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sciendo

120 ENDOCRINE REGULATIONS, Vol. 55, No. 2, 120–130, 2021

doi:10.2478/enr-2021-0013

Extra-forebrain impact of antipsychotics indicated by c-Fos or FosB/ΔFosB expression: A minireview

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It is apparent that the c-Fos and FosB/ΔFosB immunohistochemistry has generally become a useful tool for determining the different antipsychotic (AP) drugs activities in the brain. It is also noteworthy that there are no spatial limits, while to the extent of their identification over the whole brain axis. In addition, they can be in a parallel manner utilized in the unmasking of the brain cell phenotype character activated by APs and by this way also to identify the possible brain circuits underwent to the APs action. However, up to date, the number of APs involved in the extra-striatal studies is still limited, what prevents the possibility to fully understand their extra-striatal effects as a complex as well as differentiate their extra-striatal impact in qualitative and quantitative dimensions. Actually, it is very believable that more and more anatomical/functional knowledge might bring new insights into the APs extra-striatal actions by identifying new region-specific activities of APs as well as novel cellular targets affected by APs, which might reveal more details of their possible side effects of the extra-striatal origin.

Key words: antipsychotics, c-Fos, FosB/ΔFosB, brain extra-forebrain structures

Antipsychotics (APs) are a type of psychiatric medication, which are licensed to treat certain types of mental health problems, whose symptoms include psychotic experiences, including schizophrenia, schizoaffective disorder, some forms of bipolar disorders, severe depression or to treat other health problems (Gardner et al. 2005; Meltzer 2013; Huhn et al. 2019). The majority of the Fos related investigations on the central effect of APs has mainly been directed to the forebrain structures, including the striatum, septum, nucleus accumbens, and the prefrontal cortex (Wan et al. 1995; Robertson and Fibiger 1996; Korf et al. 1997). However, the APs act via different receptors, which presence has also been demonstrated in many extra-forebrain areas, but the impact of APs outside the forebrain structures has not been investigated so extensively. From many brain structures, the investigation has also been engaged in: 1) the paraventricular nucleus of the hypothalamus (PVN), 2) the paraventricular nucleus of the thalamus (PVT), 3) the arcuate nucleus of the hypothalamus (ARC), 4) the locus coeruleus (LC), and 5) the amygdala (AMY). Currently, many studies have indicated a special interest to investigate the APs impact in extra-striatal brain areas and the above-mentioned ones will be touched in this minireview.

C-Fos and **FosB/ΔFosB** proteins (prototypical members of the Fos family) have generally been considered as markers of neuronal activation (Sagar et al. 1988; Dragunow and Faull 1989) and have been used to map the brain regions activated by APs in numerous studies (Robertson and Fibiger 1992, 1996; Fink-Jensen and Kristensen 1994; Deutch and Duman 1996; Sumner et al. 2004; de Bartolomeis et al. 2017). They can be activated by different extracellular stimuli, whereas the c-fos mRNA and c-Fos protein

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belong to the first products to be expressed after an appropriate acute stimulation and hence referred as an immediate early gene. C-fos mRNA is rapidly and transiently up-regulated within 15 minutes of stimulation followed by the c-Fos protein expression 60–120 minutes later, i.e., time interval generally used for their qualitative/quantitative evaluations (Imaki et al. 1995). FosB/ΔFosB is a truncated splice variant of the FosB that accumulates in the brain after acute as well as chronic treatments, being detectable for a long time after the treatment (Chen et al. 1997). Owing to the high stability, the FosB/ΔFosB presence reflects long-lasting transcriptional changes.

Paraventricular nucleus of the hypothalamus

The paraventricular nucleus of the hypothalamus (PVN) is one of the most important autonomic and homeostatic control centers in the brain, with neurons playing an essential role in controlling stress, metabolism, growth, reproduction, immune, and other autonomic functions (Ferguson et al. 2008; Qin et al. 2018). The PVN is formed by a heterogeneous collection of neurons bilaterally located on either side of the third ventricle constituting one of the principal motor output systems of the hypothalamus (Swanson and Sawchenko 1980).

