European Neuropsychopharmacology (2011) 21, 918–927

www.elsevier.com/locate/euroneuro

Effects of olanzapine on extracellular concentrations and tissue content of neurotensin in rat brain regions

Susanne H.M. Gruber[a], Francesco Angelucci[b], George G. Nomikos[c], Aleksander A. Mathé[a,*]

[a] *Institution of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Huddinge University Hospital, S-141 86 Huddinge, Sweden*
[b] *IRCCS Santa Lucia Foundation, Department of Clinical and Behavioral Neurology, Rome, Italy*
[c] *Takeda Global Research & Development Center Inc, Deerfield, IL 60015, USA*

Received 7 November 2010; received in revised form 25 December 2010; accepted 9 January 2011

KEYWORDS
Neurotensin;
Olanzapine;
D-amphetamine;
Schizophrenia;
Striatum;
Cortex;
Microdialysis

Abstract

We have previously shown that both the psychostimulant D-amphetamine and the antipsychotics haloperidol and risperidone affect extracellular concentrations and tissue content of neurotensin (NT) in distinct brain regions. This study investigated the effects of acute olanzapine (1, 5 mg/kg, s.c.) on extracellular NT-like immunoreactivity (−LI) concentrations in the ventral striatum (vSTR) and the medial prefrontal cortex (mPFC), and the effects of acute D-amphetamine (1.5 mg/kg, s.c.) on extracellular NT-LI in these brain regions after a 30-day olanzapine (15 mg/kg, p.o.) administration in rats. The effects of a 30-day olanzapine (3, 15 mg/kg, p.o.) administration and D-amphetamine (1.5 mg/kg, s.c.) coadministration during either the last day (acute) or the last 8 days (chronic) on NT-LI tissue content in distinct rat brain regions were also studied. Acute olanzapine increased extracellular NT-LI, in both the vSTR and the mPFC. Chronic olanzapine increased and decreased basal extracellular NT-LI in the vSTR and the mPFC, respectively, and abolished the stimulatory effects of acute D-amphetamine on extracellular NT-LI in these brain regions. Chronic olanzapine as well as acute and chronic D-amphetamine affected NT-LI tissue content in a brain region-dependent manner. Chronic olanzapine prevented the effects of acute and chronic D-amphetamine on NT-LI tissue content in certain brain regions. The fact that olanzapine and D-amphetamine affected extracellular NT-LI in the vSTR and mPFC as well as NT-LI tissue content in distinct brain regions further supports the notion that NT plays a role in the therapeutic actions of antipsychotic drugs and possibly also in the pathophysiology of schizophrenia.

* Corresponding author. Tel.: +46 8 58586626; fax: +46 8 300972.
E-mail address: aleksander.mathe@ki.se (A.A. Mathé).

0924-977X/$ - see front matter © 2011 Elsevier B.V. and ECNP. All rights reserved.
doi:10.1016/j.euroneuro.2011.01.003

1. Introduction

Although the pathophysiology of schizophrenia remains unknown, several neuronal mechanisms have been implicated. Considerable attention has been focused on the mesotelencephalic dopaminergic projections to the ventral striatum (vSTR) and the medial prefrontal cortex (mPFC). Hyperdopaminergia in the nucleus accumbens, a subdivision of the vSTR, has been implicated in psychosis (Davis et al., 1991; Kalivas and Nakamura, 1999), whereas a decrease in neuronal activity in the mPFC has been suggested to underlie negative symptoms and impaired cognition (Goldman-Rakic and Selemon, 1997). In addition, abnormal inputs from other limbic structures, such as the hippocampus, to the vSTR have been posited as a model for certain schizophrenia-like symptoms (Bogerts, 1999; Grace, 2000; Moore et al., 1999; Weinberger and Lipska, 1995).

