

Nitric oxide (NO) and central dopamine (DA) D₃ receptor reactivity to quinpirole in rats

Ryszard Brus¹, Ryszard Szkilnik¹ and
Richard M. Kostrzewa²

¹Department of Pharmacology, Silesian Academy of Medicine, 38 H. Jordan St., 41-808 Zabrze, Poland; ²Department of Pharmacology, College of Medicine, East Tennessee State University, Johnson City, TN 37614, USA

Abstract. Nitric oxide (NO) has been implicated in large number of pathologies and in normal physiological function of the brain. The aim of this study was to recognize the effect of Nitro-L-Arginine Methyl Ester •HCl (NAME) and L-Arginine Ethyl Ester.HCl (ARGININE) on reactivity of the central DA D₃ receptor to agonist (Quinpirole) in rats. For this reason we have been used specific behavioural procedure such yawning behaviour which is mediated *via* central DA D₃ receptors. Experiments were performed in adult male Wistar rats treated daily with quinpirole (0.05 mg/kg IP) or vehicle (0.9% NaCl) for the first 11 days from birth to obtain of the central D₃ receptor supersensitivity. NAME and ARGININE in different way modified response of the central DA receptor to quinpirole estimated by means yawning behavioural procedure.

Key words: nitric oxide, dopaminergic, central nervous system, rats, yawning

INTRODUCTION

Recent evidence suggest that nitric oxide (NO), a potent activator of the guanyl-cyclase-cyclic GMP enzyme system in the brain and in peripheral tissues, acts as a novel intracellular messenger of the central nervous system (CNS) (Bruhwyler et al. 1993, Southam and Garthwaite 1993). It has been suggested that in the CNS, NO is implicated with physiological function such a memory and learning, regulation of cerebrovascular flow, food and water intake and mediation of nociception (Bruhwyler et al. 1993, Estall et al. 1993). It has also been involved in the neurotoxicity of Alzheimer's and Huntington's diseases, in cerebral ischemia and stroke, in alcohol - induced brain damage, and in the release and uptake of neurotransmitters in mammalian brain (Nowicki et al. 1991, Lancaster 1992, Dawson and Dawson 1994).

Because central DA systems are known to be involved in the many physiological and pathological activities in mammals and in the human the aim of this study was to examine the role of NO-synthase inhibitor and NO-donor on the reactivity of the central DA D₃ receptor reactivity to agonist. For this reason we have been used specific behavioural procedure such yawning behaviour.

METHODS

Female Wistar albino pregnant rats were bred in a home colony and housed at $22 \pm 1^\circ$ on a light/darkness 12 h cycle (light on at 7⁰⁰) and allowed free access to palleted food and water. When animals delivered, litters were treated daily IP with quinpirole •HCl (RBI, Natic, USA) 0.05 mg/kg or saline (0.9% NaCl 1.0 ml/kg) for 11 consecutive days to obtain permanent central DA D₃ receptor supersensitivity (Kostrzewa and Brus 1991, Kostrzewa et al. 1993).

Yawning behaviour was observed in adult 3 month old male offspring. Rats were placed in individual clear glass cages in a quiet, well-ventilated and well-lighted room, and were given 30 min to acclimate. Afterwards, each rat was injected IP with saline vehicle and observed for 60 min beginning

immediately after injection. At the end of this session, each rat was injected IP with quinpirole •HCl 0.0125 mg/kg and observed for 60 min again. Then rats were challenged day by day by increased doses of quinpirole •HCl (0.025, 0.05, 0.1 or 0.2 mg/kg) and observations were repeated as above. Results were expressed in the form of dose response curves.