There is no doubt that PVN belongs to most studied structures of the brain, however, the studies concerned on the effect of antipsychotics (APs) have much more often been directed to the prefrontal brain structures than the PVN. Literature data and the results of our studies have shown that many of APs acute treatments may induce c-Fos and repeated treatments FosB/ΔFosB expression in the PVN, whereas both types of Fos profiles often exhibit spatial as well as density differences across all the PVN functional compartments, depending on the AP type, concentration, and exposure duration (Kiss 2018; Kiss and Osacka 2021).

PVN cell phenotypes activated with APs. The anatomical and the functional consequences of the APs action in the PVN depend on the PVN subdivisions targeted and the phenotype cells within these subdivisions activated. Several PVN subdivisions with different functions (i.e., functional compartments) have generally been accepted and immersed into three PVN divisions designated as the anterior, middle, and the posterior ones (Swanson and Kuypers 1980; Hou-Yu et al. 1986). Nowadays, however, mainly three from many other PVN neuropeptides (Ceccatelli et al. 1989), including corticotrophin-releasing hormone (CRH) concentrated in the middle PVN, arginine vasopressin (AVP) accumulated in the middle and the posterior PVN, and oxytocin (OXY) located in the middle and the posterior PVN, are coming into the consideration as a potential target of APs.

Current data indicate that the CRH region of the middle PVN division appears to be frequently targeted with APs (Figure 1). Data of our study analyzing the acute effect of ten sorts of APs on c-Fos expression (Kiss 2018) have revealed that only six of them including aripiprazole (ARI, 10 mg/kg/b.w.), clozapine (CLO, 10 and 20 mg/kg/b.w.), haloperidol (HAL, 2 mg/kg/b.w.), amisulpride (AMI, 30 mg/kg/b.w.), olanzapine (OLA, 10 mg/kg/b.w.), risperidone (RIS, 2 mg/kg/b.w.) may induce distinct c-Fos expression in the PVN CRH area, whereas these hypophysiotropic CRH-expressing neurons are known to play a prominent role in mediating the effect of stressors on the hypothalamic-pituitary-adrenal axis, i.e., they are the part of an important hypothalamic neuroendocrine system responding to different stressors. Park et al. (2011a) have even shown that ziprasidone (ZIP, 2.5 mg/kg/b.w., 21 days), which had no effect on CRH mRNA in the PVN under basal conditions, prevented the CRH mRNA expression increase in response to immobilization stress, indicating that ZIP might play a role in the treatment of depressive mood symptom associated with stress paradigms.

The second type of cells in the middle PVN activated by APs is manifested by magnocellular OXY-ergic cells, whereas OXY as a hormone/neurotransmitter is involved in childbirth, breast-feeding, and also stress response (Nishioka et al. 1998). The third type of cells, i.e., the magnocellular AVP-ergic population of cells that mainly occupies the middle PVN and secretes AVP into the peripheral circulation in response to a high serum osmolarity or body fluid deprivation (Roberts et al. 1993), has not been reported to be significantly affected by acute or repeated APs challenges (Figure 1).

Detailed analysis of c-Fos incidence in AVP and OXY perikarya in different rat PVN cell segregations (Hou-Yu et al. 1986): the anterior, the dorsal cup, the wing-shaped, the periventricular zone, the circle-shaped core and shell of the core, and the posterior (pPVN) after an acute treatment with OLA (5 mg/kg/b.w.), AMI (20 mg/kg/ b.w.), quetiapine (QUE, 15 mg/kg/b.w.), and ARI (10 mg/kg/b.w.) has revealed considerable diversity, whereas the stimulatory power of QUE was most distinct, ARI only moderate, and OLA and AMI minor (Kiss and Osacka 2021). Substantial variabilities in the stimulatory effect have also been observed in other

