sciendo

ENDOCRINE REGULATIONS, Vol. 54, No. 2, 77–84, 2020

doi:10.2478/enr-2020-0010

Effect of amisulpride, olanzapine, quetiapine, and aripiprazole single administration on c-Fos expression in vasopressinergic and oxytocinergic neurons of the rat hypothalamic supraoptic nucleus

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Objective. The goal of this study was to reveal the impact of four types of atypical antipsychotics including amisulpride (AMI), olanzapine (OLA), quetiapine (QUE), and aripiprazole (ARI), with different receptor-affinity profile and dissociation constant, on the activity of hypothalamic supraoptic nucleus (SON) vasopressinergic and oxytocinergic neurons.

Methods. Male Sprague Dawley rats received a single injection of vehicle (VEH) (0.1 ml/100g), AMI (20 mg/kg), OLA (5 mg/kg), QUE (15 mg/kg/) or ARI (10 mg/kg). Ninety min after treatment, the animals were fixed by transcardial perfusion, the brains removed, and cryocut into serial coronal sections of 35 μm thickness. The sections were processed for c-Fos staining using an avidin-biotin-peroxidase complex and visualized by nickel intensified diaminobenzidine to reach black end product. Afterwards, the sections were exposed to vasopressin (AVP) and oxytocin (OXY) antibodies and the reaction product visualized by biotin-labeled fluorescent Alexa Fluor 568 dye. The data were evaluated from c-Fos and AVP or OXY merged sections.

Results. The present study shows that all four antipsychotics applied induced c-Fos expression in the SON. With respect to the stimulation efficacy of the individual antipsychotics, estimated based on the quantity of c-Fos-labeled AVP and OXY neurons, could be a preferential action assigned to QUE over moderate effect of ARI and lower effect to OLA and reduced effect of AMI (VEH < AMI < OLA < ARI < QUE).

Conclusion. The present data for the first time provide an insight into the quantitative pattern of brain activity within the clusters of SON AVP and OXY cells in response to different atypical antipsychotics single treatment.

Key words: c-Fos-immunohistochemistry, amisulpride, olanzapine, quetiapine, aripiprazole, hypothalamic supraoptic nucleus, rat

The supraoptic nucleus (SON) is a part of the hypothalamic magnocellular neurosecretory system. Its magnocellular neurons synthesize mainly oxytocin and vasopressin, which are transported via the supraoptico-neurohypophyseal tract to the posterior pituitary, where they are released into the peripheral circulation (Brownstein et al. 1980; Castel et al. 1984; Kawamoto and Kawashima 1985). Both the vasopressin (AVP) and oxytocin (OXY) exert a wide spectrum of central and peripheral effects as neurohormone, neurotransmitter, or neuromodulator and play an important role in the regulation of different physiological functions (Kiss and Mikkelsen 2005).

The AVP and OXY are involved in the regulation of body fluid homeostasis (Johnson et al. 2015). Classically, OXY was considered to have two main func-

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tions – inducing milk letdown and stimulation of the uterine smooth muscle cells contractions. However, recently a multiple and quite different functions have been attributed to this hormone (Kiss and Mikkelsen 2005; Emiliano et al. 2007). OXY secretion has been shown to be essential in parturition, lactation and also during suckling during lactation (Oliet and Bonfardin 2010). OXY, but not AVP, via local positive feedback, has been proven to induce synchronized burst-firing of the SON neurons (Russell and Brunton 2017). The local SON OXY release from the cell soma, axons, and dendrites of neurosecretory cells can stimulate OXY receptors and activate themselves as well as neighboring neurons for further OXY release (so called OXY-induced OXY release) via autocrine or paracrine systems (Shen and Sun 1995).

The AVP is a neurohypophyseal hormone released also from the posterior pituitary by magnocellular neurosecretory cells located within the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus. The SON AVP is involved in the regulation of body fluid homeostasis. The level of plasma AVP is regulated physiologically by changes in plasma osmolality, blood volume, and blood pressure (Bisset and Chowdrey 1988). The neurosecretory activity of AVP neurons of the SON has not been shown to be changed in schizophrenic patients under the neuroleptic medication (Malidelis et al. 2005).

