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c-Fos expression response to olanzapine, amisulpride, aripiprazole, and quetiapine single administration in the rat forebrain: Effect of a mild stress preconditioning

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ABSTRACT

Antipsychotics have been shown to stimulate different forebrain areas, whereas some of them are sensitive to stress. In the present study, effect of a single administration of olanzapine (OLA), amisulpride (AMI), aripiprazole (ARI), and quetiapine (QUE) on the activity of cells in the striatal dorsolateral (stDL) area, the periventricular zone (peVZ), the septal ventrolateral (seVL) nucleus, and the accumbens nucleus shell (shACC) and core (coACC) was investigated in male rats preconditioned with a mild stress complex (CMS) for 20 days. The objective of the study was to extend the anatomical-functional knowledge on the mechanism of selected antipsychotics with the goals: 1) to analyze the ability of the selected antipsychotics to induce c-Fos protein expression in the above mentioned forebrain structures and to map the pattern of their topography and 2) to find out whether longer-lasting mild stress preconditioning may modify the impact of the selected antipsychotics on the activity of cells in the forebrain areas in adult rats. Ten groups of rats were used. CMS complex contained five stressors: cage crowding, air-puff noising, wet bedding, predator stress, and forced swimming. AMI (20 mg/kg), OLA (5 mg/kg), QUE (15 mg/kg), and ARI (10 mg/kg/b.w.) were administered intraperitoneally and 90 min later the animals transcardially perfused by fixative. c-Fos was visualized by ABC complex. In unstressed animals, OLA and ARI elevated c-Fos expression in all areas studied, AMI and QUE in all areas except stDL, seVL and coACC, shACC FL-2 (shACC posterior level), respectively. CMS potentiated the effect of AMI in coACC, and QUE in shACC FL-2 and suppressed the effect of AMI in peVZ, and ARI in peVZ and seVL. The present data provide new insights into activity of cells in response to CMS challenge, which might be helpful in understanding the diverse clinical effects of atypical antipsychotics.

1. Introduction

Antipsychotics are group of psychotropic drugs widely used in the treatment of mental disorders with the main indications for the treatment of schizophrenia and the bipolar disorder (Taylor et al., 2018). A common mechanism of the antipsychotic action is the dopamine (DA) receptors blockade (Kapur and Mamo, 2003), but their affinity to DA receptors and other pharmacological characteristics differ substantially (Horacek et al., 2006). Olanzapine (OLA), amisulpride (AMI), and quetiapine (QUE) belong to the second, while aripiprazole (ARI) is considered to be a representant of the third generation of atypical antipsychotics (Mailman and Murthy, 2010). OLA and QUE, for their multiple receptor affinities, are classified as MARTA (Multi-acting Receptor Targeted Antipsychotics). QUE together with the prototype atypical clozapine are characteristic by fast dissociation from D_2 receptors (Kapur and Seeman, 2000; Seeman, 2014). AMI is a benzamide derivate with high-affinity for dopaminergic D_2/D_3 and affinity for 5-HT_7 receptors, which are supposed to be the route of the mechanism of its antidepressant properties (Schoemaker et al., 1997; Abbas et al., 2009). ARI, representing the third generation of antipsychotics, is characterised by a partial agonistic activity on the D_2 receptor subpopulations (Assie et al., 2008) and 5-HT_{1A} receptors and as antagonist on 5-HT_{2A} receptors (Swainston-Harrison and Perry, 2004). All four antipsychotics have characteristics of atypical group, whereas OLA, ARI, and QUE are neuroleptics with low potency for the extrapyramidal side effects (EPS) (Nemeroff et al., 2002; Natesan et al., 2006).

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Although AMI induces EPS and hyperprolactinaemia (Montejo, 2008), its effect on the negative and depressive syndromes classifies it as an atypical neuroleptic (Pani and Gessa, 2002; Mandal et al., 2014).

Antipsychotic drugs produce different, but characteristic patterns of immediate early gene (c-Fos) expression in rat brain. c-Fos immunohistochemistry has generally been accepted as a useful tool to map functional circuits in the central nervous system (Bullitt, 1990; Herdegen and Leah, 1998; Slattery et al., 2005). Pharmacological and pre-clinical studies have supported the fact that c-Fos may serve as an indicator of anatomical sites, which may have clinically predictive aspects (Sumner et al., 2004). At present, c-Fos has been broadly used as an anatomical-functional indicator of a short-lasting cell stimulation in a number of neuroactive drugs (Yanagida et al., 2016). All the above-mentioned antipsychotics have been shown to induce c-Fos mRNA (Wan et al., 1995; Kaczmarek and Robertson, 2002; Pereira et al., 2014; Batista et al., 2016) or c-Fos protein expression (Semba et al., 1996; Seillier et al., 2003) in different brain areas (Wisden et al., 1990).

The stress diathesis has been shown to be a risk factor for the development of different mental disorders including schizophrenia (Jones and Fernyhough, 2007). Marrocco (2013) has indicated that early life stress may affect the effect of antipsychotics leading to a protection against extrapyramidal motor effects in the adulthood. A linkage between the persistent stress challenges and emotional, social, and physiological dysfunctions have been demonstrated in rodents (Amat et al., 2005; Berton et al., 2006; Tsankova et al., 2006). It is believed that complex of mild stressors used in animal models may mimic a number of unpredictable stressors of the human natural environment (Nyuyki et al., 2012). It has also been shown that stress may indirectly interfere with the effect of different drugs or psychopharmacologic agents and act harmfully on the human health (Post, 1992; Tennant, 2002).