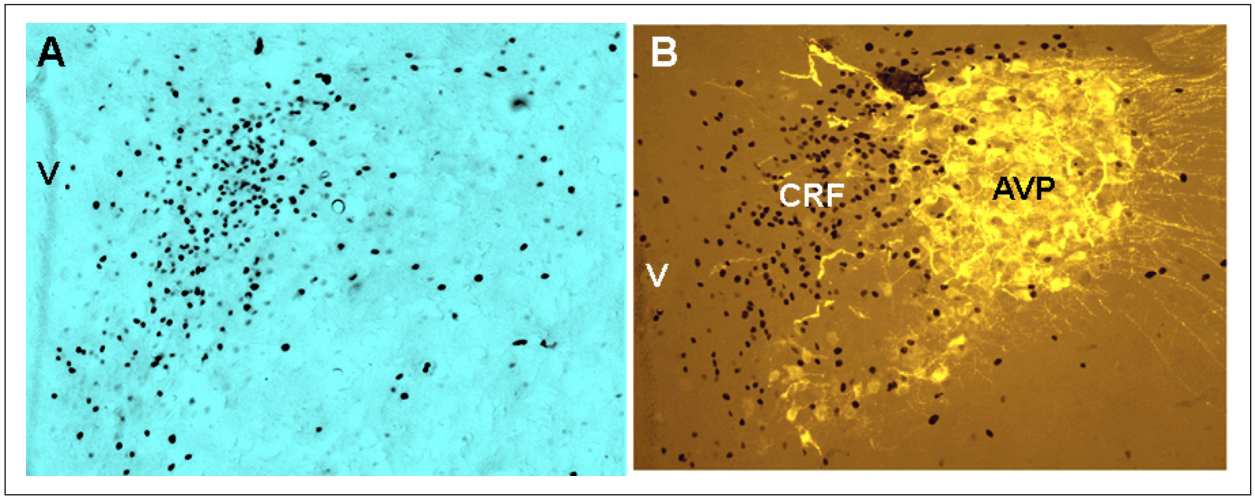


Figure 1. Distribution and arrangement of c-Fos profiles in the PVN middle division after a single treatment with olanzapine (10 mg/kg/b.w.) **(A)** and effect of a single dose of aripiprazole (10 mg/kg/b.w.) on the c-Fos expression in the same PVN division **(B)**. Note that the circle-shaped core formed by magnocellular AVP perikarya (AVP-yellow) are free of c-Fos-AVP colocalizations. Abbreviations: PVN – paraventricular nucleus of the hypothalamus; AVP – vasopressin; CRH – corticotropin-releasing hormone; V – lower part of the third brain ventricle.

set of APs, including of HAL (1 mg/kg/b.w.), CLO (30 mg/kg/b.w.), OLA (30 mg/kg/b.w.), and RIS (2 mg/kg) on the quantity of Fos-OXY, and Fos-AVP colocalizations in the PVN with the preferential action of CLO over OLA and RIS and HAL (Kiss et al. 2010). All these divergent effects of APs displaying different pharmacological profiles might be helpful to understand more precisely the extent of their extra-forebrain actions with a possible presumption of their functional impact and side effect consequences.

In contrast to the middle PVN area, OXY- and AVP-producing cells in the posterior PVN division, which give rise to autonomic-related projections to the brainstem and spinal cord innervating the caudal parasympathetic brainstem and spinal cord sympathetic structures (Swanson and Kuypers 1980; Swanson and Sawchenko 1980; Badoer 2001; Ferguson et al. 2008; Knobloch et al. 2012), have been shown to be activated by repeated asenapine (ASE) treatment (0.3 mg/kg/b.w. for 14 days) followed by induction of FosB/ΔFosB-AVP and FosB/ΔFosB-OXY coexpressions (Kiss and Majercikova 2017) or QUE (15 mg/kg/b.w.) and ARI (10 mg/kg/b.w.) treatments followed by induction of c-Fos-OXY (Figure 2) and c-Fos-AVP coexpressions (Kiss and Osacka 2021) indicate that all these APs under certain conditions might be involved in some of the PVN caudal brainstem and spinal cord regulative circuits, i.e., determining the PVN as an autonomic "premotor nucleus" (Badoer 2001; Stefanidis et al. 2008). However, since not all the APs may target the PVN cells, it is undisputable that this structure might not be considered as a common extra-striatal target for all APs. However, distinct c-Fos anatomical as well as expression divergences in the PVN AVP and OXY neurons might be helpful in the prediction of their possible extra-forebrain functional impact. Especially, the OXY-ergic projections from the PVN to the central amygdala (CEA) have been shown to play a crucial role for the discrimination of both positively and negatively valence emotional states (Ferretti et al. 2019; Knobloch et al. 2012). In addition, the hypothalamic oxytocinergic system has been shown to play an important role in a fear memory engram and its plasticity (Hasan et al. 2019).

