available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Differential involvement of ventral tegmental $GABA_A$ and $GABA_B$ receptors in the regulation of the nucleus accumbens dopamine response to stress

*Michael Doherty, Alain Gratton**

Douglas Hospital Research Center, Department of Psychiatry, McGill University, 6875 LaSalle Blvd, Montréal Verdun, Québec, Canada, H4H 1R3

ARTICLE INFO

Article history:
Accepted 23 February 2007
Available online 6 March 2007

Keywords:
Voltammetry
Stress
Baclofen
Phaclofen
Muscimol
Bicuculline

ABSTRACT

Evidence indicates that dopamine (DA) transmission in nucleus accumbens (NAcc) is modulated by glutamate (GLUT) projections from medial prefrontal cortex (PFC) to NAcc and the ventral tegmental area (VTA). Local NMDA receptor blockade in NAcc has previously been shown to enhance the DA stress response in this region as well as in the VTA. This raises the possibility that the NAcc DA stress response is regulated by GLUT acting at NMDA receptors located on NAcc GABA output neurons that project to the VTA where GABA is known to regulate DA cell activity. Thus, in the present study, we used voltammetry to examine the effects of intra-VTA administration of $GABA_A$ and $GABA_B$ agonists and antagonists on restraint stress-induced increases in NAcc DA. The results show that local VTA $GABA_B$ receptor activation with baclofen (0.01, 0.1 and 1.0 nmol) dose-dependently inhibited the NAcc DA stress response whereas $GABA_B$ receptor blockade with phaclofen had the opposite effect, resulting in a dose-dependent potentiation of the stress response. A similar potentiation of the NAcc DA stress response was observed following VTA $GABA_A$ receptor blockade with bicuculline, but only at the highest dose (1.0 nmol). Interestingly, intra-VTA injection of the $GABA_A$ receptor agonist, muscimol, at the lowest dose (0.01 nmol) but not at the higher doses (0.1 or 1.0 nmol) also potentiated the NAcc DA stress response, suggesting an action mediated primarily at $GABA_A$ receptors located on non-DA neurons. These results indicate that the NAcc DA stress response is regulated by GABA afferents to VTA DA cells and that this action is differentially mediated by $GABA_A$ and $GABA_B$ receptors. The data suggest that the relevant $GABA_B$ receptors are located on DA neurons whereas the $GABA_A$ receptors are located on GABA interneurons and perhaps also on DA cells. The present findings are also consistent with the idea that the corticofugal GLUT input to NAcc indirectly regulates stress-induced DA release in this region through the GABA feedback pathway to VTA.

* *Corresponding author*. Fax: +1 514 888 4461.
E-mail address: alain.gratton@mcgill.ca (A. Gratton).

0006-8993/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2007.02.081

1. Introduction

Stress will stimulate dopamine (DA) transmission in both the medial prefrontal cortex (PFC) and the nucleus accumbens (NAcc) (Abercrombie et al., 1989). It appears, however, that the NAcc DA response to stress is modulated by a DA-sensitive mechanism in PFC such that increased DA transmission in this cortical region acts to dampen the NAcc DA response to a variety of stimuli including stress (Deutch et al., 1990; Doherty and Gratton, 1996; Vezina et al., 1991). There is evidence implicating also PFC glutamate- (GLUT-) containing neurons some of which are known to project to NAcc and to the ventral tegmental area (VTA) where the mesocorticolimbic DA system originates (Carr et al., 1999; Carr and Sesack, 2000; Sesack and Pickel, 1992).