The objective of the present study was to extend the anatomical-functional knowledge on the mechanism of selected antipsychotics with the goals: 1) to analyze the ability of the selected antipsychotics to induce c-Fos protein expression in the selected forebrain structures, including the striatal dorsolateral area, the periventricular zone, the septal ventrolateral nucleus, and the accumbens nucleus shell and core and to map the pattern of the c-Fos topography and 2) to find out whether longer-lasting mild stress preconditioning may modify the impact of the selected antipsychotics on the activity of cells in the forebrain areas in adult rats. The regions of interest were chosen based on the fact that they could enhance c-Fos expression according to their pharmacological profile in these regions (Ananth et al., 2001) and that the general activity of these regions is supposed to be distinctly affected by CMS (Gudelsky et al., 1989; Meltzer et al., 1989; Cullinan et al., 1995; Sebens et al., 2001).

2. Materials and methods

2.1. Animals

Adult (9–10 weeks old) male Sprague Dawley rats (n = 74), purchased from Velaz (Prague, Czech Republic) weighing 280–300 g, were housed three or four per cage in a room with controlled temperature (22 ± 1 °C), light (12-h light/dark cycle with lights on at 06:00 h), and humidity (55%). Animals were provided with a regular rat chow (dry pellets) and tap water *ad libitum*. Principles of the laboratory animal care and the experimental procedures used were approved by the State Veterinary and Food Administration of the Slovak Republic Committee (Approval protocol number 1461/17–221). The investigation conditions were in accordance with the guidelines of the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

2.2. Stress preconditioning mode and treatments

The rats were divided into 10 groups: 1) vehicle (VEH, n = 5); 2) AMI (n = 6); 3) OLA (n = 5); 4) QUE (n = 6); 5) ARI (n = 5); 6) VEH injected animals exposed to mild unpredictable stress complex – CMS, CMS + VEH (n = 5); 7); CMS + AMI (n = 6); 8) CMS + OLA (n = 6); 9) CMS + QUE (n = 6); and 10) CMS + ARI (n = 5). Five types of stressors were used: crowding (CR, instead of regular number 3–4, 7–8 rats were placed into the cage 380 × 590 × 200 mm of size, for 24 h), air-puff (AP, air noise divided into 45 episodes, each of them lasting 1 min, randomized by a computer for 24 h), wet bedding (WB, 500 ml of water poured into the cages for 24 h), predator stress (PS, 5 × 5 × 10 cm large wood piece wrapped by a rag and saturated by a cat odor for three days for 24 h), and forced swimming (FS, immersion of the rats in a 45 cm tall and 25 cm wide glass cylinder filled with 24 ± 1 °C water for 10 min). The animals were exposed to stressors for 20 days with the following sequence of the stressors application: crowding, air-puff, wet-bedding, crowding, predator stress, forced swimming, air-puff, wet-bedding, crowding, predator stress, forced swimming, air-puff, wet-bedding, crowding, predator stress, wet-bedding, air-puff, forced swimming, crowding, and predator stress. Except the forced swimming, which lasted 10 min, the time exposure to other stressor lasted 24 h (from 8:30 a.m. of the one day to 8:30 a.m. of the next day). After cessation of the forced swimming, the animals were returned to their home cages and exposed to warming lamp until get dry.

On the 21st day of the experiment, after cessation of the 20 days-lasting CMS preconditioning, the rats were free of the stress exposure. On the 22nd day, approximately 24 h after the last CMS exposure, both stressed and nonstressed groups of animals were acutely injected intraperitoneally with vehicle or a particular antipsychotic. All antipsychotics were purchased from Sigma-Aldrich (Germany). Antipsychotics were administered in the following doses: olanzapine (2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, purity > 99%) 5 mg/kg, amisulpride (4-Amino-N-[(1-ethylpyrrolidin-2-yl)methyl]-5-ethylsulfonyl-2-methoxybenzamide, purity > 98%) 20 mg/kg, aripiprazole (7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone, purity > 99%) 10 mg/kg, and quetiapine (2-[2-(4-Dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol hemifumarate, purity > 99%) 15 mg/kg of the body weight (b.w.). All antipsychotics were dissolved in 4% DMSO (Sigma-Aldrich, Germany) in saline. VEH group received 4% DMSO in saline. The antipsychotics doses were selected based on the literature survey (Oka et al., 2004; Park et al., 2011; de Bartolomeis et al., 2013) and our pilot study (Kiss, 2018), whereas very high and low doses were eliminated to keep a space for the possible stress preconditioning impact. For the evaluation of the CMS efficacy, body weight (measured every second day) and weight of the thymus and adrenals were measured and compared between the non-stressed (n = 12) and stressed (n = 16) groups of rats.

Ninety min after the treatments (the time needed for an effect of antipsychotics was selected based on a pilot study, in which c-Fos expression was tested 90, 120, and 150 min of post-antipsychotics treatment), the rats were anesthetized by a combination of Zoletil (30 mg/kg, Virbac, Carros, France) and Xylariem (15 mg/kg, Riemser Germany) in the volumes 0.1 ml and 0.24 ml/300 g b.w., respectively and sacrificed by a transcardial perfusion with 60 ml of saline containing 450 µl of heparin (5000 IU/l, Zentiva, Slovakia) followed by 250 ml of fixative containing 4% paraformaldehyde (Sigma-Aldrich, Germany) in 0.1 M phosphate buffer (PB, pH 7.4). The brains, thymi, and adrenals were removed from the rats. The weight of thymi and adrenals was immediately measured and the brains further postfixed in a fresh fixative overnight. Thereafter, the brains were washed two times in 0.1 M PB, infiltrated with 30% sucrose for 2 days at 4 °C, cut into 30 µm thick coronal sections using Reichert-Jung, cryo-cut E (Austria), and collected in a cryoprotectant solution at −20 °C until used.