The studies focused on the c-Fos (as a marker of neuronal stimulation) balance in SON AVP and OXY cells under different experimental conditions have been widely published. We have observed that different experimental conditions may variously affect the c-Fos expression in the SON neuronal perikarya, e.g. hypertonic saline osmotic challenge activated more than 50% of AVP and OXY neurons in the SON, while IMO less than 4% indicating for the existence of functional dissimilarities in response to different exogenous stimuli (Pirnik and Kiss 2005). Hypotension and hemorrhage have been shown to induce an extensive c-Fos like immunoreactivity in the rat SON, especially in the vasopressinergic neurons (Shen and Sun 1995). Morphine withdrawal also increased c-fos and OXY gene expression in SON neurons (Johnstone et al. 2006). Water deprivation for 24 and 48 h, but not water rehydration, significantly elevated the number of c-Fos-positive cells in the SON (Ji et al. 2005). AVP and OXY neurons have been shown to express c-Fos in response to hypovolemic stimuli, whereas the amount of expressed c-Fos graded with a graded intensity of the stimulus; in addition, these increases corresponded with the amount of AVP hormone released into the peripheral blood. (Roberts et al. 1993). In our previous study, we also have observed that in AVP deficient homozygous Brattleboro rats, the α2-adrenoceptor stimulation by xylazine may activate more than 80% of SON OXY-ergic neurons (Bundzikova et al. 2008a).

The antipsychotic action in the brain has mainly been evaluated in the prefrontal and striatal structures (Robertson and Fibiger 1996; Oka et al. 2004; Majercikova et al. 2014; Kiss et al. 2019), i.e. in structures involved in their assumed therapeutic effects (Deutch et al. 1992). However, their impact on cells located in the extrastriatal brain areas, where their possible side effects could be observed, has not been so extensively studied. Previously we have shown that some typical and atypical antipsychotics (clozapine, olanzapine, risperidone, haloperidol) induced a different extent of AVP and OXY neurons stimulation in the hypothalamic PVN and SON (Kiss et al. 2010). The attempt of this study was to broaden the extrastriatal anatomical view on the impact of four types of atypical antipsychotics including AMI, OLA, QUE, and ARI, i.e. antipsychotics with different receptor-affinity profile and dissociation constant (Seeman 2001), on the activity of SON vasopressinergic and oxytocinergic cells. Combined light and fluorescence immunohistochemistry was used to reveal c-Fos-AVP and c-Fos-OXY colocalizations in the SON.

Materials and methods

Animals. Adult male Sprague-Dawley rats (n=30), 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).

Experimental groups and antipsychotic treatments. The rats were divided into 5 groups: 1) vehicle (VEH, n=5); 2) amisulpride (AMI, n=6); 3) olanzapine (OLA, n=6); 4) quetiapine (QUE, n=6); and 5) aripiprazole (ARI, n=7). The animals were injected intraperitoneally (i.p.) with vehicle or a particular antipsychotic. The VEH group was injected with

4% DMSO dissolved in saline (0.1 ml/100 g). The antipsychotic-treated animals received the following doses of the drugs: AMI – 20 mg/kg, OLA – 5 mg/kg, QUE – 15 mg/kg, and ARI – 10 mg/kg of the body weight (b.w.). All the antipsychotics were dissolved in the vehicle.

Perfusion of animals. Ninety min after the antipsychotic treatment, the rats were anesthetized by a combined treatment with 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. They were 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 were postfixed in a fresh fixative overnight, washed two times in 0.1 M PB, infiltrated with 30% sucrose for 2 days at 4 °C, cut into 35 µm thick coronal sections using Reichert-Jung, cryo-cut E (Austria), and free floating collected in a cryoprotective solution at –20 °C until used.

c-Fos immunohistochemistry. Free floating sections were repeatedly washed in cold 0.05 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 0.05 M PB and incubated with a polyclonal c-Fos antiserum (No. 12-5) diluted 1:1500 in 0.05 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-Aldrich, Germany) 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 8–10 min. The developing process was monitored under a light microscope and stopped when the heavy metal-intensification of DAB elicited bright black color of c-Fos labeled nuclei.

