Pharmacological Reports 66 (2014) 984–990

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

The effect of risperidone on the mirtazapine-induced changes in extracellular monoamines in the rat frontal cortex

Katarzyna Kamińska, Krystyna Gołembiowska, Zofia Rogóż *

Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland

ARTICLE INFO

Article history:
Received 20 February 2014
Received in revised form 21 May 2014
Accepted 5 June 2014
Available online 21 June 2014

Keywords:
Mirtazapine
Risperidone
Monoamines release
Rats

ABSTRACT

Background: The aim of our study was to understand the mechanism of clinical efficacy of the combination of an antidepressant and risperidone in drug-resistant depression.
Methods: We studied the effect of an antidepressant (mirtazapine) and risperidone (atypical antipsychotic), given separately or jointly on extracellular levels of dopamine (DA), serotonin (5-HT) and noradrenaline (NA) in the rat frontal cortex. The animals were given a single intraperitoneal injection of risperidone (1 mg/kg) and mirtazapine (10 and 20 mg/kg). The release of monoamines in the rat frontal cortex was investigated using a microdialysis in freely moving animals, and monoamine levels were assayed by HPLC with coulochemical detection.
Results: Risperidone increased the cortical extracellular levels of DA, 5-HT and NA. Similarly, mirtazapine dose-dependently increased the cortical extracellular levels of the monoamines studied. A combination of mirtazapine either at the higher dose (20 mg/kg) or at both doses (10 and 20 mg/kg) with risperidone produced a significant effect on DA and NA release, respectively compared to the effect of any drug given alone. The increase in the DA (but not NA) release induced by mirtazapine plus risperidone was partly blocked by the selective 5-HT_{1A} antagonist WAY 100635 (0.2 mg/kg).
Conclusions: Our data indicate that the increase of cortical extracellular levels of DA and NA by combined administration of mirtazapine and risperidone may be of crucial importance to the pharmacotherapy of drug resistant depression, and that, among other mechanisms, 5-HT_{1A}, 5-HT_{2A}, α_2-adrenergic and histamine H_1 receptors may play some role in this effect.

Introduction

Major depressive disorder (MDD) is a chronic mental illness with a life time prevalence of 5–12% in adult men and 9–26% of adult women (*e.g.*, [1]). Although initial antidepressant (AD) therapy significantly reduces symptoms of depression in many patients, only 50–60% of persons with MDD respond to the treatment. Moreover, *ca.* 30–40% of MDD patients never achieve symptom resolution by means of a standard AD therapy [2,3]. The problem of AD-resistant depression has been the subject of a number of thorough studies, with no apparent therapeutic success, though. Hence, there is a strong need for an alternative antidepressant treatment. Atypical antipsychotics (*e.g.*, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) belong to the agents that are expected to potentiate the efficacy of ADs [1,4–6]. Several clinical reports have postulated a beneficial effect of an additional low dose risperidone to ongoing treatment with ADs (in particular, selective serotonin reuptake inhibitors (SSRI), such as fluoxetine, fluvoxamine or paroxetine [7–11]. Like other atypical antipsychotic drugs, risperidone is known to produce minimal extrapyramidal side-effects compared to classical antipsychotics (*e.g.*, chlorpromazine) [12]. This drug is *ca.* 20–50 times more potent in its binding to 5-HT_{2A} serotonin receptors than to α_1-adrenergic, dopamine D_2, histamine H_1 and α_2-adrenergic receptors [13,14]. It has been proposed that risperidone in lower doses acts mainly by blocking 5-HT_{2A} serotonin receptors, while at higher doses it mostly blocks D_2 dopamine receptors. Moreover, it has been shown that mirtazapine, a noradrenergic and specific serotonergic antidepressant is an agonist of 5-HT_{1A} receptor and an antagonist of the central α_2-auto- and hetero-adrenoreceptors. It also blocks 5-HT_2 and 5-HT_3 receptors and displays a very low affinity for DA receptors and a high affinity for histamine H_1 ones, but does not inhibit the uptake of NA and 5-HT [15]. Our previous studies indicated that risperidone applied at low doses (0.05 or 0.1 mg/kg) enhanced the antidepressant-like activity