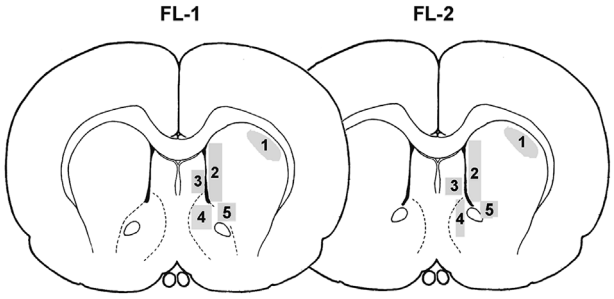

Fig. 1. Drawings of two sections at levels 1.92–1.68 mm (FL-1) and 1.68–0.96 mm (FL-2) of the bregma (Paxinos and Watson, 2007) illustrating the forebrain areas selected for the c-Fos counting after antipsychotics administrations. 1 – dorsolateral striatum (stDL), 2 – periventricular zone (peVZ), 3 – ventrolateral septal nucleus (veVL), 4 – shell of the nucleus accumbens (shACC), 5 – core of the nucleus accumbens (coACC).

2.3. Brain areas investigated

Five brain areas including the striatal dorsolateral (stDL) area, the striatal periventricular zone (peVZ), the septal ventrolateral (seVL) nucleus, and the shell (shACC) and core (coACC) of the nucleus accumbens were investigated at two forebrain levels (FL) designated as FL-1 (Bregma 1.20–1.60 mm, visually indicated by a large distance between the commissura anterior and the ventral tip of the lateral ventricles) and FL-2 (Bregma 0.70–0.48 mm, visually indicated by almost no distance between the commissura anterior and the ventral tip of the lateral ventricles) (Fig. 1). The coordinates were selected based on the atlas of rat brain in stereotaxic coordinates (Paxinos and Watson, 2007). c-Fos counting was performed manually in Adobe Photoshop 7.1 window grid program from photomicrographs (4–6 sections/structure) captured on Axio-Imager A1 light microscope (Carl Zeiss) coupled to a video camera and monitor. The counting of c-Fos profiles was provided by persons who were blind to the particular groups of animals in predetermined forebrain regions demarcated by rectangular grids (one grid size = 100 μm^2) of defined number for each structure: at the FL-1 level 20 × 100 μm^2 (stDL), 36 × 100 μm^2 (peVZ), 16 × 100 μm^2 (seVL), 7 × 100 μm^2 (shACC), and 5 × 100 μm^2 (coACC) and at the FL-2 level 20 × 100 μm^2 (stDL), 42 × 100 μm^2 (peVZ), 16 × 100 μm^2 (seVL), 7 × 100 μm^2 (shACC), and 5 × 100 μm^2 (coACC). The counting area of each structure was selected based on the above-mentioned coordinates. The contrast of the final histological figures was increased by an Adobe Photoshop 7.1 software.

2.4. Single c-Fos immunohistochemistry

One set of free-floating sections was repeatedly washed in cold 0.1 M PB and preincubated in a blocking solution of 0.3% H_2O_2 in 0.1 M PB (Fisher Scientific, Fair Lawn, NJ, USA) for 20 min at room temperature (RT). Then the sections were rinsed 3 × 10 min in 0.1 M PB and incubated with a rabbit polyclonal c-Fos antiserum (12-5) diluted 1:1500 in 0.1 M PB containing 4% normal goat serum (Gibco, Grand Island, NY, USA), 0.5% Triton X-100 (Koch-Light Lab. Ltd., Colnbrook Berks, England), and 0.1% sodium azide (Sigma Chemical Ltd. St. Louis MO, USA) for 48 h at 4 °C. After several rinsing in PB, the sections were incubated with biotinylated goat anti-rabbit IgG (1:500, VectorStain Elite ABC Kit, Vector Lab., Burlingame, CA, USA) in PB for 90 min at RT. Next PB rinsing was followed by incubation with the avidin-biotin peroxidase complex (1: 250) for 90 min at RT. After several washings in 0.05 M sodium acetate buffer (SAB, pH 6.0), c-Fos antigenic sites were visualized by nickel-enhanced 3,3′-diaminobenzidine tetrahydrochloride (0.0625% DAB, 2.5% nickel chloride, Sigma-Aldrich, No. 7718-54-9), in SAB containing 0.0006% hydrogen peroxide. Developing time was 6–10 min and the c-Fos emergence was monitored in the microscope. The heavy metal-intensification of DAB yielded black staining in the c-Fos labeled nuclei. The tissue sections were mounted on positive charged adhesive slides, dried at RT for 120 min, coverslipped with Pertex (Stockholm, Sweden), and stored in dark histological boxes. The antibodies specificity test was performed by omission of the primary antibody in the immunohistochemical procedure.

2.5. Antibodies

The primary polyclonal rabbit anti-c-Fos antibody was a gift (see Acknowledgement).

2.6. Statistical analysis

The distribution character (parametric or nonparametric) of all data obtained was established by Kolmogorovov-Smirnovov test using STATISTICA 7.0 (StatSoft). Data of adrenals and thymus weights showed parametric distribution and were analyzed by *t*-test. Data of the weight gain showed nonparametric distribution and were analyzed by Mann-Whitney Rank Sum test. Concerning the brain areas, the c-Fos data of the peVZ, shACC FL-1, and shACC FL-2 areas showed parametric distribution and were analyzed by two-way ANOVA (factors treatment and conditions) followed by the Fisher LSD post hoc test and the c-Fos data of the stDL, seVL, and coACC areas showed nonparametric distribution and were evaluated by the nonparametric Kruskal-Wallis test STATISTICA 7.0 (StatSoft) followed by post-hoc test. All the results are reported as mean ± S.E.M. Differences were considered significant at $p < 0.05$. The outliers were excluded if the data points were more than 1.5 interquartile ranges below the first or above the third quartile.

3. Results

3.1. Body, adrenals, and thymus weight

The body weight response was calculated as a difference between the body weights at the end and at the beginning of the experiment. Mann-Whitney Rank Sum Test revealed significant difference between the weight gain in the stressed and unstressed animals on the 22nd day of the experiment ($T = 1267$, $p < 0.001$). The rats exposed to CMS gained less body mass than the unstressed controls (Table 1). T-test also revealed marked adrenals enlargement [($t(62) = -3.2$, $p = 0.002$)] in CMS rats and no change in the thymus size (both organs were expressed per 100 g of the body weight) in unstressed ones (Table 1).