A novel cellular target of atypical APs, ependymal cells, occurring at the level of the posterior PVN subdivision, have been detected and at the same time, 5-HT2A receptors have been determined as a substantive mediator of the APs action (Joshi and Panicker 2018). Our study has revealed a distinct increase in c-Fos expression in OXY-ergic cells located in ependymal and subependymal layers at the level of the posterior PVN subdivision (Figure 3) after acute administration of QUE (15 mg/kg/b.w.) (Kiss and Osacka 2021). This periventricularly localized population of OXY-ergic cells has previously been assigned as a possible OXY source of the cerebrospinal fluid (CSF) (Xiao et al. 2005). Actually, in patients suffering from psychotic diseases, increased OXY levels have been reported in CSF (Beckmann et al. 1985).

Paraventricular nucleus of the thalamus

The paraventricular nucleus of the thalamus (PVT) is a part of the midline and intralaminar thalamic nuclei that receives and sends projections to brain regions essential for fear and anxiety indicating that the PVT may be a critical point in the brains fear and anxiety network (Li et al. 2014; Penzo et al. 2015). The PVT is also connected with circuits that mediate positive and negative emotional behavior and it may be involved in emotional arousal (Li et al. 2010). The PVT, as a connecting point between the reticular formation and forebrain dopamine systems, may also be involved in certain APs impact (Deutch et al. 1995).

The effect of APs on the Fos expression in the PVT considerably varies. CLO administration has been shown to markedly increase both the number of cells expressing c-Fos protein-like immunoreactivity and the amount of c-Fos protein in the PVT (Deutch et al. 1995). The administration of loxapine and very high doses of HAL have also been demonstrated to cause a small but significant increase of c-Fos expression in the PVT, while comparable doses of several dopamine D2-like antagonists, including raclopride, sulpiride, remoxipride, and HAL, did not. Ritanserin, a 5-hydroxytryptamine antagonist, alone or in combination with sulpiride as well as the 5-hydroxytryptamine D2 antagonist RIS, also did not elevate c-Fos expression in the PVT (Deutch et al. 1995). Single HAL and CLO administration increased c-Fos immunoreactivity in PVT, suggesting that increased activity in PVT cells may share the clinical

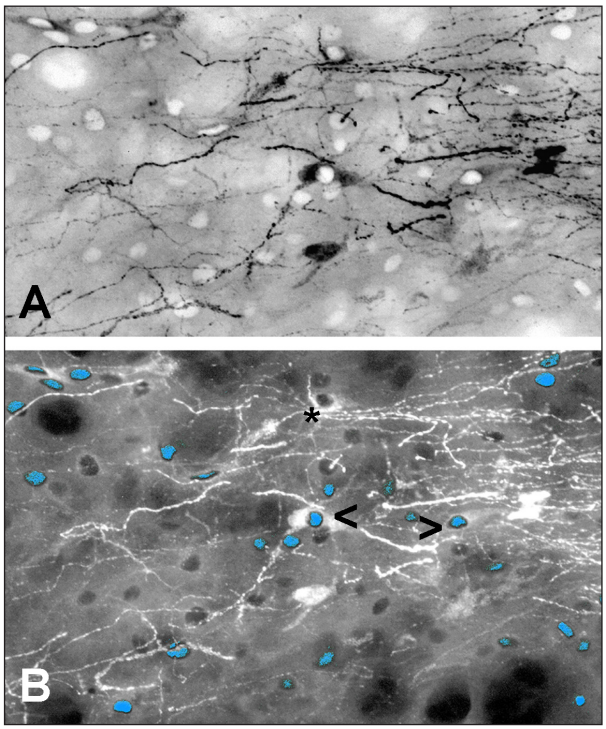


Figure 2. Induction of FosB/ΔFosB profiles in OXY-producing cells in the PVN posterior division, which give rise to the caudal brainstem and spinal cord projections, activated by repeated asenapine (ASE, 0.3 mg/kg/b.w.) administration for 14 days in the rat. **A** – shows complete population of FosB/ΔFosB profiles in the PVN posterior division, while **B** – depicts only those that emerged after the ASE treatment (blue circles), some of them being colocalized with OXY-ergic perikarya. Abbreviations: OXY – oxytocin; PVN – paraventricular nucleus of the hypothalamus; arrowheads – FosB/ΔFosB profiles colocalized with OXY-producing cells, asterisk – FosB/ΔFosB profile not colocalized with OXY-producing cells.