* Corresponding author.
E-mail address: rogoz@if-pan.krakow.pl (Z. Rogóż).

http://dx.doi.org/10.1016/j.pharep.2014.06.009
1734-1140/

of ADs in the forced swimming test in animals [16–18]. Moreover, the frontal cortex has been proposed as an area involved in depression, since positron emission tomography studies revealed functional changes in this structure in depressed patients [19–21]. It has been suggested that the stimulation of DA transmission in the prefrontal cortex (PFC) has a role in the AD action [22,23]. In addition, disturbances not only in DA but also in 5-HT and NA neurotransmitter systems have been postulated to be involved in the pathogenesis of mood disorders including depression [24–26].

In the light of these observations, the aim of the present study was to determine the influence of mirtazapine (10 and 20 mg/kg) and risperidone (1 mg/kg), given separately or jointly, on the extracellular levels of DA, 5-HT and NA in the rat frontal cortex of freely moving rats using microdialysis. Furthermore, we used a 5-HT_{1A} receptor antagonist to determine the role of these receptors in the change in extracellular levels of DA, 5-HT and NA after the combined treatment with risperidone and mirtazapine. The effect of co-treatment with risperidone and mirtazapine, on the extracellular levels of monoamines in the rat frontal cortex, measured by microdialysis has not been studied, yet.

Materials and methods

Animals

All experiments were performed on male Wistar-Han rats (280–350 g) derived from Charles River (Germany). Animals were kept in temperature- and humidity-controlled rooms with a 12-h light–dark cycle (the light on at 7 a.m.), and with free access to water and food. The experimental procedures were conducted in strict accordance with Polish legal regulations concerning experiments on animals (Dz. U. 05.33.289). The experimental protocols were approved by Local Ethics Commission for Experimentation on Animals at the Institute of Pharmacology, Polish Academy of Sciences in Kraków.

Drugs administration

Animals were administered a single intraperitoneal (*ip*) injection of risperidone (RIS, Tocris, Bristol, UK) at a dose of 1 mg/kg or mirtazapine (Tocris, Bristol, UK) at doses of 10 and 20 mg/kg. Mirtazapine and risperidone were dissolved in 0.1 M tartaric acid and the solution was adjusted to pH 6–7 with 0.1 N NaOH. Both drugs were given as indicated in the figures. WAY 100635 (Tocris, Bristol, UK) at a dose of 0.2 mg/kg was dissolved in a 0.9% NaCl and given (*sc*) 10 min before mirtazapine and risperidone administration. All the chemicals used for high performance liquid chromatography (HPLC) were from Merck (Warszawa, Poland).

Microdialysis

Rats were anaesthetized with ketamine (75 mg/kg *im*) and xylazine (10 mg/kg *im*), placed in a stereotactic apparatus (David Kopf Instruments, Tujunga, CA, USA) and subsequently a microdialysis probe was implanted in the rat frontal cortex with coordinates (mm) $A + 2.8$, $L + 0.8$, $V - 6.0$ from the dura. Twenty four hours after implantation, probe inlets were connected to a syringe pump (CMA, Sweden) which delivered an artificial CSF (aCSF) composed of (mM): NaCl 147, KCl 4.0, $CaCl_2$ 1.2, $MgCl_2$ 1.0 at a flow rate of 2 μl/min. Baseline samples were collected every 30 min after the washout period. Appropriate drugs were then administered and dialysate fractions were collected for 180 min. At the end of the experiment, the rats were sacrificed and their brains were examined histologically to validate probe placement.