3.2. Single c-Fos expression immunohistochemistry

In unstressed animals, the distribution and quantity pattern of c-Fos expression were evaluated after a single administration of OLA, AMI, ARI, and QUE in the seVL, stDL, stVZ, shACC, and coACC (Fig. 1). The spatial arrangement and quantitative values of c-Fos expression differed markedly and each of the above-mentioned antipsychotics revealed characteristic pattern of c-Fos profile anatomical distribution. Since the number of c-Fos profiles at both FL-1 and FL-2 striatal levels, except the

Table 1
Effect of the CMS on the body, adrenals, and thymus weight. The rats exposed to CMS gained less body mass than the unstressed controls ($T = 1267$, $p < 0.001$). T-test also revealed marked adrenals enlargement [($t(62) = -3.2$, $p = 0.002$)] in CMS rats and a slight reduction in the thymus size (both calculated per 100 g b.w.) in unstressed ones.

Experimental group	Body weight (g)	Adrenals weight (mg/100 g b.w.)	Thymus weight (mg/100 g b.w.)
Unstressed	62.79 ± 3.5	15.13 ± 0.39	122.86 ± 3.89
CMS	44.75 ± 2.39*	16.65 ± 0.29*	113.97 ± 3.25

*$p < 0.05$ vs. unstressed animals.

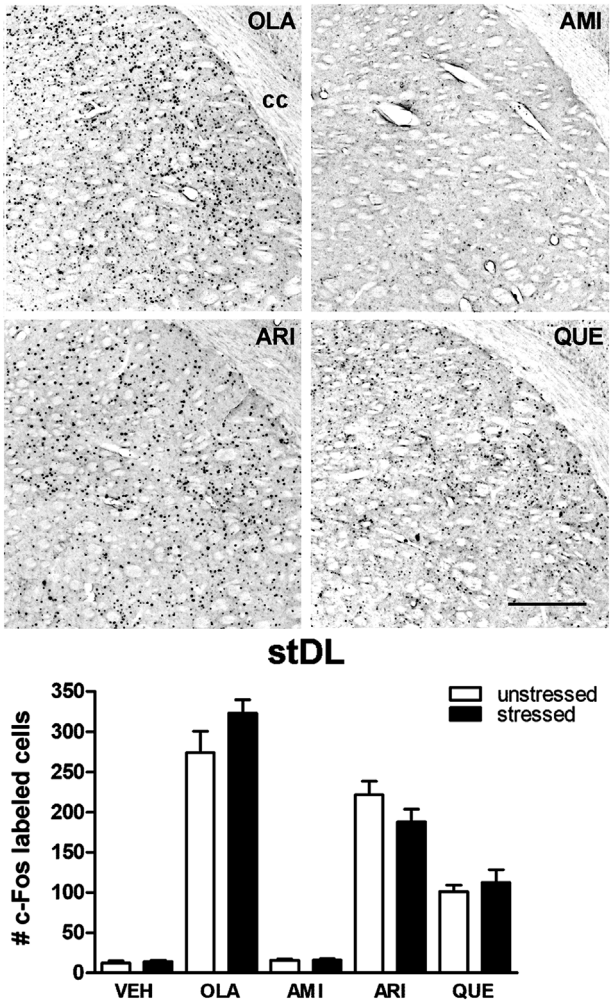

Fig. 2. Top – photomicrographs illustrating the effect of OLA, AMI, ARI, and QUE on the c-Fos expression in the stDL. Bar scale = 80 μm. Bottom – graph demonstrating the effect of individual antipsychotics on c-Fos expression in unstressed and CMS preconditioned (stressed) rats. Abbreviations: OLA – olanzapine, AMI – amisulpride, ARI – aripiprazole, QUE – quetiapine, CMS – complex of mild stressors, cc – corpus callosum, stDL – dorsolateral striatum. Unstressed groups comparisons (white collumns): OLA and ARI vs. VEH and AMI ($p < 0.01$); Stressed groups comparisons (black columns): OLA and ARI vs. VEH and AMI ($p < 0.01$).

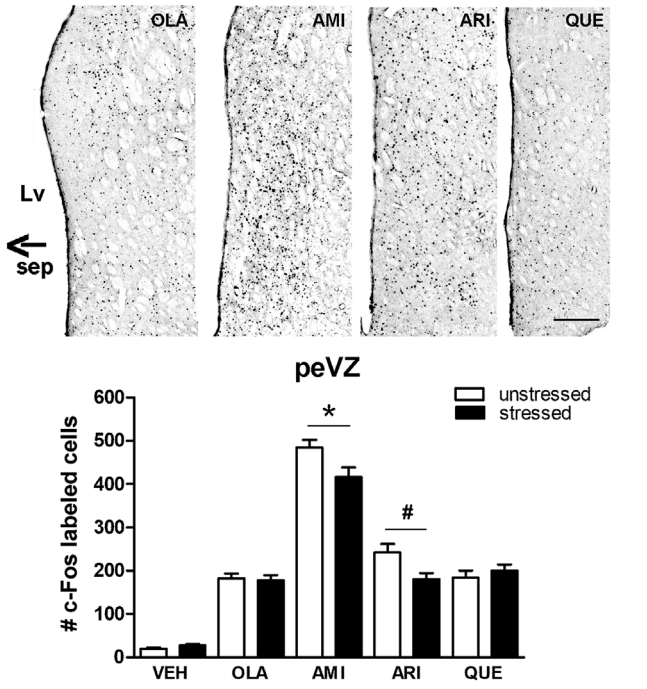

Fig. 3. Top – photomicrographs illustrating the effect of OLA, AMI, ARI, and QUE on the c-Fos expression in the peVZ. Bar scale = 70 μm. Bottom – graph demonstrating the effect of individual antipsychotics on c-Fos expression in unstressed and CMS preconditioned (stressed) rats. Abbreviations: OLA – olanzapine, AMI – amisulpride, ARI – aripiprazole, QUE – quetiapine, CMS – complex of mild stressors, peVZ – periventricular zone, Lv – lateral ventricle, sep – septum, arrow - indicates the septal side of the sections. Unstressed groups comparisons (white columns): OLA, AMI, ARI, QUE vs. VEH ($p < 0.001$); AMI vs. OLA, ARI, QUE ($p < 0.001$). Stressed groups comparisons (black columns): OLA, AMI, ARI, QUE vs. VEH ($p < 0.001$); AMI vs. OLA, ARI, QUE ($p < 0.001$). Comparisons between groups (white vs. black columns): AMI vs. AMI CMS ($^{*}p < 0.001$); ARI vs. ARI CMS ($^{\#}p = 0.036$).

shACC, was very similar the c-Fos data in these structures were calculated as one.