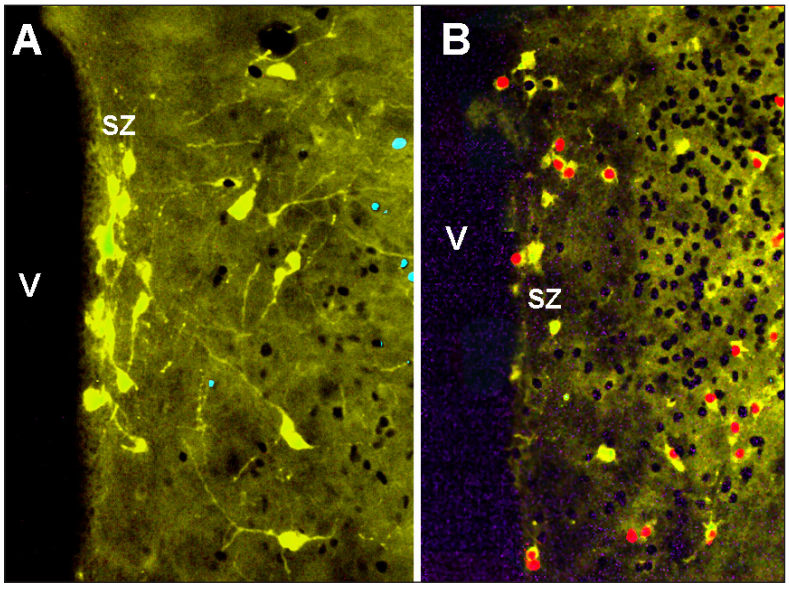


Figure 3. In contrast to controls **(A)**, a distinct increase in the number of c-Fos profiles (red circles) in periventricularly localized population of OXY-ergic cells at the level of the PVN posterior subdivision was elicited by an acute treatment with quetiapine (15 mg/kg/b.w.) **(B)**. Abbreviations: OXY – oxytocin; PVN – paraventricular nucleus of the hypothalamus; V – lower part of the third brain ventricle, SZ – subependymal zone.

effects of AP drugs mediated in part through actions on the thalamus (Cohen and Wan 1996). Single doses of typical neuroleptics HAL (1 mg/kg/b.w.), chlorpromazine (20 mg/kg/b.w.) and thioridazine (20 mg/kg/b.w.) and the atypical neuroleptics CLO (20 mg/kg/b.w.), the specific dopamine antagonist raclopride (3 mg/kg/b.w.), the mixed dopamine/serotonin antagonist risperidone (3 mg/kg/b.w.) have been shown to increase the expression of Fos-like protein not only in the PVT but also in the surrounding centromedian and rhomboid nuclei, and the nucleus reuniens, indicating that midline thalamic nuclei may participate in neural circuits mediating some of the shared effects of certain sort of APs (Cohen et al. 1998). It appears that the neuroanatomical positioning of the PVT is ideal for information's integration, regarding the environmental stimuli and internal states, translating them into the motivated actions. Thus, the PVT is an important part of an extended neural network subserving different actions of the AP drugs (Deutch et al. 1995; Cohen et al. 1998).

Arcuate nucleus of the hypothalamus

The arcuate nucleus of the hypothalamus (ARC) is an agglomeration of neurons concentrated in the mediobasal hypothalamus, adjacent to the third ventricle and the median eminence. It is an important neuroendocrine center created by a rich assortment of chemically variable neurons that: 1) control hormone secretion from the anterior pituitary (Everitt et al. 1986) and 2) integrate the circulating signals of hunger and satiety reflecting energy stores and nutrient availability (Kalra et al. 1999; Joly-Amado et al. 2014). ARC with other brain structures have been implicated in appetite regulation, whereas the acute treatment with CLO (atypical), chlorpromazine (CHC, typical) and fluphenazine (FLU, typical) differentially influenced c-Fos expression in ARC and other related appetite-related brain centers. The patterns of the effects of these APs are related to their hyperphagic properties. However, the neuronal structures that underlie hyperphagic effects are not fully understood yet (Rajkumar et al. 2013). Actually, the body mass gain is one of the serious side effects of many APs and may vary from discrete to severe level (Bak et al. 2014).