The neuropeptide neurotensin (NT) has been suggested to be involved in the pathophysiology of schizophrenia and the mechanism of action of antipsychotic drugs. For example, schizophrenic patients show lower NT cerebrospinal fluid concentrations compared to control subjects (Lindström et al., 1988), and treatment with antipsychotic drugs normalizes NT concentrations to control values (Breslin et al., 1994; Sharma et al., 1997). Neurotensin is colocalized with dopamine (DA) in the mesolimbocortical, but not the nigrostriatal, dopaminergic neurons (Bean et al., 1989; Hökfelt et al., 1984; Kalivas, 1993). In addition, the majority of NT receptors in the caudate is associated with nigrostriatal DA nerve terminals and is thought to influence DA release (Kitabgi, 1989; Masuo et al., 1990; Quirion, 1983). Earlier experiments show that changes in dopaminergic neurotransmission elicited by administration of the psychostimulants, D-amphetamine and phencyclidine (PCP), are accompanied by increased extracellular NT-like immunoreactivity (−LI) concentrations in the vSTR and the mPFC (Hertel et al., 1996). Moreover, we have also reported interactions between NT and the DA-ergic system in response to D-amphetamine. Thus, D-amphetamine-evoked increase in extracellular NT-LI concentrations is mediated through both DA-D_1 and DA-D_2 receptors, given that this action of D-amphetamine is abolished after SCH 23390 or raclopride pretreatment, respectively (Gruber et al., 2002b). Centrally administered NT has been found to produce the same effects as peripherally administered antipsychotic drugs. For example, NT injected intracerebrally antagonizes psychostimulant-induced locomotor hyperactivity (Joliceur et al., 1993; Robledo et al., 1993). Moreover, administration of the NT analog, NT69L, blocks the hyperactivity induced by cocaine and D-amphetamine (Boules et al., 2001). In view of the NT–DA interaction and the findings that NT counteracts psychostimulant-induced behavioral effects, it has been suggested that NT may function as an endogenous neuroleptic (Nemeroff et al., 1992). Several studies on the effects of antipsychotic drugs on the NT system have provided evidence supporting the notion of an altered NT neurotransmission in DA-ergic projection regions as an important component of antipsychotic drug action (Binder et al., 2001; Huang and Hanson, 1997; Merchant and Miller, 1994). For example, the selective DA-D_2 receptor antagonists, raclopride and sulpiride, produce an increase in NT mRNA expression in striatum (Augood et al., 1991). Chronic treatment with antipsychotic drugs has also an effect on basal extracellular concentrations of NT-LI in vSTR as well as on striatal tissue concentrations, and additionally diminishes the increase in NT-LI concentrations induced by D-amphetamine (Gruber et al., 2002a, 2006).

The multireceptor targeting, atypical antipsychotic drug olanzapine exhibits a favorable clinical profile in terms of both efficacy and extrapyramidal side-effects compared to typical antipsychotic drugs (see, e.g., Bymaster et al., 1999; Tollefson and Kunz, 1999). The present study was undertaken to further investigate whether acute as well as chronic olanzapine administration affects the extracellular NT-LI concentrations in the vSTR and the mPFC. Changes in extracellular NT-LI concentrations in these brain regions after pretreatment with olanzapine in combination with acute D-amphetamine were also studied. In addition, effects of chronic administration of olanzapine in combination with acute and chronic D-amphetamine administration on NT-LI tissue content in distinct regions of the brain were also examined.

2. Experimental procedures

2.1. Animals and drug administration

Four separate experiments were carried out (see Tables 1 and 2) using male Wistar rats, (B&K Lab, Sollentuna, Sweden), weighing 320–380 g at the end of the experiment. The animals were given free access to water and food and were housed 4–5 per cage under standard conditions of humidity, room temperature and 12-h light/dark cycle (lights on at 7:00 a.m.). The experiments were approved by the Ethical Committee on Animal Experiments and were conducted in conformity with the Karolinska Institutet´s Animal Care Guidelines. The various treatment groups and the design of the experiments are outlined in Tables 1 and 2; animals assigned to different experiments received similar treatments so that direct comparisons within the present study and between this and our previous studies could be made.

2.1.1. Experiment 1: microdialysis; acute olanzapine

All animals were administered 30 days of vehicle *per os* (p.o.; drinking water with the addition of sweetener, 0.2% saccharin, Apoteket AB, Sweden; pH 6). On the day of the experiment (day 30), the animals were given a subcutaneous (s.c.) injection of either olanzapine (1 or 5 mg/kg) or saline (0.9% NaCl, pH 5.6) in a volume of 1 ml/kg (see succeeding discussion). Olanzapine (supplied by Eli Lilly & Company, USA) was dissolved in saline and acidified with 1 M HCl to pH 5. The doses of olanzapine used in this experiment were in the range of doses previously used in preclinical, neurochemical studies (see, e.g.,

Table 1 Microdialysis experiments: treatment groups and drug administration.

Days 1–30	Day 30: microdialysis
Experiment 1: microdialysis; acute olanzapine	
Vehicle (p.o.)	Saline (s.c.)
Vehicle (p.o.)	Olanzapine1 (s.c.)
Vehicle (p.o.)	Olanzapine5 (s.c.)
Experiment 2: microdialysis; chronic olanzapine	
Vehicle (p.o.)	Saline (s.c.)
Vehicle (p.o.)	Amphetamine (s.c.)
Olanzapine15 (p.o.)	Saline (s.c.)
Olanzapine15 (p.o.)	Amphetamine (s.c.)

Animals received p.o. vehicle (Vehicle) or olanzapine 15 mg/kg (Olanzapine15), s.c. olanzapine 1 mg/kg (Olanzapine1), olanzapine 5 mg/kg (Olanzapine5), D-amphetamine 1.5 mg/kg (Amphetamine) or saline (Saline), according to the schedule above.