In the stDL, Kruskal-Wallis test confirmed the effect of the independent groups [$H(9,105) = 92.28$, $p < 0.00001$)] on the c-Fos immunoreactivity. In the unstressed animals, OLA and ARI administrations increased the c-Fos expression in the whole striatum, however, most robustly in the stDL, in comparison with the unstressed VEH controls (Fig. 2). On the other hand, AMI and QUE treatments did not induce c-Fos expression in the stDL (Fig. 2). In the stDL of unstressed rats, the number of c-Fos immunopositive cells induced by the individual antipsychotics could be ranged as follows: OLA (100%) > ARI (78%) > QUE (34%) > AMI (6%). In CMS animals, CMS + OLA and CMS + ARI, induced also significant c-Fos expression elevation in comparison with the CMS + VEH ones (Fig. 2).

In the peVZ, two-way ANOVA found effect of the treatment [$F(4,108) = 208.853$, $p < 0.001$)] and interaction of the treatment and stress exposure [$F(4,108) = 3.095$, $p = 0.019$)] on the c-Fos immunoreactivity. In the unstressed animals, all antipsychotics significantly elevated c-Fos expression in comparison with the unstressed VEH ones (Fig. 3). However, most distinct effect was seen in the AMI group. AMI treatment significantly overrided the effect of OLA, ARI, and QUE (Fig. 3). In contrast to other antipsychotics, which induced c-Fos expression over the whole striatum, AMI effect on c-Fos expression was limited only to a narrow line following the whole extent of the lateral ventricles (Fig. 3). The level of the c-Fos immunopositive cells induced by the particular antipsychotics in the peVZ of unstressed rats could be ranged as follows: AMI (100%) > ARI (66%) > OLA (52%) > QUE (50%). In the CMS preconditioned rats, treatment with OLA, AMI, ARI, and QUE also significantly increased the c-Fos expression in the peVZ in comparison with the CMS + VEH controls, whereas in CMS + AMI and CMS + ARI groups, CMS preconditioning significantly lowered the effect of AMI and ARI on the c-Fos expression in comparison with their unstressed pairs (Fig. 3).

In the seVL, Kruskal-Wallis test confirmed the effect of the independent groups [$H(9,109) = 76.32$, $p < 0.00001$)] on the c-Fos immunoreactivity. In the unstressed rats, most intensive c-Fos expression was induced by OLA followed by ARI, QUE, and AMI, which in contrast to OLA displayed significantly less powerful stimulatory effect on c-Fos induction (Fig. 4). The level of the number of c-Fos immunopositive cells induced by the individual antipsychotics in the seVL of unstressed rats could be ranged as follows: OLA (100%) > ARI (62%) > QUE (54%), and AMI (49%). Notably In CMS + ARI group, CMS preconditioning significantly reduced the stimulatory effect of ARI on the c-Fos expression (Fig. 4).

In the coACC, Kruskal-Wallis test confirmed the effect of independent groups [$H(9,107) = 39.74$, $p < 0.00001$)] on the c-Fos immunoreactivity. Generally, coACC revealed low quantity of c-Fos profiles, at all (Fig. 5). In unstressed rats, OLA and AMI significantly

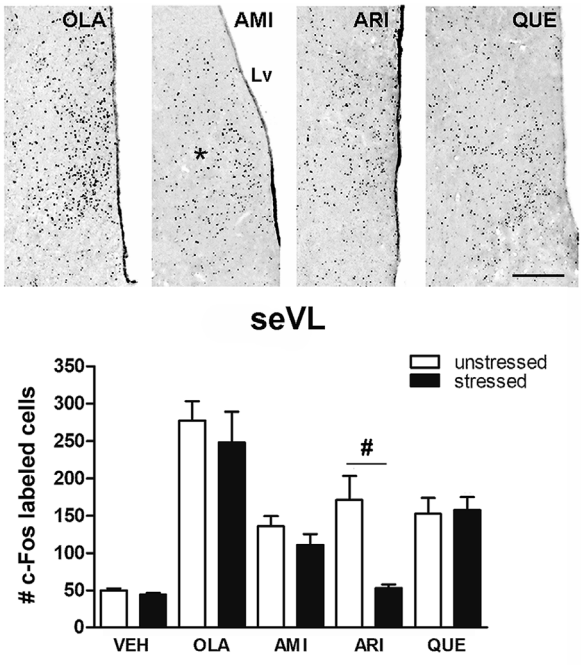

Fig. 4. Top – photomicrographs illustrating the effect of OLA, AMI, ARI, and QUE on the c-Fos expression in the seVL. Bar scale = 75 µm. Bottom – graph demonstrating the effect of individual antipsychotics on c-Fos expression in unstressed and CMS preconditioned (stressed) rats. Abbreviations: OLA – olanzapine, AMI – amisulpride, ARI – aripiprazole, QUE – quetiapine, seVL – ventrolateral septal nucleus, Lv – lateral ventricle, CMS – complex of mild stressors, asterisk – middle of the seVL. Unstressed groups comparisons (white columns): OLA vs. VEH ($p < 0.01$). Stressed groups comparisons (black columns): OLA and QUE vs. VEH ($p = 0.01$); OLA vs. ARI ($p < 0.01$); QUE vs. ARI ($p = 0.012$). Comparisons between groups (white vs. black columns): ARI vs. ARI CMS ($^{\#}p = 0.035$).