AVP and OXY immunohistochemistry. The c-Fos stained SON sections were divided into two sets, i.e. for AVP and OXY immunohistochemistry. They were 3 x 10 min washed in cold 0.05 M PB and incubated with anti-AVP or anti-OXY polyclonal antibodies, both diluted 1:2000, in 0.1 M PB containing 4% normal goat serum (Gibco, Grand Island, NY, USA), 0.5% Triton X-100 (Sigma-Aldrich, Germany), and 0.1% sodium azide (Sigma-Aldrich, Germany) for 48 h at 4 °C. After several rinsing in PB, the sections were incubated with goat anti-rabbit IgG linked with Alexa Fluor 568 (1:500) in 0.05 M PB overnight. After several washes in 0.05 M PB, the sections were mounted in a semi-darkness room onto slides, left to dry in RT for 60 min, coverslipped with Pertex (Stockholm, Sweden), and stored in dark boxes.

SON AVP and OXY cells delineation. Several descriptions regarding the anatomical arrangement of the SON AVP- and OXY-ergic cell groups have been reported (Rhodes et al. 1981; Hou-Yu et al. 1986). We took a preference in the AVP- and OXY-immunolabeled perikarya SON arrangement from the mapping work of Hou-Yu et al. (1986). For our study, the SON pars principalis has been chosen, since it accounts for 80% of the total cell population of this nucleus and has very well-defined boundaries (Leranth et al. 1975).

c-Fos-AVP and c-Fos-OXY colocalizations evaluation. Quantitative evaluation (counting) of c-Fos colocalizations with AVP and OXY perikarya in SON was performed on merged pictures created in the Adobe Photoshop software (APS). The c-Fos profiles were captured in black and white color and AVP and OXY perikarya visualized by Alexa 568 fluorescence using Axio-Imager A1 light-fluorescent microscope (Carl Zeiss) coupled to a video camera and monitor. Photomicrographs with black c-Fos profiles on the gray background were by the APS threshold function transferred into black c-Fos profiles on the white background. Using inversion function, the c-Fos profiles were inverted into white and the background into black colors. Switching on the APS RGB function, the white c-Fos profiles were, using the channel mixer, adjusted to light blue and by the hue/saturation channel into the final red or dark blue colors. To obtain c-Fos-AVP and c-Fos-OXY merged pictures, yellow AVP and OXY perikarya were overlapped with red or blue c-Fos profiles. The number of activated vs. nonactivated cell phenotypes in the individual groups was calculated from 4–6 representative sections and expressed in percentage.

Antibodies. The primary polyclonal rabbit anti-c-Fos antibody was a gift (see Acknowledgement). The primary polyclonal rabbit anti-AVP (39363), polyclonal rabbit anti-OXY (ab2078) and the secondary goat anti-rabbit Alexa Fluor 568 (ab175471) antibodies were purchased from Abcam (Cambridge, UK).

Results

In contrast to the VEH-treated group, AMI, OLA, QUE, and ARI single administration elevated c-Fos expression over the whole SON, as indicated by DAB-Ni intensified ABC immunocytochemistry (Figure 1). The AVP- and OXY-synthesizing neurons also clearly emerged over the whole SON after employing Alexa Flour 568 fluorescence dye. Overlapping the AVP- and OXY-immunoreactive perikarya with c-Fos staining revealed the existence c-Fos-AVP and c-Fos-OXY colocalizations in the SON.

In the SON pars principalis, QUE treatment showed most distinct impact on the vasopressinergic neurons stimulation (Figure 2). OLA and ARI also showed stimulatory effect on c-Fos expression in vasopressinergic perikarya, however, this effect was markedly lower in comparison with the effect of QUE (Figure 2). Impact of AMI on the c-Fos expression was low, but still effective in comparable with the effect of the vehicle (Figure 2).

In the SON pars principalis, QUE treatment had again highest impact on the oxytocinergic neurons stimulation, as indicated by the extensive occurrence of the c-Fos-OXY colocalizations. ARI administration also quite distinctly elevated the c-Fos expression in the SON pars principalis (Figure 3), but the effect of OLA was slightly lower in comparison with ARI (Figure 3). The effect of AMI on the c-Fos expression was the lowest in all 4 antipsychotics used and comparable with the effect of the VEH treatment (Figure 3).

