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Research Report

The role of NMDA and $GABA_A$ receptors in the inhibiting effect of 3 MPa nitrogen on striatal dopamine level

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ABSTRACT

Nitrogen pressure exposure, in rats, resulted in a decreased dopamine (DA) level by the striatal terminals of the substantia nigra pars compacta (SNc) dopaminergic neurons, due to the narcotic potency of nitrogen. In the SNc, the nigrostriatal pathway is under glutamatergic and GABAergic control mediated by ion-channel NMDA and $GABA_A$ receptors, main targets of volatile anesthetics. The aim of this study was to investigate the role of these receptors in the regulation of striatal dopamine level under nitrogen narcosis. Under general anesthesia, male Sprague-Dawley rats were bilaterally implanted in the striatum with dopamine-sensitive electrodes and, in the SNc, with guide cannulae for drug injections. After recovery from surgery, the striatal dopamine level was quantified using differential pulse voltammetric measurements in freely moving rats. Focal injections of agonists (NMDA/muscimol) and antagonists (AP7/gabazine) of NMDA/$GABA_A$ receptors were made within SNc. Both normobaric condition and 3 MPa nitrogen pressure were studied. Control experiments confirmed a direct glutamatergic control on the striatal DA level through NMDA receptors. Both direct and indirect GABAergic control through two different types of $GABA_A$ receptors located on GABAergic interneurons and on DA cells were indicated. Under nitrogen pressure, the decrease in dopamine level (20%) was suppressed by both NMDA and $GABA_A$ agonist infusion. There was an unexpected increasing DA level, induced by AP7 (about 10%) and gabazine (about 30%). These results indicate that NMDA receptors remain functional and suggest a decreased glutamate release. The findings also describe an increase of $GABA_A$ receptor-mediated inhibition on DA cells under nitrogen pressure exposure.

1. Introduction

Inert gases at raised pressure induce neurochemical changes in the central nervous system associated with a set of motor and cognitive symptoms called inert gas narcosis (Bennett and Rostain, 2003). Previous works have demonstrated the implication of the nigrostriatal pathway, which control motor and locomotor processes, in the occurrence of the neurological symptoms of nitrogen narcosis.

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Abbreviations: AP7, D-2-amino-7-phosphonoheptanoic acid; DA, dopamine; GABA, gamma-amino-butyric acid; GP, globus pallidus; MPa, mega-Pascal; NMDA, N-methyl-D-aspartate; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nuclei

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Exposures to nitrogen pressure resulted in a decreased DA level by striatal terminals of the substantia nigra pars compacta (SNc) dopaminergic neurons of about 20% (Balon et al., 2002a, 2003a,b; Lavoute et al., 2005, 2006). Equivalent decreasing effects were recorded under nitrous oxide, an anesthetic gas at atmospheric pressure (0.1 MPa) as well as under argon (2 MPa) that only shows narcotic potency at pressure (Balon et al., 2002a; Turle et al., 1998). In contrast, exposure to helium, a non-anesthetic gas at 3 MPa, induced an increase of the striatal dopamine level (Abraini and Rostain, 1991). Thus, the nitrogen-induced decrease of dopamine level is attributed to a narcotic effect rather than to a pressure *per se* effect.

At the SNc level, the nigrostriatal pathway would be under the control of excitatory glutamatergic afferents (Gerfen and Wilson, 1996), originating from prefrontal cortex and subthalamic nucleus, acting on *N*-methyl-D-aspartate (NMDA) receptors located on dopaminergic neurons (Albers et al., 1999; Wedzony et al., 2001), as demonstrated by the increased activity of dopaminergic neurons (Christoffersen and Meltzer, 1995) and by the enhanced striatal DA release (Balon et al., 2003a; Westerink et al., 1992) following NMDA administration in SNc. In addition, most afferents in SNc are GABAergic (Bolam and Smith, 1990) and mediate an inhibitory control on the nigrostriatal pathway preferentially through $GABA_A$ receptors (Paladini et al., 1999) localised on DA cells (Sugita et al., 1992). This inhibitory control originating from the substantia nigra pars reticulata (SNr) and/or collaterals of nigro-thalamic output pathway controls directly the striatal dopamine level, or indirectly by intercalated interneurons in the SNc (Balon et al., 2002b; Hebb and Robertson, 2000; Lacey et al., 1989).