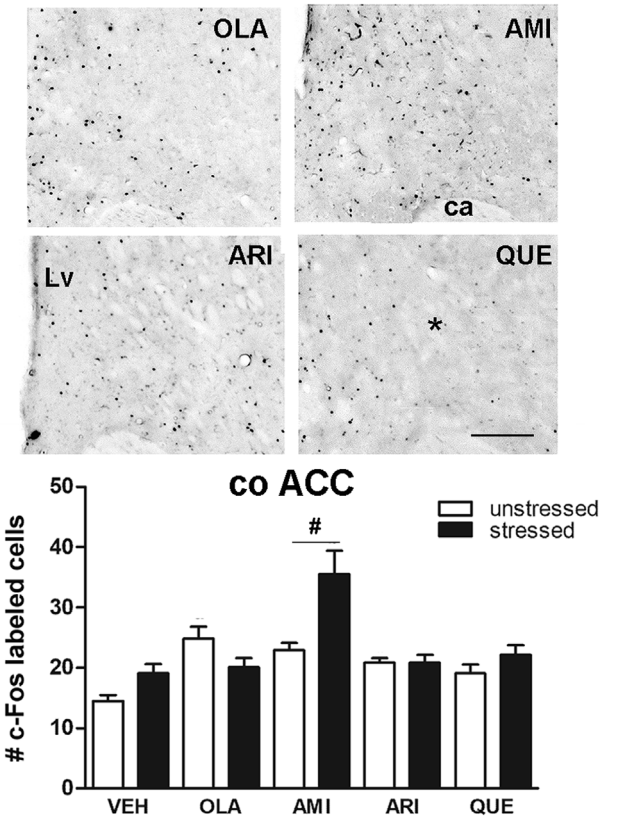

Fig. 5. Top – photomicrographs illustrating the effect of OLA, AMI, ARI, and QUE on the c-Fos expression in the coACC. Bar scale = 85 µm. Bottom – graph demonstrating the effect of individual antipsychotics on c-Fos expression in unstressed and CMS preconditioned (stressed) rats. Abbreviations: OLA – olanzapine, AMI – amisulpride, ARI – aripiprazole, QUE – quetiapine, coACC – shell of the nucleus accumbens, ca – commisura anterior, CMS – complex of mild stressors, asterisk – middle of the measured coACC area. Unstressed groups comparisons (white columns): OLA vs. VEH ($p = 0.004$). AMI vs. VEH ($p = 0.013$), AMI vs. AMI CMS ($^{\#}p = 0.016$).

elevated c-Fos expression in comparison with VEH group. In the CMS + AMI group, CMS significantly potentiated the effect of AMI on the expression of c-Fos in this forebrain area (Fig. 5). The effect of CMS in CMS + AMI group was also significantly higher in comparison with CMS + OLA, CMS + ARI, and CMS + QUE groups.

In the shACC anterior part (FL-1 level), two-way ANOVA revealed the effect of the treatment [$F(4,55) = 80.459$, $p < 0.001$)] on the c-Fos immunoreactivity. At the FL-1 level, the c-Fos profiles were densely aggregated in the top of the shACC, i.e. area laying immediately below the seVL boundary and medially they reached the wall of the lateral ventricle ventral tip (Fig. 6). In the unstressed animals, OLA, AMI, ARI, and QUE significantly stimulated c-Fos expression in comparison with the VEH (Fig. 6). Similar response in c-Fos expression was observed in CMS + OLA, CMS + AMI, CMS + ARI, and CMS + QUE groups in comparison with their CMS + VEH controls. In this shACC portion, the CMS did not affect the c-Fos expression induced by antipsychotics (Fig. 6).

In the shACC posterior part (FL-2 level), two-way ANOVA revealed effect of the treatment [$F(4,53) = 10.133$, $p < 0.001$)] on the c-Fos immunoreactivity. In the unstressed animals, OLA, AMI, and ARI significantly increased c-Fos expression in comparison with the unstressed controls. Similarly, CMS + OLA, CMS + AMI, CMS + ARI, and CMS + QUE groups revealed significant increase in the number of c-Fos profiles in comparison with CSM + VEH controls (Fig. 7). In CMS + QUE group, CMS potentiated the effect of QUE (Fig. 7).

4. Discussion

The present data show that: 1) the spatial distribution and quantitative values of c-Fos expression differed markedly after treatment with chosen antipsychotics; 2) in unstressed animals, OLA and ARI elevated c-Fos expression in all areas, AMI and QUE in all areas except stDL, seVL and coACC, shACC FL-2, respectively; 3) CMS potentiated the effect of AMI in coACC and QUE in shACC FL-2 and suppressed the effect of AMI in peVZ, and ARI in peVZ and seVL. CMS significantly lowered the body and increased the adrenals weight indicating a proper level of the CMS efficacy.