In the next part of the study single dose of quinpirole •HCl caused maximal effect was used (0.05 mg/kg) for further study, only. Ten minutes before quinpirole •HCl IP apply, N-Nitro-L-Arginine Methyl Ester •HCl (NAME, Sigma) 25 mg/kg IP or L-Arginine Ethyl Ester •HCl (L-ARGININE, Sigma) 300 mg/kg IP were injected, and number of yawns was counted for 60 min as above. Beside the effects of NAME and L-ARGININE on yawning behaviour in the same animals were observed 10 min after vehicle (0.9% NaCl 1.0 ml/kg) challenge for 60 min as above.

Behavioural data from treated and control groups of rats were compared by an analysis of variance (ANOVA).

RESULTS

A challenge dose of quinpirole •HCl increased yawning behaviour in both group of rats (Fig. 1). However, quinpirole-induced yawning was increased to a great extend in the group of rats that was ontogenically primed with quinpirole (1-11 postnatal day).

NAME 25 mg/kg IP by itself caused similar response in the term of number of yawns in both (control and primed) groups of rats (Fig. 2). Quinpirole caused lower effect in both examined groups when in was pretreated with NAME 25 mg/kg as compare to control (quinpirole alone). Effect was more expressed in control (non-primed) group.

L-ARGININE 300 mg/kg IP by itself does not influenced on number of yawns in both examined groups of rats as compare to control (Fig. 3). L-ARGININE does not modified effect of quinpirole on yawning behaviour in both groups of rats (control and primed).

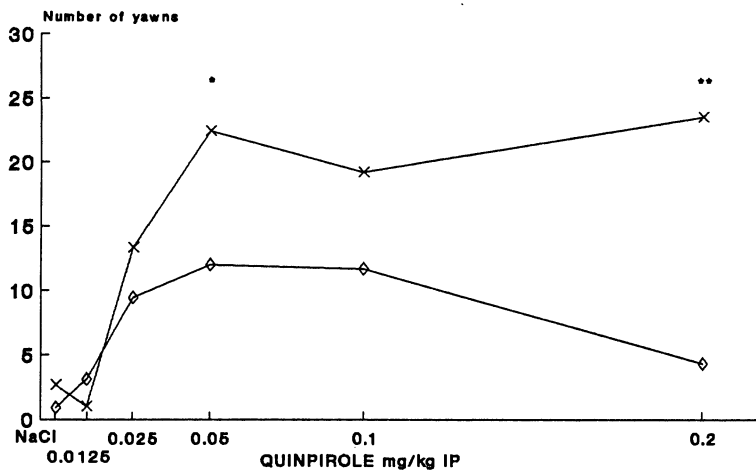


Fig. 1. Effect of quinpirole \cdot HCl on number of yawns in control and neonatally primed with quinpirole male Wistar rats ($n=8$). Explanation: diamond, control 0.9% NaCl 1.0 ml/kg IP 1-11 day of postnatal life ex, primed Quinpirole \cdot HCl 0.05 mg/kg IP 1-11 day of postnatal life * $2 P<0.05$; ** $2 P<0.005$.