Discussion

In the present study, c-Fos protein expression, visualized by DAB-Ni intensified ABC immunocytochemistry, was employed as a marker to reveal the stimulated AVP- and OXY-synthesizing neurons visualized by Alexa Flour 568 fluorescence dye after a single treatment with antipsychotics including AMI, OLA, QUE, and ARI in the SON pars principalis. With respect to the stimulation efficacy of the individual antipsychotics, estimated based on the quantity of c-Fos-labeled neurons, could be a preferential action assigned to QUE over moderate effect of ARI and lower effect of OLA and the lowest effect of AMI (VEH < AMI < OLA < ARI < QUE).

Our data provide insight into the quantitative pattern of brain activity within the clusters of magnocellular OXY cells in the SON associated with the four sorts of antipsychotics acute treatment. As expected, the stimulatory effect of each antipsychotic was different, but generally stimulation of AVP- and OXY-synthesizing SON perikarya with them might

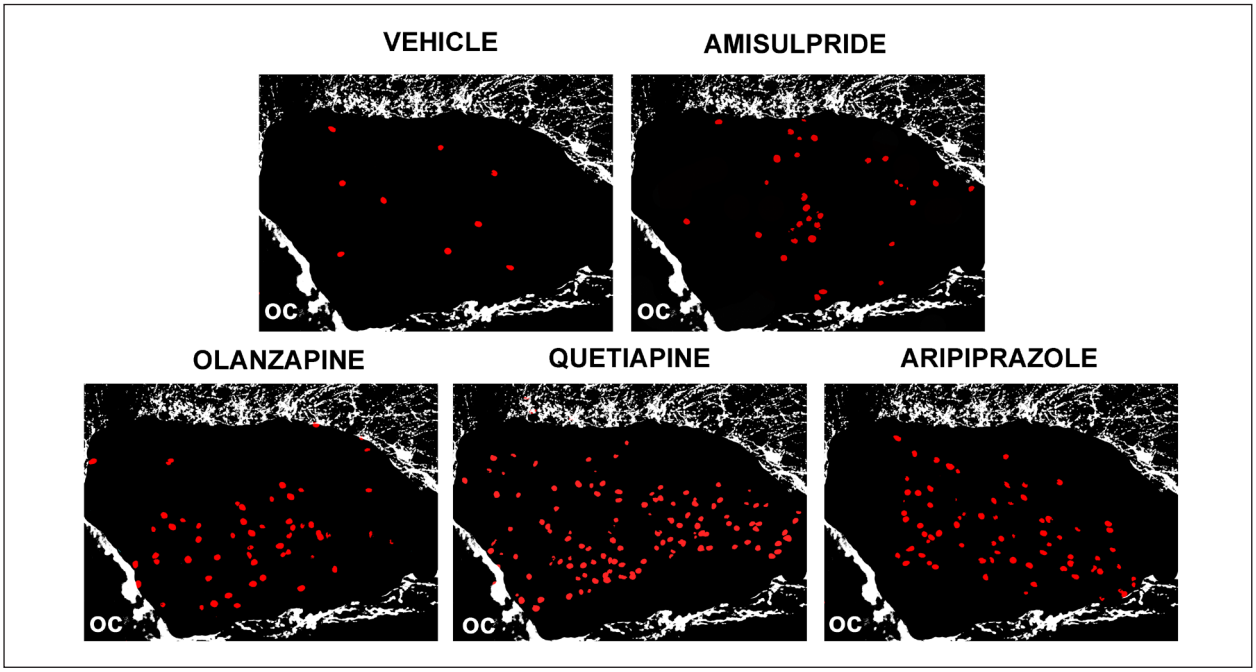
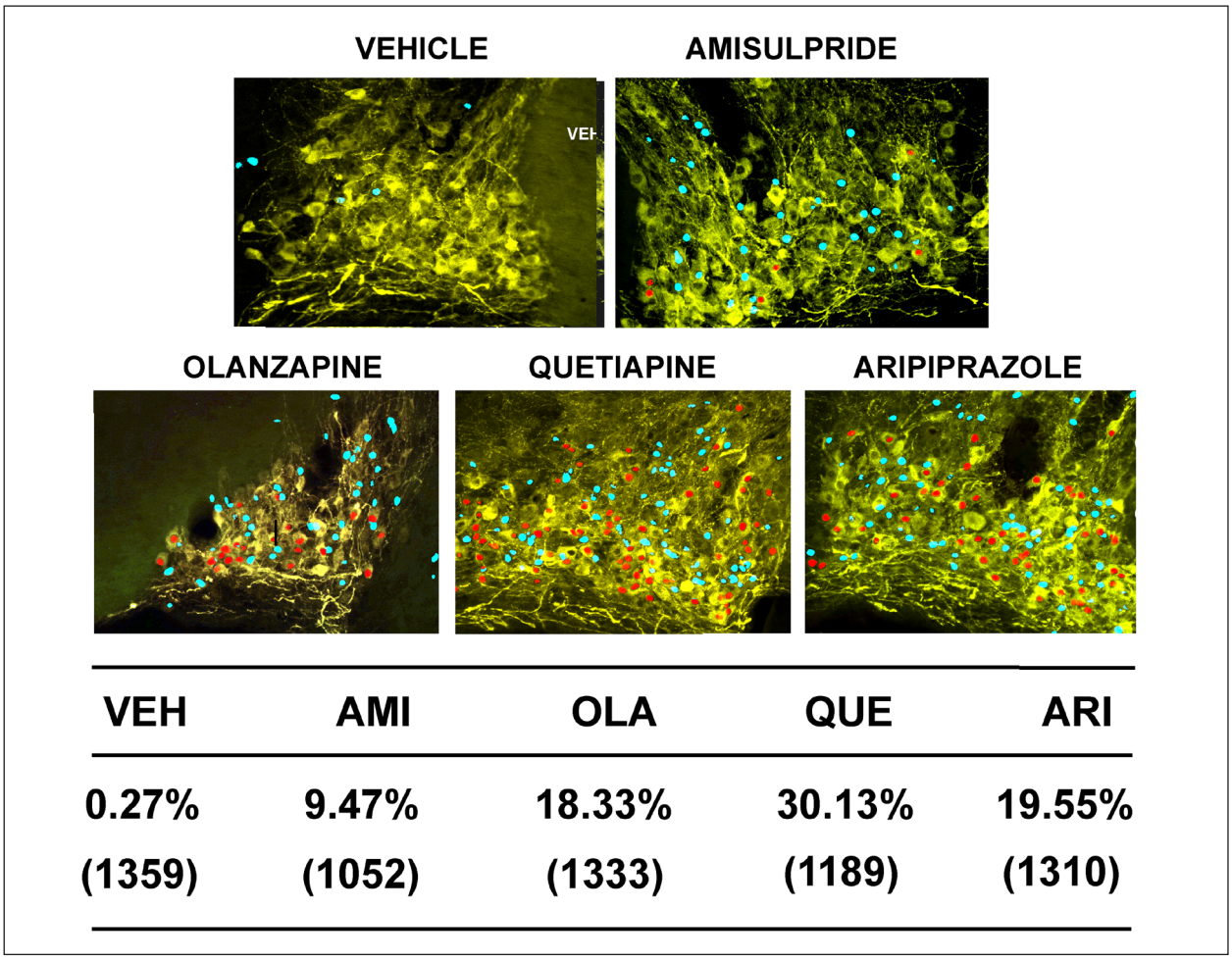