The anatomical boundaries of the striatum have been shown to be associated with at least three distinct functional circuits, i.e. the caudate-putamen ventral parts (shACC and coACC) that are implicated in the emotional processings and salience, the anterior and lateral parts that are involved in the learning, and the dorsolateral caudate-putmen (known as extrapyramidal region) that is involved in the motor control (Nakano et al., 2000; Haber, 2016). In the present study, all the drugs used distinctly affected the spatial distribution of c-Fos in the striatum. OLA induced a marked c-Fos expression in the stDL, which is comparable with a number of other antipsychotics effect including asenapine (Majercikova et al., 2014), haloperidol (Deutch et al., 1992; Palacios et al., 1996; Suzuki et al., 1998), risperidone (Fink-Jensen and Kristensen, 1994), chlorpromazine, fluphenazine, loxapine, and molindone (Robertson et al., 1994). On the other hand, AMI action on c-Fos expression was higher in the striatal peVZ area (medial region of the striatum), i.e. area, which does not appear to be a common target for many other antipsychotics. This finding is in accordance with the anatomical data of de Bartolomeis et al. (2013), who have demonstrated that effect of AMI, which induced changes in the postsynaptic

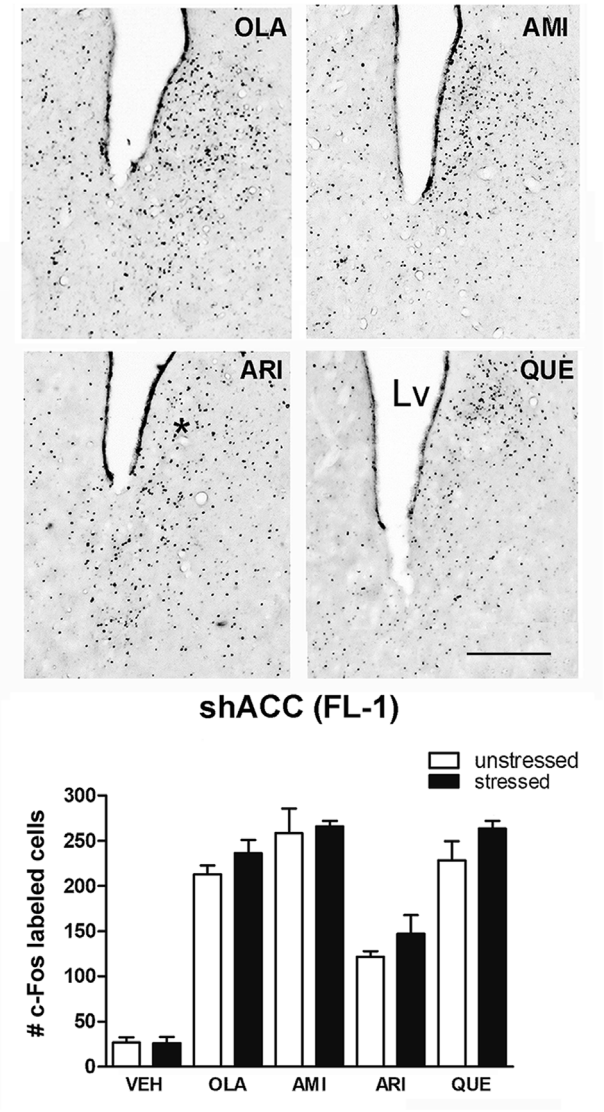

Fig. 6. Top – photomicrographs illustrating the effect of OLA, AMI, ARI, and QUE on the c-Fos expression in the shACC at the level of FL-1. Bar scale = 90 µm. Bottom – graph demonstrating the effect of individual antipsychotics on c-Fos expression in unstressed and CMS preconditioned (stressed) rats. Abbreviations: OLA – olanzapine, AMI – amisulpride, ARI – aripiprazole, QUE – quetiapine, shACC – shell of the nucleus accumbens, FL-1 frontal level of the striatum, CMS – complex of mild stressors, asterisk – middle of the measured dorsal shACC area. Unstressed groups comparisons (white columns): OLA, AMI, ARI, QUE vs. VEH ($p < 0.001$); OLA, AMI, QUE vs. ARI ($p < 0.001$); AMI vs. OLA ($p = 0.041$). Stressed groups comparisons (black columns): OLA, AMI, ARI, QUE vs. VEH ($p < 0.001$); OLA, AMI, QUE vs. ARI ($p < 0.001$).

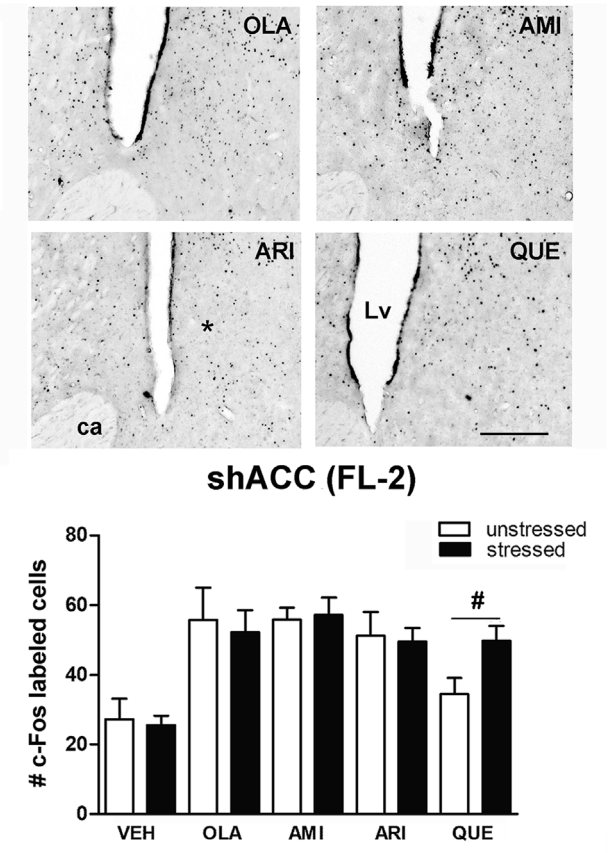

Fig. 7. Top – photomicrographs illustrating the effect of OLA, AMI, ARI, and QUE on the c-Fos expression in the shACC at the level of FL-2. Bar scale = 80 µm. Bottom – graph demonstrating the effect of individual antipsychotics on c-Fos expression in unstressed and CMS preconditioned (stressed) rats. Abbreviations: OLA – olanzapine, AMI – amisulpride, ARI – aripiprazole, QUE – quetiapine, shACC – shell of the nucleus accumbens, FL-2 caudal level of the striatum, ca – commisura anterior, asterisk – middle of the measured dorsal shACC area. CMS – complex of mild stressors. Unstressed groups comparisons (white columns): OLA vs. VEH ($p < 0.003$); AMI vs. VEH ($p < 0.002$); ARI vs. VEH ($p = 0.029$); QUE vs. VEH (($p = 0.02$). Stressed groups comparisons (black columns): OLA vs. VEH ($p = 0.006$); AMI vs. VEH ($p = 0.005$); ARI vs. VEH ($p = 0.011$); QUE vs. VEH ($p = 0.01$). Comparisons between groups (white vs. black columns): QUE vs. QUE CMS ($^{\#}p = 0.027$).

