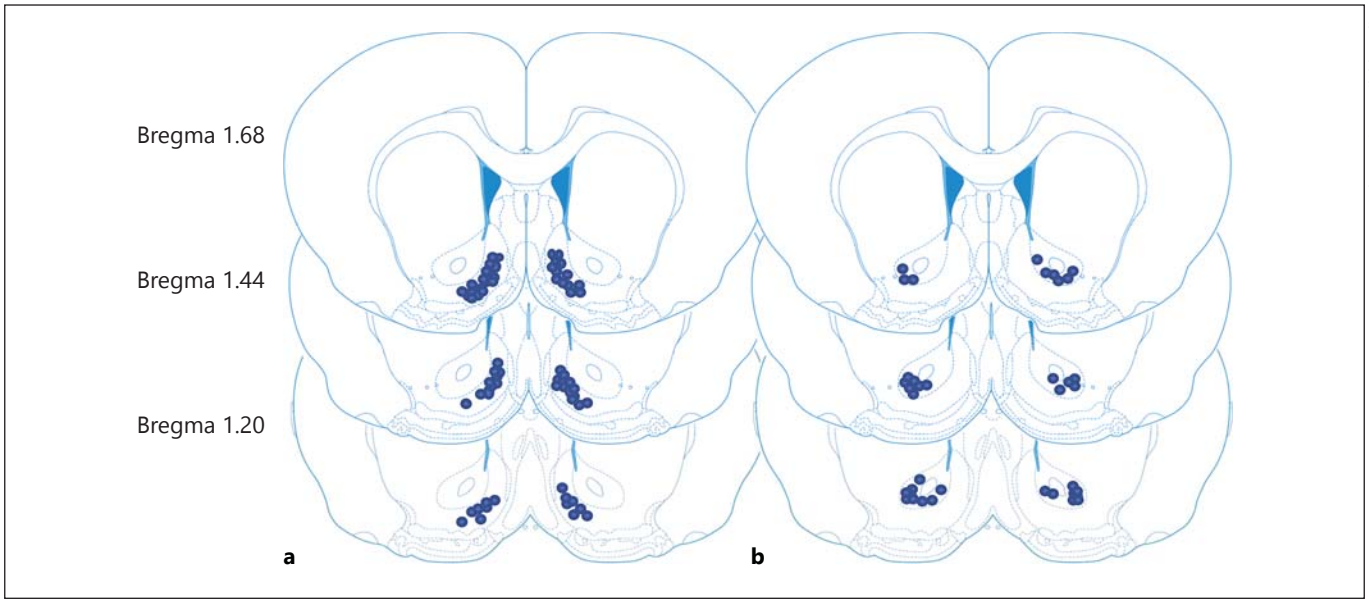

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Fig. 1. Schematic representation of the location of injection sites in the nucleus accumbens shell (**a**) and core (**b**). The plane is taken from the Rat Brain Atlas [20] and numbers on the left indicate the distance (mm) from the bregma.

(San Diego, CA, USA) was used for data analysis. The level of statistical significance was considered to be $p < 0.05$. Repeated measures or one-way analysis of variation, followed by Tukey's post-hoc test, were used to analyse the effect of naloxone-induced morphine withdrawal on locomotor activity and the difference between study groups. Newman-Keuls Multiple Comparison Test and unpaired 2-tailed *t* tests were used to compare the results of muscimol and baclofen microinjection into the NAcSh and baclofen microinjection into the NAcC.

Results

The Effect of Morphine Withdrawal on Locomotor Activity

Sprague-Dawley rats were randomly divided into 3 groups (with 13 rats in each group). Stereotaxic surgery and cannula implantation procedures were not applied to these groups. The basal locomotor activity of the rats was compared to that observed just prior to administration of the 2 morphine pellets, and during morphine withdrawal. There were no statistically significant differences in the number of stereotypic movements between these groups. The number of ambulatory movements was significantly different in rats undergoing morphine withdrawal compared to the basal or morphine-treated groups. A statistically significant increase in the number of vertical movements was detected during morphine withdrawal compared to the basal number of vertical movements and the number observed in morphine-treated rats. The total floor distance covered in the cage during morphine withdrawal was also significantly higher than the basal levelor that was seen in the morphine-treated group (Fig. 2). There were no statistically significant differences between basal locomotor activity and that resulting from morphine treatment.