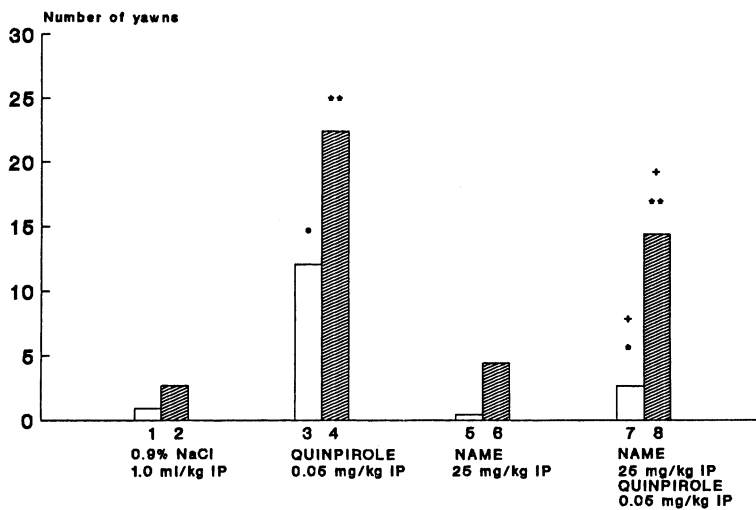


Fig. 2. Effect of NAME on quinpirole induced number of yawns in control and primed male Wistar rats ($n=8$). Explanation: 1, 3, 5, 7 - control 0.9% NaCl 1.0 ml/kg IP 1-11 day of postnatal life 2, 4, 6, 8 - primed Quinpirole \cdot HCl 0.05 mg/kg IP 1-11 day of postnatal life * $1/3$; $5/7 - 2P<0.01$, ** $2/4$; $6/8 - 2P<0.001$, + $3/7$; $4/8 - 2P<0.05$.

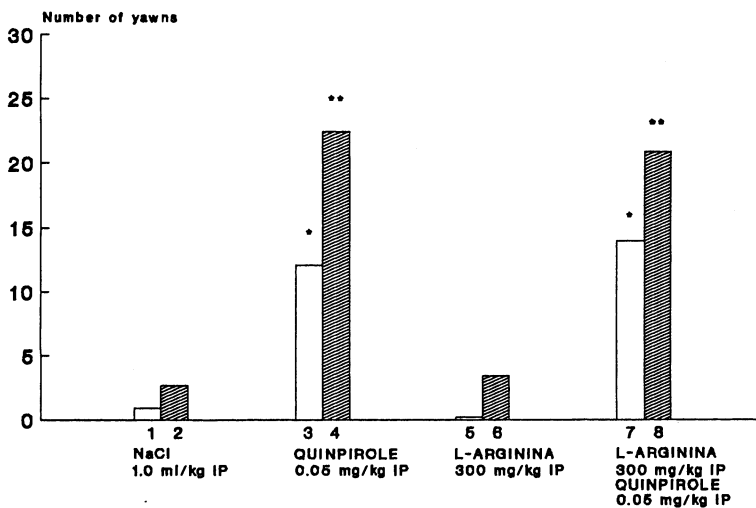


Fig. 3. Effect of L-ARGININE on quinpirole induced number of yawns in control and primed male Wistar rats ($n=8$). Explanation as in Fig. 2.

DISCUSSION

Central DA agonists are known to induce yawning behaviour in male rats (Mogilnicka and Klimek 1977, Grower et al. 1984, Yamada et al. 1990). Because D₃ receptors have 113-fold great affinity for quinpirole as compare to D₂ (Sokoloff et al. 1990), and because low doses of quinpirole induced yawning behaviour, it has been postulated that D₃ receptor is responsible for DA agonist - induced yawning behaviour (Kostrzewa and Brus 1991, Damsma et al. 1993). Recently, we found that ontogenic treatments with the DA agonist quinpirole would sensitize receptors to quinpirole - induced yawning responses in adulthood (Kostrzewa et al. 1993), and in present experiment we have confirm previous finding.

NO is also known to inhibit DA release in the striatum of rats, but on the other hand it does not affect amphetamine - stimulated DA release in nucleus accumbens and inhibits DA uptake in rat striatal synaptosomes (Pogun et al. 1994). Some authors have shown that NO is capable of inducing DA release from striatal slices (Zhu and Luo 1992, Lonart et al. 1993). On the behavioural level it has been shown that NO participates in yawning behaviour of rats after apomorphine challenge. Peripheral and central administration of NAME and NMMA (N-monomethyl-L-arginine), the inhibitors of NO synthase prevents apomorphine - induced yawning (Melis and Argiolas 1993). We have confirm above results using more specific D₃ agonist - quinpirole. Beside we have shown that exogenous NO donor L-ARGININE does not influenced reactivity of the central D₃ receptor in rats.

In conclusion, our results suggest that NO play important modulatory role as an agent of the central DA D₃ receptor activity.

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