Figure 1. Demonstration of a single effect of the individual antipsychotics on the c-Fos expression in the SON principal part. Abbreviations: oc – optic chiasm; SON – hypothalamic supraoptic nucleus.

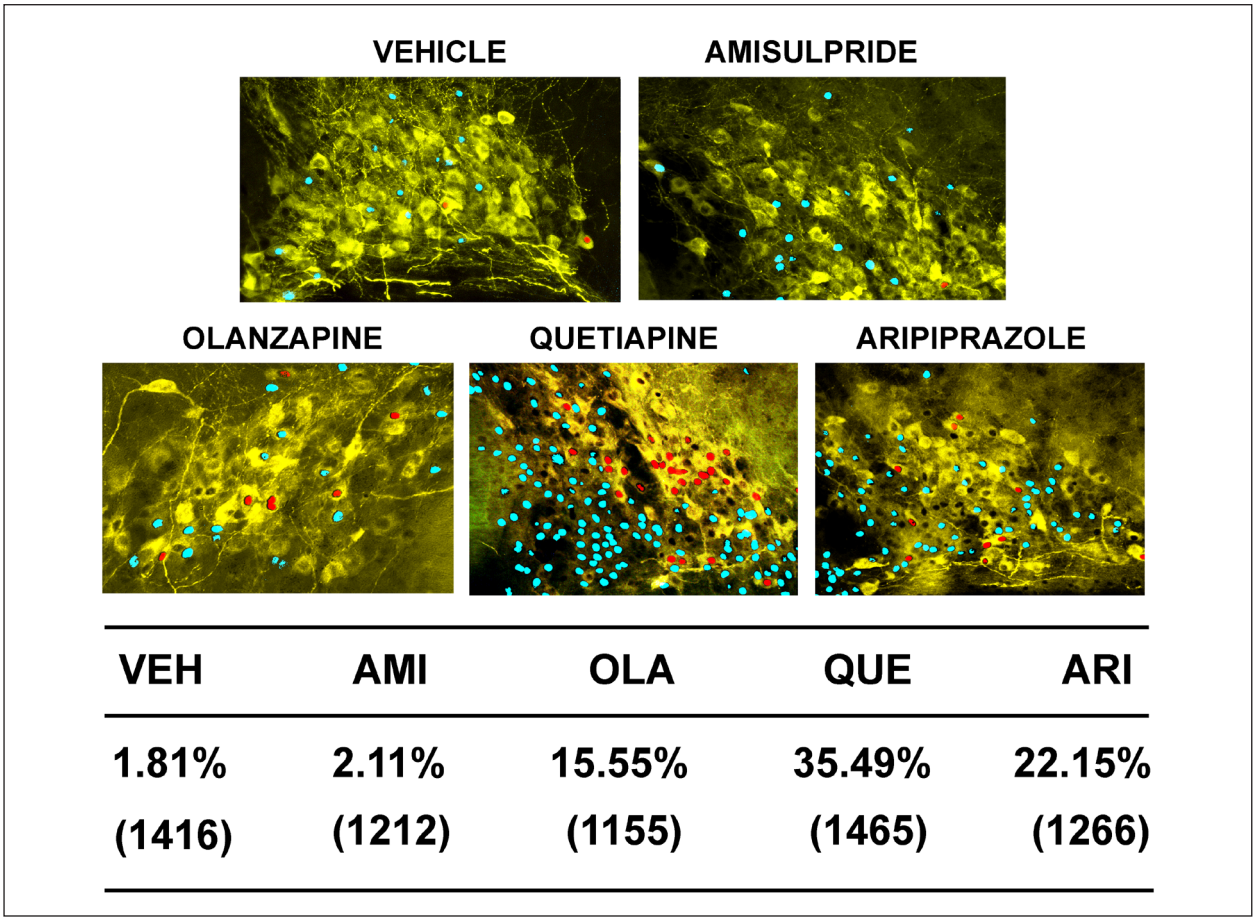


VEH	AMI	OLA	QUE	ARI
0.27%	9.47%	18.33%	30.13%	19.55%
(1359)	(1052)	(1333)	(1189)	(1310)

Figure 2. Illustration of a single effect of the individual antipsychotics on the c-Fos-AVP colocalization in the SON principal part (red dots – c-Fos profiles present in the AVP perikarya; blue dots – free c-Fos profiles). The level of colocalization is expressed in percentage (first line) and calculated from the total number of immunohistochemically identified vasopressinergic perikarya (second line – numbers in parenthesis) in the SON. The data shown in the table represent the sum of AVP cells from all the representative sections (also for percentage calculation sum of AVP cells expressing c-Fos from all the representative sections was used). Abbreviations: SON – hypothalamic supraoptic nucleus; AVP – vasopressin; VEH – vehicle, AMI – amisulpride, OLA – olanzapine, QUE – quetiapine, ARI – aripiprazole.

bear some similarities in their functional outcome. OXY secreted from the SON OXY perikarya in response to antipsychotics may either act locally and via OXY receptors affect the own OXY population of cells, for example inducing their synchronization (Oliet and Bonfardin 2010), or act periferally via OXY released into the systemic circulation (Higashida 2016). In the present study, the amount of activated AVP and OXY neurons might not to be maximal, since the concentration of the antipsychotics applied does not reach their saturated doses when compared with the literature data. The data coming out from the studies dealing with the c-Fos expression response to different external stimuli indicate that the response of c-Fos expression is strongly dependent on: 1) the exposure time to the given physical or chemical stimuli, including antipsychotics, 2) the concentration of the applied chemical substance, 3) the accuracy of the experimental time termination, i.e. time when the c-Fos levels culminate, and 4) the half-life (characteristic for antipsychotics) or the real time of action. Roberts et al. (1993) have pointed out that c-Fos expression in SON and PVN is proportional to stimulus intensity and may reveal functional heterogeneity among magnocellular neurons.