The Effect of Administration of Baclofen into the NAcC, NAcSh or Muscimol Administration into the NAcSh on Naloxone-Induced Morphine Withdrawal Symptoms

Thirty-five Sprague-Dawley rats were divided into 5 groups (7–11 rats in each group). Naloxone-induced morphine withdrawal symptoms were evaluated following baclofen microinjections into the NAcC, NAcSh or muscimol microinjections into the NAcSh of chronic morphine-treated rats. Baclofen microinjection into the NAcC or NAcSh decreased jumping behaviour significantly compared to the control group, which received aCSF. Wet dog shake behaviour and weight loss also decreased significantly with baclofen microinjections into the NAcC or NAcSh, compared to the control group. However, baclofen microinjection neither into the NacC nor into the NAcSh had any effect on teeth chattering. Muscimol had no statistically significant effect on weight

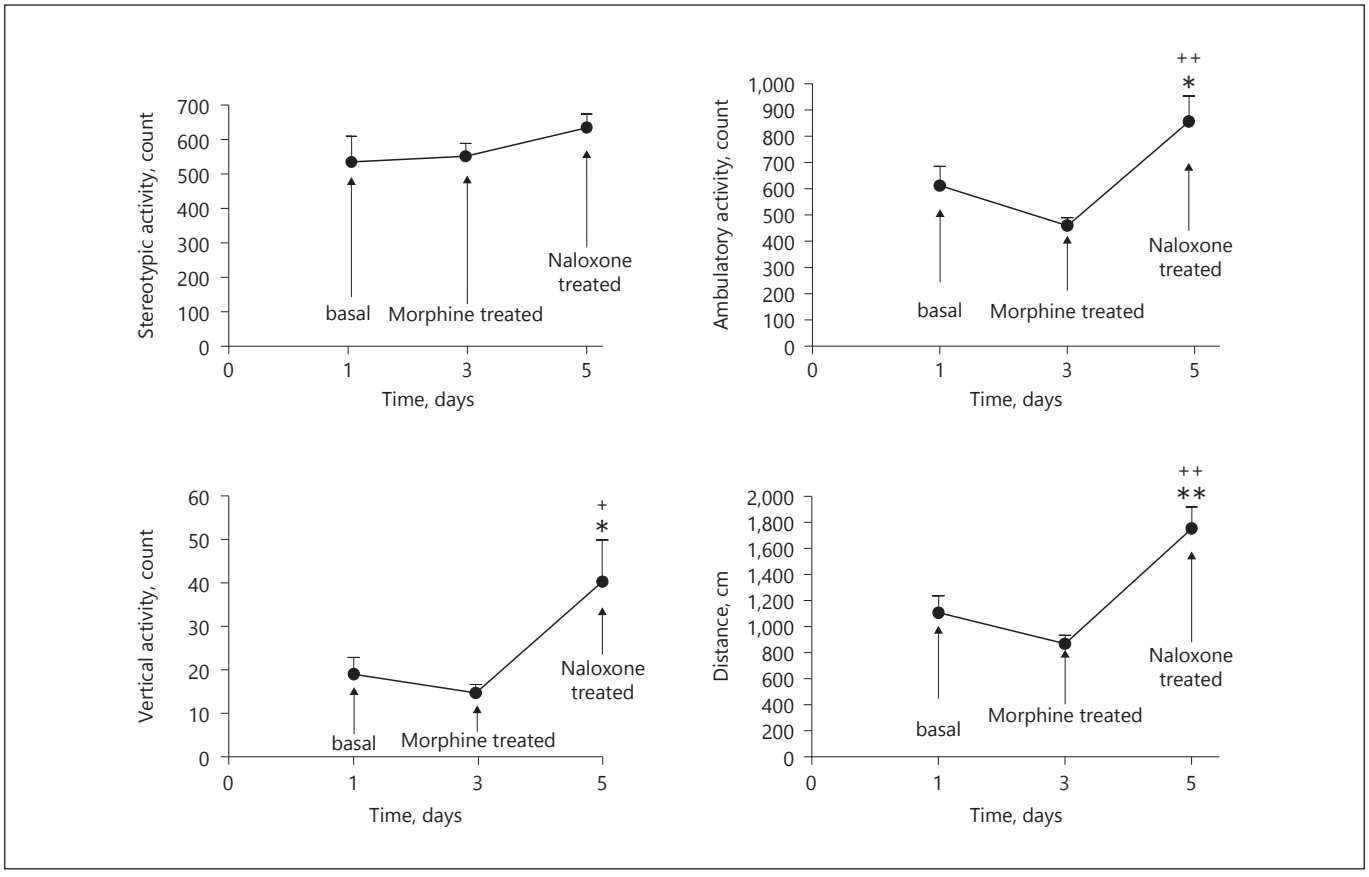

Fig. 2. The effect of naloxone-induced morphine withdrawal on locomotor activity (* $p < 0.05$, ** $p < 0.01$ compared to the basal group; $^{+}$ $p < 0.05$, $^{++}$ $p < 0.01$ compared to the morphine-treated group).

loss or teeth chattering during morphine withdrawal, while jumping and wet dog shake behaviours were found to decrease significantly following injection of the drug (Fig. 3).