The mechanism of action of general anesthetics or inert gases according to the "membrane theory" (Miller et al., 1973) or "binding theory" resulting in changes in neuronal function involves the superfamily of ion-channel receptors such as NMDA and $GABA_A$ receptors (for review, see Franks and Lieb, 1994; Little, 1996). Firstly, the neurochemical effects of nitrogen were attributed to an antagonistic action, in SNc, on NMDA receptors, as does nitrous oxide (Balon et al., 2003a). However, recently, results obtained under nitrogen pressure exposure, in SNc, have excluded the hypothesis of a totally antagonistic effect of nitrogen on NMDA receptors and suggested different action sites according to narcotic gases used (Lavoute et al., 2006).

Alternatively, neurochemical and behavioural studies demonstrated a similar effect of intracerebroventricular (i.c.v.) infusion of GABA and nitrogen pressure exposure on striatal DA level (David et al., 2001). These results suggested that nitrogen could induce its sedative subanesthetic action on locomotor and motor activity by interacting with $GABA_A$ receptors (David et al., 2001), but not $GABA_B$ receptors (Abraini et al., 2003).

From these findings, the decrease of striatal DA level recorded under nitrogen pressure up to 3 MPa could be explained by an increase of the inhibitory control mediated by $GABA_A$ receptors. To confirm this hypothesis, focal administration in the SNc of agonists and antagonists of NMDA and $GABA_A$ receptors were investigated to appreciate the role of glutamatergic and GABAergic control on striatal dopamine level in nitrogen narcosis versus normobaric conditions.

2. Results

2.1. *Drug control effects*

2.1.1. *PBS administration*

The administration of the vehicle (PBS) in the SNc (Figs. 1 and 2, open diamonds, $n=7$, ns) did not induce any change on the basal dopamine release during the 3-h control period.

2.1.2. *NMDA or AP7 administration (Fig. 1)*

At atmospheric pressure, the basal extracellular dopamine level, significantly modified by the administration of 0.5 nM NMDA ($n=5$, $H=22.98$, $p<0.001$; Fig. 1, filled triangles), produced a significant increase (+5% for 1 h, $n=5$, *U*-test, $p<0.01$) compared to no effect upon administration of 0.05 nM NMDA (Balon et al., 2003a) and a very strong effect upon administration of 1 nM NMDA (data not shown).

In contrast, administration of 1 nM AP7, a dose used to increase the threshold pressure of the occurrence of the behavioural patterns of symptoms of high-pressure nervous syndrome (Millan et al., 1989) as well nitrogen narcosis (Abraini et al., 2003), produced ($n=4$, $H=169.9$, $p<0.001$, Fig. 1, open triangles) a significant decrease of −10% for the first 50 min, reaching a minimum value of −20% after 150 min ($n=4$, *U*-test, $p<0.01$). The decreased extracellular dopamine level induced by AP7 administration persisted for 4 h, before returning to the control values that were obtained prior to the administration of the drug (results not shown). Changes in the striatal dopamine release induced by NMDA and AP7 injections were significantly different from each other (*U*-test, $p<0.001$; data not shown).

2.1.3. *Muscimol or gabazine administration (Fig. 2)*

Administration of 10 nM muscimol ($n=4$, $H=134.1$, $p<0.001$; Fig. 2, filled squares), a dose used to have more pronounced response than 1 nM (results not shown), produced a significant increase after 30 min, reaching 20% (after 100 min) of the striatal level of DA ($n=4$, *U*-test, $p<0.01$). The increased dopamine release induced by muscimol persisted for 4 h, before returning to the control value recorded before drug administration (results not shown).

Injection of 1 μM gabazine ($n=4$, $H=41.1$, $p<0.001$; Fig. 2, open squares), a dose used to avoid epileptic seizures produced by a higher dose (10 μM), induced a transient increase of 5% for 30 min, and then had no further effect ($n=4$, *U*-test, ns).

2.2. *Exposure to 3 MPa nitrogen*

Exposure to 3 MPa of nitrogen led to a significant decrease in the amplitude of DA electrochemical response in the striatum ($n=10$, $H=133.5$, $p<0.001$) that reached a minimum value of −20% ($n=10$, *U*-test, $p<0.001$) after a 40-min period of stay at 3 MPa. This decrease persisted until the end of the exposure to 3 MPa (Figs. 3 and 4, open circles).

2.2.1. *Nitrogen with PBS administration*

The nitrogen-induced decrease of striatal dopamine release was not significantly altered by local PBS injection in SNc (Figs. 3 and 4, open diamonds; $n=7$, *U*-test, ns).