ARC cell phenotypes activated with APs. The level of gain per RIS has been supposed to induce the obesity by modulating central signals and many patients medicated with RIS for the treatment of psychiatric disorders experienced a substantial body mass gain indicating that RIS might induce obesity via central mechanisms (Wan et al. 2020). Actually, in RIS-treated mice, a significant c-Fos expression elevation has also been observed, whereas more than 68% of c-Fos-positive neurons were NPY-expressing neurons and 95% of 5-HT2c receptors were colocalized with NPY positive neurons (Xiao et al. 2020).

A small number of the orexin/hypocretin (OXH) expressing neurons located in the classical "feeding area" of the lateral hypothalamus and the perifornical area (LH/PFA) (de Lecea et al. 1998; Sakurai et al. 1998) is critically involved in the body weight regulation and arousal. The OXH are potent regulators of feeding and arousal (Kilduff and Peyron 2000) and their axons are dispersed over the whole brain (Peyron et al. 1998). It has been shown that APs with significant weight gain liability may increase c-Fos expression in OXH neurons, but APs with low or absent weight gain liability do not. The correlation of weight gain liability of CLO with the degree of c-Fos induction in OXH neurons of the lateral LH/PEF area revealed c-Fos expression in 75% of the OXH neurons projecting to the cortex, which appears to be associated with activation of only a distinct group of OXH neurons. This indicates for the existence of anatomically and functionally heterogeneous populations of OXH neurons in the lateral LH/PEF area (Fadel et al. 2002). However, it has also been reported that not all APs have an equal effect on the weight gain. A meta-analysis of 81 articles has revealed that after 10 weeks of the treatment, atypical APs tested could be ranked in terms of their negative impact in the order from highest to lowest: CLO > OLA > RIS > ZIP, with ZIP inducing no weight gain (Allison et al. 1999).

Distinct clusters of neurons in the ARC produce peptides such as neuropeptide Y (NPY) coexpressed with agouti-related peptide (AgRP) and the amino acid γ-aminobutyric acid (GABA), galanin (GAL) and the opioid dynorphin, and pro-opiomelanocortin (POMC)-derived β-endorphin and α-melanocyte-stimulating hormone (α-MSH) coexpressed with cocaine- and amphetamine-regulating transcript (CART). Ablation of AgRP neurons resulted in robust (5- to 10-fold) activation of Fos gene expression in many brain regions that are innervated by AgRP neurons, including the ARC (Wu et al. 2008). The AgRP neurons are now viewed as an important bridge between central detection of nutrient availability and peripheral nutrient partitioning, thus providing a mechanistic link between obesity and obesity-related disorders (Denis et al. 2014). Recent updates in the field have opened a new light on the role of the ARC neurons in the coordinated regula-

tion of peripheral organs involved in the control of nutrient storage, transformation, and substrate utilization independent of food intake.

Locus coeruleus

The locus coeruleus (LC) ("blue spot") is a heavily melanin pigmented nucleus located in the posterior area of the rostral pons in the lateral floors of the fourth ventricle formed by a relatively small and uniform group of neurons. The LC is the principal site for brain norepinephrine (NE) synthesis and the largest of the brain noradrenergic cell groups that provides the pivotal source of NE innervation to the entire cerebral cortex as well as the hippocampus, amygdala, cerebellar cortex, and the spinal cord (Samuels and Szabadi 2008; Benarroch 2009; Sara 2009). In the brain, NE functioning as a neurotransmitter or neuromodulator acting via alpha- and beta-adrenergic receptors.

The LC is involved in controlling the autonomic function resulting from both the direct projections to the spinal cord and the projections directed to autonomic nuclei (Samuels and Szabadi 2008). It has been shown that dysregulation of LC-NE-ergic neurotransmission may have implications in a variety of psychiatric disorders the neuropsychiatric processes that head towards to formation of clinical depression, post-traumatic stress disorder (PTSD), panic attacks, and anxiety (Berridge and Waterhouse 2003). The degeneration of LC neurons has been postulated that it may contribute to Parkinson and Alzheimer diseases (Giorgi et al. 2017).