The Effect of Administration of Baclofen into the NAcC, NAcSh or Muscimol Administration into the NAcSh on Locomotor Activity Behaviour during Naloxone-Induced Morphine Withdrawal

Changes in locomotor activity during naloxone-induced morphine withdrawal were evaluated following bilateral baclofen microinjection into the NAcC or NAcSh of chronic morphine-treated rats. Baclofen injection into the NAcC or NAcSh appeared to have no effect on stereotypic activity, while ambulatory movement was significantly decreased following drug administration into the NAcC or NAcSh. Baclofen injection into the NAcC or NAcSh significantly suppressed vertical movement compared to the control group, which received aCSF. The total floor distance covered in the cage also significantly decreased with baclofen injection into the NAcC. Muscimol treatment did not affect the locomotor activity (Fig. 4).

Discussion

The first finding of our study was the suppressive effect of baclofen microinjection into the NAcSh on specific withdrawal symptoms such as jumping and wet dog shakes. Preclinical [12] and clinical [14] studies have shown that systemic administration of baclofen suppressed behavioural changes related to morphine dependence and withdrawal, and these effects were associated with a reduction in dopamine levels in the NAc. In an in vivo study, pretreatment with baclofen (which was given intraperitoneally) brought about a dose-dependent decrease in dopamine release in the NAcSh in rats administered morphine, nicotine or cocaine [21]. In another study, extracellular dopamine levels in the NAc

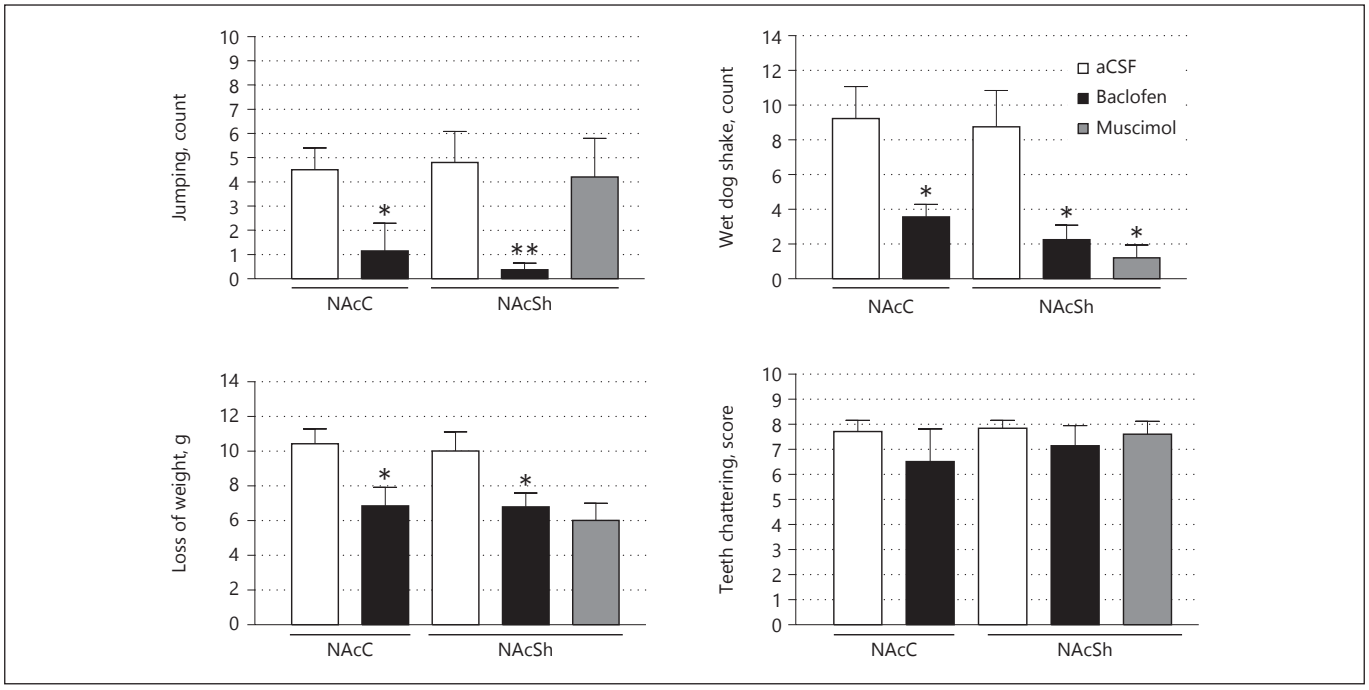

Fig. 3. The effect of bilateral aCSF baclofen or muscimol microinjection into the NAcSh or NAcC on the symptoms of naloxone-induced morphine withdrawal (* $p < 0.05$, ** $p < 0.01$ compared to the aCSF group).