In addition to stimulating DA transmission, stress will also increase PFC and NAcc levels of GLUT (Moghaddam, 1993) and there is evidence indicating that the NAcc DA response to stress is modulated locally by a GLUT-sensitive mechanism (Keefe et al., 1993; Saulskaya and Marsden, 1995; Wheeler et al., 1995). We have previously reported that the NAcc DA stress response is potentiated by local NMDA receptor blockade (Doherty and Gratton, 1997). In that study we also reported evidence that the local action of GLUT on the NAcc DA stress response is mediated by NMDA receptors located on NAcc output neurons that project to the VTA. Part of this output system comprises GABA neurons that project to VTA either directly or indirectly via the ventral pallidum (Kalivas et al., 1993; Walaas and Fonnum, 1980; Yim and Mogenson, 1980). In VTA, GABA is known to hyperpolarize DA cells, inhibiting their activity by a direct $GABA_B$ receptor-mediated action (Chen et al., 2005; Erhardt et al., 2002). The activity of VTA DA cells is also regulated by GABA acting at $GABA_A$ receptors although here the evidence indicates both a direct inhibitory action as well as a predominant indirect disinhibitory action presumably mediated presynaptically by $GABA_A$ receptors on non-DA interneurons (Churchill et al., 1992; Johnson and North, 1992; Kalivas et al., 1990; Klitenick et al., 1992; O'Brien and White, 1987; Sugita et al., 1992). Local VTA $GABA_A$ and $GABA_B$ receptor activation has been shown previously to modulate DA transmission in NAcc and VTA (Kalivas et al., 1990; Klitenick et al., 1992; Westerink et al., 1996; Xi and Stein, 1998). However, to our knowledge, similar information has not been obtained for the NAcc DA response to stress. Thus, the present study was designed to examine the role of VTA GABA in the NAcc DA response to stress. To this end, we used voltammetry and monoamine selective probes to investigate the effects of intra-VTA administration of $GABA_A$ and $GABA_B$ receptor selective agonists and antagonists on the NAcc DA response to restraint stress.

2. Results

The animals used in the present study had been randomly assigned to one of three dose groups. On 5 consecutive daily sessions, animals in each group were stressed either without pretreatment (control) or following intra-VTA injections of vehicle (VEH) or of one dose of baclofen (BAC), muscimol (MUSC), phaclofen (PHAC) or bicuculline (BICU). All animals within a group received the same dose (0.01. 0.1 or 1.0 nmol) of each drug. Differences in the peak amplitude and the duration of stress-induced increases in electrochemical signal were tested for statistical significance using a repeated-measures 2-way analysis of variance (ANOVA) with one between-subject (dose) and one within-subject (treatment) variable. Post hoc comparisons were performed using a simple effects analysis or, when indicated, Tukey's Honestly Significant Difference (HSD). Peak amplitude was defined as the maximum increase in electrochemical signal, following onset of restraint stress, relative to the signal level recorded just prior to restraining the animal. Duration of the stress response was defined as the time, from onset of restraint stress, for the electrochemical signal to return to levels recorded just prior to restraining the animal.

The data analysis is based on 24 animals (n=8/dose group) with histologically confirmed NAcc electrode and VTA cannula placements. Animals were also excluded from the analysis because of unusually large differences (>40%) in the peak amplitude of their stress response under the two non-drug conditions (VEH and control); this may have resulted from repeated exposure to stress which can lead to a progressive enhancement of the acute NAcc DA stress response. In other animals, testing was terminated and the data discarded when restraint stress under the control (no pretreatment) condition failed to elicit a robust increase in electrochemical signal or when stress-induced increases in electrochemical signal had red:ox ratios of less than 0.5. In the NAcc, reliable increases in electrochemical signals are typically recorded within 2–3 min of onset of restraint stress. Signals continue to rise steadily, generally reaching peak amplitude during the latter half of the 10-minute stress period before slowly declining towards pre-stress levels. In the present study, the mean red:ox ratio at the peak of the stress response was 0.634±0.042. Previous work has shown that, with the Nafion-coated carbon fiber electrode used here, red:ox ratios in this range are indicative of an increase in DA concentration; they also rule out ascorbic acid (AA) and 5-HT as significant contributors to the stress-induced signal increase recorded in NAcc (Doherty and Gratton, 1997; Gerhardt et al., 1999; Glaser et al., 2005).

The results show that stress-induced increases in NAcc DA signals are differentially affected by intra-VTA injections of $GABA_A$ and $GABA_B$ receptor selective agonists and antagonists. The statistical analysis revealed a significant dose-by-treatment interaction ($F_{14,147}$=4.22, p<0.001) and a significant main effect of treatment ($F_{7,21}$=31.22, p<0.001) on the peak amplitude of the NAcc DA response to stress (Figs. 1A and 2A). Post hoc comparisons to the vehicle condition indicated that the stress response was significantly attenuated by the $GABA_B$ receptor agonist baclofen at the intermediate (0.1 nmol; p<0.01) and high (1.0 nmol; p<0.05) doses (Fig. 1A). In contrast $GABA_A$ receptor activation with muscimol significantly enhanced the NAcc stress response but only at the lowest dose (0.01 nmol, p<0.01). In Fig. 2A, it can be seen that both the intermediate (0.1 nmol) and high