Analytical procedure

DA, 5-HT and NA were analysed by HPLC with coulochemical detection. Chromatography was performed using an Ultimate 3000 System (Dionex, USA), coulochemical detector Coulochem III (model 5300, ESA, USA) with a 5020 guard cell, a 5014B microdialysis cell and a Hypersil Gold-C18 analytical column (3 × 100 mm). The mobile phase was composed of 0.05 M potassium phosphate buffer adjusted to pH = 3.6, 0.5 mM EDTA, 16 mg/L 1-octanesulfonic acid sodium salt, and a 2% methanol. The flow rate during analysis was 0.7 ml/min. The applied potential of a guard cell was +600 mV, while those of microdialysis cell were E1 = −50 mV, E2 = +300 mV and a sensitivity was set at 50 nA/V. The chromatographic data were processed by Chromeleon v. 6.80 (Dionex, USA) software run on a PC computer.

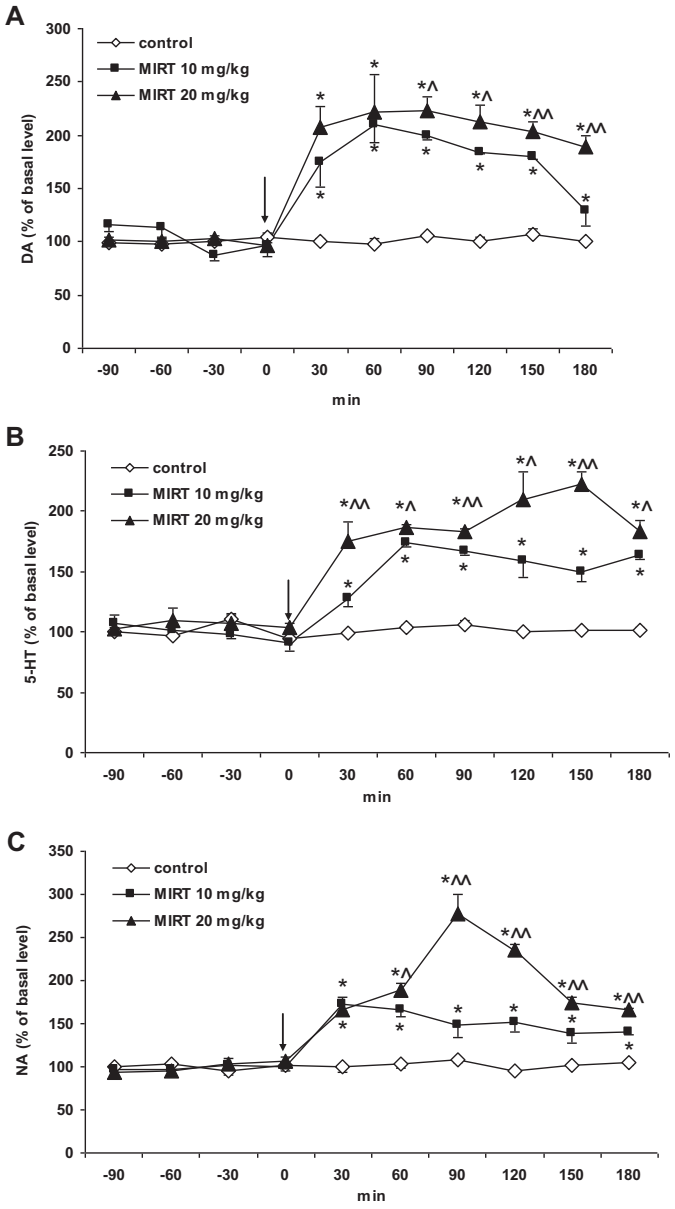

Fig. 1. The effect of mirtazapine (MIRT) 10 and 20 mg/kg on extracellular level of DA (A), 5-HT (B) and NA (C) in the rat frontal cortex. The drugs were given *ip* as indicated with an arrow. Each value is the mean ± SEM of 6–8 measurements and is expressed as a % of the basal level. $^{*}p < 0.01$ *vs.* control group; $^{\wedge}p < 0.05$, $^{\wedge\wedge}p < 0.01$ MIRT 10 mg/kg *vs.* MIRT 20 mg/kg group (repeated measures ANOVA and Tukey's *post hoc* test).