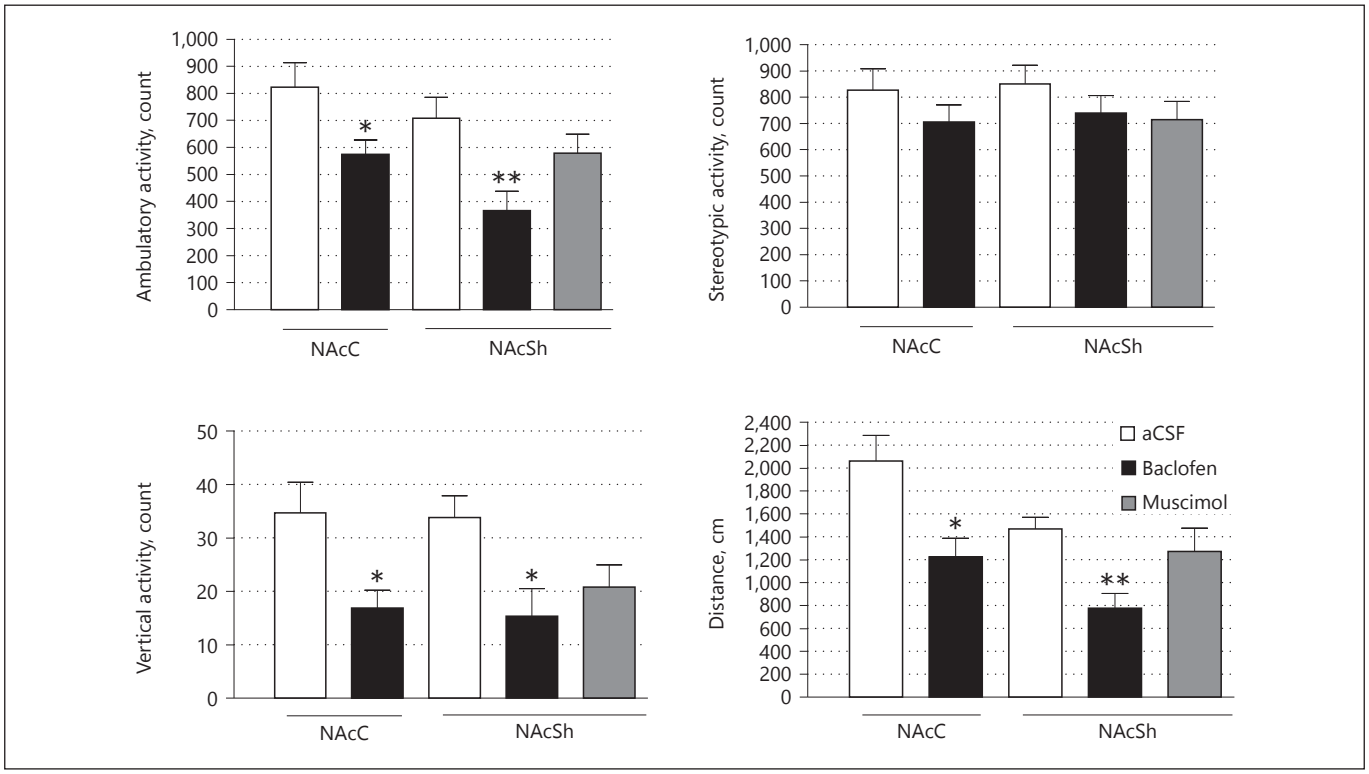

Fig. 4. The effect of bilateral aCSF baclofen or muscimol microinjection into the NAcSh or NAcC on locomotor activity during naloxone-induced morphine withdrawal (* $p < 0.05$, ** $p < 0.01$ compared to the aCSF group).

were found to decrease following local administration of baclofen into the VTA [22]. Xi and Stein [23] reported that baclofen microinjection into the VTA decreased dopamine release induced by heroin self-administration, although baclofen administration into the NAc did not show the same effect. Therefore, this inhibitory effect of baclofen on dopamine release was thought to be mediated via $GABA_B$ receptors in the VTA. In light of these studies, the role of baclofen in opioid dependence and withdrawal is believed to be associated with the VTA, which receives dopaminergic projections from the NAc. However, other data does support the involvement of GABA receptors in the NAc in dopaminergic regulation, in addition to data indicating a GABA-dopamine interaction between the VTA and NAc [24].