LC cell neuropeptides activated with APs. The LC is a structure consisting of a homogenous group of predominantly NE-neurons (Figure 4), whereas subpopulations of these cells contain peptides such as NPY, galanin (GAL), and AVP, having different functions (Olpe and Steinmann 1991). Efferent projections of LC NPY-, tyrosine hydroxylase (TH)- and GAL-containing cells to the spinal cord, hypothalamus, and cerebral cortex, have been demonstrated. Since the LC peptide-containing neurons have different efferent projections to the spinal cord, hypothalamus, and cerebral cortex, there is an indication that the LC may be composed of several specific functional subdivisions based on the neurotransmitter/neuropeptide(s) content and their efferent projections (Holets et al. 1988).

A number of both typical and atypical APs has been shown to activate LC neurons (Figure 4). Acute administration of OLA and CLO has been shown to may activate the NE neurons in the rat LC and subcoeruleus accompanied by NE extracellular level increase as well as c-Fos expression elevation. This increase of NE activity in LC neurons may play an important role in the efficacy of OLA and CLO in treating both the negative symptoms and cognitive impairment observed in schizophrenic patients (Ohashi et al. 2000; Dawe et al. 2001).

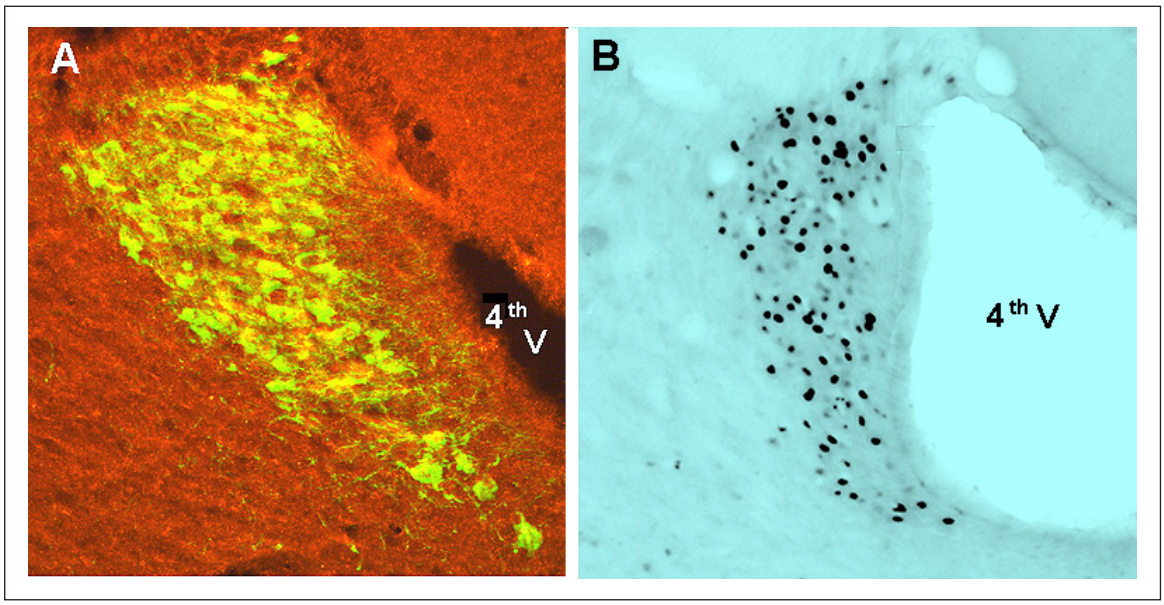


Figure 4. Typical spatial arrangement of NE-neurons (yellow-labeled perikarya) in the rat locus coeruleus visualized by tyrosine hydroxylase immunohistochemistry **(A)** and appearance of c-Fos profiles after an acute treatment with asenapine (0.3 mg/kg/b.w.) **(B)**. Abbreviations: NE – norepinephrine; 4th V – the lateral part of the fourth ventricle.

Amygdala

The amygdala (AMY) is one of the limbic related sub-cortical nuclei that plays an important role in the emotional response, anger, fear, regulation of cardiovascular system, memory processes and learning, and in pathophysiology of many diseases such as epilepsy, schizophrenia, chorea of Huntington and Alzheimer (LeDoux 2007). The AMY is composed of several different nuclei containing a wide range of neuropeptides, particularly its central nucleus (CEA), which is the major output region of the AMY and recipient of inputs from the rest of the amygdaloid nuclei (Pitkanen et al. 1997). A pattern of increased c-Fos-expression in CEA has been reported in response to a single intraperitoneal injection of HAL (1 mg/kg/b.w.), CLO (20 mg/kg/b.w.), OLA (5 mg/kg/b.w.), and ARI in three different doses (1, 10 and 30 mg/kg/b.w., i.p.) has also been revealed as a potent stimulator of c-Fos expression in the AMY central and the basolateral nuclei (Park et al. 2011b).