The effect of antipsychotics used in the present study on the SON neurons may be mediated directly or indirectly. The presence of several types of receptors



VEH	AMI	OLA	QUE	ARI
1.81%	2.11%	15.55%	35.49%	22.15%
(1416)	(1212)	(1155)	(1465)	(1266)

Figure 3. Illustration of a single effect of the individual antipsychotics on the c-Fos-OXY colocalization in the SON principal part (red dots – c-Fos profiles present in the OXY perikarya; blue dots – free c-Fos profiles). The level of colocalization is expressed in percentage (first line) and calculated from the total number of immunohistochemically identified oxytocinergic perikarya (second line – numbers in parenthesis) in the SON. The data shown in the table represent the sum of OXY cells from all the representative sections (also for percentage calculation sum of OXY cells expressing c-Fos from all the representative sections was used). Abbreviations: SON – hypothalamic supraoptic nucleus; OXY – oxytocin; VEH – vehicle, AMI – amisulpride, OLA – olanzapine, QUE – quetiapine, ARI – aripiprazole.

including serotonergic (Makarenko et al. 2002), D1, D2, and D4 dopaminergic (Parker and Crowley 1992; Yang et al. 1991; Price and Pittman 2001), mu-opioid (Liu et al. 1999), and catecholaminergic (Bundzikova et al. 2008b) may partially speak out for a favor of a possible direct effect of antipsychotics. However, on the other hand, the SON receives also a rich afferentation field originating in different brain areas. The subfornical organ, median preoptic nucleus, organum vasculosum of the lamina terminalis and medial septal nucleus are the sources of the largest numbers of the SON-projecting neurons. Several smaller projections come from the ipsilateral locus coeruleus, preoptic area, lateral parolfactorial area, dorsomedial nucleus of the hypothalamus, lateral parabrachial nucleus, and ventrolateral medulla. Some projections reach only the region distributed dorsally to the SON, including lateral septal nucleus, diagonal band of Broca, ventral tegmental nucleus, and the supramamillary nucleus. Additional target areas have been identified with retrograde fluorescent label immediately dorsal to SON and/or to SON itself. All about mentioned areas might be potential sources for the indirect action of antipsychotics directed to the SON neurosecretory cells (Anderson et al. 1990).

The SON is one of the main components of the hypothalamic magnocellular neurosecretory system, while the other one is the PVN. However, in contrast to the PVN, which represents a complex structure from both anatomical and functional points of view, the SON bears several own important characteristics, which lift this structure to a "model system" impor-

tant for neuroscience research (Hou et al. 2016). Although both the SON and PVN magnocellular AVP and OXY neurosecretory neurons project to the posterior pituitary, the intrinsic brain activation by antipsychotics may exert different central effects from the PVN, such as the regulation of estrous cycle (Liu et al. 2016) and of olfaction (Yu et al. 1996). Since the spatial arrangement of SON AVP and OXY functionally differently acting neurons have not been yet mapped in detail, it is not conceivable to functionally classify by the antipsychotics activated AVP or OXY neurons based on their distribution in the SON.

In summary, acute administration of antipsychotics elicits a distinct patterns of c-Fos expression in the rat SON. Colocalization of c-Fos with AVP or OXY in the SON indicates that antipsychotics may play a role in autonomic, neuroendocrine, and behavioral processes. Variabilities in the amount of c-Fos colocalizations with AVP and OXY neurons in the SON induced by different antipsychotics may be helpful to understand more precisely the extent of their extra-forebrain actions with possible presumption of their functional impact and side effect consequences.

Acknowledgements

The authors are grateful for the c-Fos antibody (12-5) supplied by Dr. Jens D. Mikkelsen (Denmark) and financial support of 2/0031/16 VEGA grant of the Slovak Academy of Sciences and APVV-15-0037 grant of the Research and Development Agency of the Slovak Republic.

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