Previous studies have shown a role for GABA receptors in the VTA [22] and LC [25] in this regard. Similar to the results of our study, administration of a $GABA_B$ agonist into the LC was shown to decrease withdrawal symptoms, while administration of a $GABA_B$ antagonist did not lead to any behavioural changes. Although microinjection of the $GABA_A$ agonist muscimol into the LC dose-dependently decreased withdrawal symptoms, $GABA_A$ and $GABA_B$ antagonists were reported to have no effect [26]. In some of the studies showing an effective suppressive action of drugs on morphine withdrawal, jumping behaviour was found to be affected in different ways – that is, increased [27], decreased [28] or not changed at all [29]. A regulatory effect of α_2-adrenergic receptors on dopaminergic receptors has been implicated by the analysis of jumping behaviour [30], whereas a regulatory effect of serotonergic transmission has been extrapolated from the wet dog shake behaviour related to withdrawal [31]. According to previous studies and our present findings, it seems possible that the dopaminergic system in the NAc is being modulated via $GABA_B$ receptors during withdrawal. In addition, the modulation of other excitatory systems, which have secondary importance, such as the serotonergic system, by $GABA_A$ receptors in the NAc, could explain the suppressive effect of muscimol on wet dog shake behaviour during withdrawal.

The distinct effects of the GABA receptor agonists, muscimol and baclofen on locomotor activity behaviour have previously been identified. Local injection of baclofen or muscimol into the dorsal raphe nucleus was found to increase locomotor activity, an effect that was reversed by the injection of GABA antagonists. Furthermore, the possibility of an association between serotonergic receptors and this interaction has been considered [32]. In addition, bilateral injection of baclofen into the VTA was reported to cause a significant dose-dependent decrease in morphine-induced locomotor activity behaviour, and the inhibitory effect of baclofen on dopaminergic receptors was related to this decrease [33]. There have been studies demonstrating the role of GABA receptors in the VTA on morphine-induced locomotor activity behaviour, and also, studies that do not show a role for these receptors in mediating locomotor activity in either morphine-treated or control rats [34]. We found that this increase was more effectively suppressed by the administration of a $GABA_B$ agonist than a $GABA_A$ agonist into the NAc, and that this suppression was independent of the centres that have well-established roles in withdrawal such as the VTA and cortex. These results indicate that GABA receptors in the NAc play as important a role as receptors in the VTA, besides the regulatory effect of the VTA on the NAc. It is well known that morphine administration increases the release of dopamine in the NAcSh in a manner similar to that of nicotine and cocaine, and systemic administration of baclofen prevents this increase [35]. A reverse relationship between the NAc and VTA has been hypothesised with respect to dopamine levels during dependence and withdrawal [36]. This reverse interaction between the VTA and NAc can be attributed to the modulatory effect of $GABA_B$ receptors in the NAc on excitatory receptors in this region that is independent of the VTA, as shown in our study, and in tandem with the distinct functioning of D_1-dopaminergic receptors in each region [37]. The subregions of the NAc, which receive distinct projections and have different outputs, interact mostly via GABAergic fibres [38]. Increased dopamine levels were detected in the prefrontal cortex during withdrawal, whereas decreased dopamine levels were shown in the NAc [39]. GABAB receptors are widely distributed in presynaptic membranes of excitatory and inhibitory neurones, and they inhibit the release of neurotransmitters from these neurones that GABAB modulation of excitatory neurotransmission – other than dopaminergic neurotransmission – in the NAc requires further investigation on whether those presynaptic mechanisms are more important than is currently recognised. This present study indicates that the NAcSh and NAcC mediate similar responses to baclofen during withdrawal. The mechanism of this effect could be investigated by further studies focusing on whether GABAergic connections between the NAcSh and NAcC or distinct projections of these regions are involved.

Conclusion

Our results show that the suppressive effect of baclofen on jumping behaviour, which implicates dopaminergic and α_2-adrenergic receptors, can be modulated by GABA$_B$ receptors in the NAcSh and the role of GABA could be tested by measuring GABA levels in this region during withdrawal. Moreover, the effects of baclofen in the NAcSh and NAcC during withdrawal could be investigated by further studies focusing on whether the dense GABAergic pathways between these 2 regions play a role in the mechanism of action of the drug.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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