Differential induction of Fos-like-immunoreactivity has been observed in the extended amygdala (EXA) (being considered for a new brain structure involved in the pharmacological effects of atypical APs) after HAL and CLO treatments. The EXA, composed of the central and medial amygdaloid nucleus, which through the sublenticular extended AMY and the interstitial nucleus of the posterior limb of the anterior commissure merging into the bed nucleus of stria terminals, has been proposed to play an important role in cognitive and affective processes (Pinna and Morelli 1999).

AMY cell neuropeptides activated with APs. The presence of numerous neuropeptide-containing cells, including CRH (Fellmann et al. 1989), methionine-enkephalin, substance P, and somatostatin (Shiosaka et al. 1983), has been identified within the CEA. The CRH-labeled perikarya has been shown to be evenly distributed in CEA (Figure 5), whereas most of the immunoreactive processes emerging from the CRH neuronal bodies seems to project to the lateral hypothalamus (Fellmann et al. 1982) and the middle PVN, acting as a neurotransmitter in the ventral amygdalo-hypothalamic pathway (Marcilhac and Siaud 1997). This amygdalofugal CRH pathways might be qualitatively important in the regulation of homeostasis in responses to fear-provoking or aversive stimuli (Magnuson and Gray 1988). However, repeated ASE treatment (0.3 mg/kg, subcutaneously) twice a day for 14 days did not significantly affect the number of FosB/ΔFosB profiles in the CEA CRH-labeled cells analyzed 16–18 hours after the last treatment; actually, the level of FosB/ΔFosB colocalization with CRH did not overcome 10% level (Majercikova and Kiss 2015) indicating that ASE effect on the activation of PVN CRH by the AMY CRH system is unlike.

Acknowledgement

This review article has been financially supported by 2/0037/19 VEGA grant of the Slovak Academy of Sciences and APVV-15-0037 grant of the Research and Development Agency of the Slovak Republic.

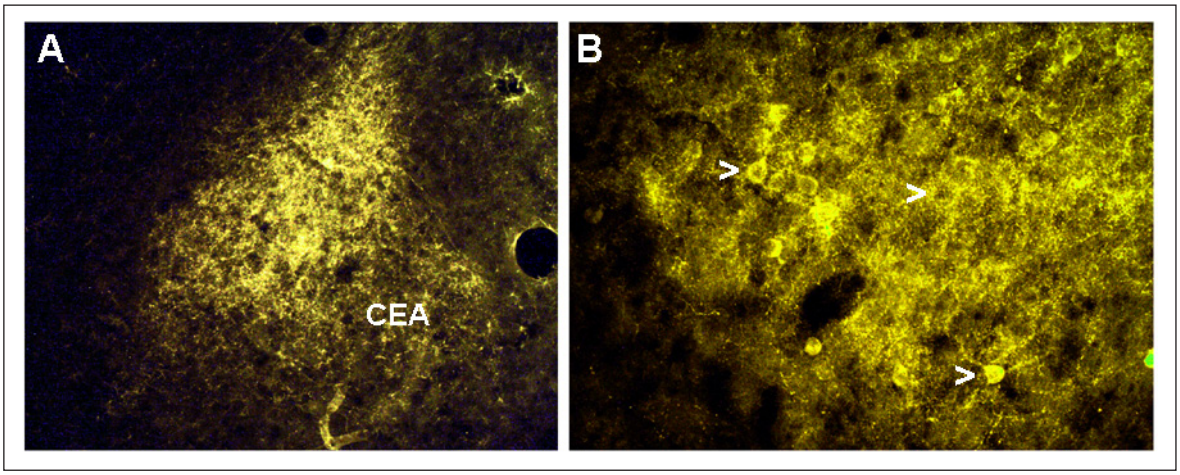


Figure 5. The spatial appearance of the amygdala central nucleus (CEA) visualized by CRH immunohistochemistry **(A)** displaying dispersed CRH-immunoreactive perikarya (arrowheads) in the normal, untreated rats **(B)**. Abbreviations: CRH – corticotropin-releasing hormone.

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