density transcripts of genes regulating the synaptic plasticity, was also preferentially directed to the medial region of the striatum. This finding indicates that this effect is probably not mediated by D_2 receptors. AMI does not induce catalepsy, which is typical for the postsynaptic D_2 blockade and does not antagonize the 5-HT_{2A} receptors, which blockade is one of the basic characteristics of the antipsychotics "atypicality" (Moller, 2003). A significant increase in the c-Fos expression in the peVZ, but not stDL, has also been demonstrated after remoxipride administration (Deutch et al., 1992). On the other hand, QUE and ARI treatments induced c-Fos expression over the whole striatum without forming any apparent c-Fos accumulations in the peVZ or stDL. It has been suggested that anatomical dissimilarities in the c-Fos expression in the striatum induced by different antipsychotics might be a predictive indicator for their potential extrapyramidal side effects (EPS). If the regional profile and quantity patterns of c-Fos distribution could generally be acceptable as criteria for the EPS inducion, which might at least in part explain their clinical potency, then the rank of the antipsychtics effect used would be OLA > ARI > QUE > AMI. The lack of AMI effect could be interpreted as its lack in EPS induction, although it has been reported that AMI may cause EPS even in lower doses (Mandal et al., 2014).

Another important forebrain locus most often affected by antipsychotics is the seVL, which receives pathways from the hippocampus, hypothalamus, and brainstem and supplies by neuronal axons the hypothalamus, habenula, thalamus, and midbrain (Risold and Swanson, 1997a, b). In spite of the fact that all antipsychotics used in this study significantly increased the c-Fos expression in the seVL, the intrinsic distribution of c-Fos profiles for particular antipsychotics in the seVL appears to be very heterogeneous. Actually, the lateral septal nucleus is divided into major rostral, caudal, and ventral parts (Swanson and Cowan, 1979) and our data cover only the rostral one, which is divided into 20 zones, regions, and domains on the basis of differential terminal fields and neurons that express particular neuropeptides and steroid hormone receptors (Risold and Swanson, 1997a). Therefore, it is very probable that antipsychotic used in this study via activation of the

lateral septum rostral part may affect rather the medially located hypothalamic structures than the laterally arranged hypothalamic behavioral system (Swanson and Cowan, 1979).

The nucleus accumbens is one of the basal ganglia, designated also as the ventral striatum, which splits into a core and shell (van Dongen et al., 2005; Salgado and Kaplitt, 2015). It has a potential role in the biology of schizophrenia via its involvement in the cortico-striato-nigral-thalamo-cortical circuit (Haber, 2003; Williams, 2017). It is noteworthy that all the antipsychotics used induced a distinct accumulation of c-Fos profiles in the upper portion of the anterior shACC FL-1, but not in more caudally occurred posterior shACC FL-2 region. This upper/dorsal portion of the shACC FL-1 partially correspond with so called "cone" shaped shACC zone designated based on the anatomy of the distribution of ChAT-containing (choline acetyltransferase) perikarya in this shACC FL-1 area (Meredith et al., 1989). Therefore, it is quite possible that cells activated by the antipsychotics studied overlaying the "cone" area might, at least partially, belong to the cholinergic population of cells playing a role in the intercompartmental shACC neuronal communication. Since many of the antipsychotics, including haloperidol, asenapine, clozapine, olanzapine, remoxipride, aripiprazole, quetiapine, and amisulpride, which display regional striatal differences in the activation of c-Fos, activate neurons in the shACC, what may signalize that the limbic shACC might be an important area for the antipsychotics action (Deutch et al., 1992).

The nucleus accumbens core is the inner compartment of the nucleus accumbens involved in the motor cognitive processing associated with the reward and reinforcement as well as the modulation of slow-wave sleep (Salgado and Kaplitt, 2015). It also appears as a critical subregion for dopamine receptor involvement in the fear prediction error (Li and McNally, 2015). All the antipsychotic used in this study stimulated c-Fos expression, whereas CMS even potentiated the effect of AMI. Although AMI has no effect on the c-Fos expression in the motor stDL area, it has been reported that D_1/D_3 receptors stimulation in the coACC may induce activation of locomotion (Barik and de Beaurepaire, 2005). However, whether stress may potentiate the AMI effect via stimulation D_2/D_3 or other types of receptors in the coACC has not been reported in the literature.

CMS significantly potentiated the effect of AMI in the coACC and QUE in the shACC FL-2 and contrariwise, suppressed the effect of AMI in the peVZ and ARI in the peVZ and seVL. Moreover, Singewald et al. (2011) have performed most comprehensive and systematic evaluation of the lateral septum role in stress responsiveness. They have suggested that this structure may promote an active stress coping behavior and is involved in a HPA (hypothalamic-pituitary-adrenocortical axis)-inhibitory mechanism that is at least in part mediated by the septal 5-HT_{1A} receptors without involving the glucocorticoid mediated feedback mechanism.

In summary, all the neuroleptics investigated including OLA, AMI, ARI, and QUE revealed clear stimulatory effect on the c-Fos expression in different forebrain areas accompanied by a specific anatomic profile of their action. Stress preconditioning in some cases potentiated and other ones inhibited the acute effect of neuroleptics. However, it should also be taken into consideration that the extent of the c-Fos protein expression induced by particular antipsychotics is also associated with the dose used and therefore, the interpretation of the present results should be perceived with a caution.

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