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Original article

Escitalopram affects spexin expression in the rat hypothalamus, hippocampus and striatum

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ABSTRACT

Background: Spexin (SPX) is a recently discovered neuropeptide that exhibits a large spectrum of central and peripheral regulatory activity, especially when considered as a potent anorexigenic factor. It has already been proven that antidepressants, including selective serotonin reuptake inhibitors (SSRI), can modulate peptidergic signaling in various brain structures. Despite these findings, there is so far no information regarding the influence of treatment with the SSRI antidepressant escitalopram on brain SPX expression.
Methods: In this current study we measured SPX mRNA and protein expression in the selected brain structures (hypothalamus, hippocampus and striatum) of rats chronically treated with a 10 mg/kg dose of escitalopram using quantitative Real-Time PCR and immunohistochemistry.
Results: Strikingly, long-term (4 week) drug treatment led to the downregulation of SPX expression in the rat hypothalamus. This supports the hypothesis that SPX may be involved in the hypothalamic serotonin-dependent actions of SSRI antidepressants and possibly also in the central mechanism of body mass increase. Conversely, SPX expression increased in the hippocampus and striatum.
Conclusions: This is the first report of the effects of a neuropsychiatric medication on SPX expression in animal brain. Our findings shed a new light on the pharmacology of antidepressants and may contribute to a better understanding of the alternative mechanisms responsible for antidepressant action.
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Introduction

Neuropeptides regulate a wide pool of diverse brain functions. Biochemical and molecular analysis of cellular interplay within brain centres has recently improved together with precise description of local neuronal networks. This coupled with the novel discoveries of new multifunctional neuropeptides such as nesfatin-1 and phoenixin [1–3] has led to a new era of understanding of neuropeptide-brain interactions.

Spexin (SPX) is one such intriguing novel neuropeptide, a product of the *Ch12orf39* gene which was found thanks to advanced bioinformatics methods [4]. The function of this regulatory factor is currently under examination with SPX demonstrating no molecular structure similarities to known neuropeptides. Rat SPX differs from the human and mouse molecules by only one amino acid at the C-terminal domain [5]. In the brain, many SPX immunopositive neural populations have been described, while neuroglia are usually negative, the highest reaction was detected in the hypothalamic paraventricular and supraoptic nuclei. Hippocampal neurons show moderate immunoreactivity as well as cerebellar Purkinje cells and brainstem neurons [6].

SPX seems to have multiple physiological functions with studies in goldfish revealing the involvement of SPX in reproduction and food-intake regulation. Treatment of animals with SPX decreased the secretion of luteinizing hormone and also suppressed appetite. Brain injection of goldfish with SPX inhibited both basal and NPY- or orexin-dependent consumatory behaviour and food intake [7]. Similarly, a new finding also reports, that in another fish; orange-spotted grouper (*Epinephelus coioides*) central

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SPX administration decreased orexin but increased POMC mRNA expression in the hypothalamus [8]. Intriguing recent results published by Walewski et al. [9] showed that SPX may be a strongly anorexigenic factor involved in weight regulation, with novel potential for obesity therapy. SPX may also be a fat-expressed satiety factor [10]. Recent findings also demonstrates a role for SPX in the control of cardiovascular/renal function and nociception [5,11]. Intracerebroventricular SPX injection decreased the heart rate of rats without modulation of the blood pressure, but with a high elevation of urine production [11]. It also reported that SPX stimulated basal aldosterone secretion from freshly isolated adrenal endocrine cells. Extended exposure of this culture to SPX resulted in a limited increase in corticosterone secretion and a significant decrease of cell proliferation [12]. In terms of mechanistic function, a ligand-receptor interaction study suggested that SPX may be a natural ligand for the GALR2/3 receptors. Moreover, SPX exhibits even higher potency toward GALR3 than galanin [13]. Interestingly an artificial SPX-based human GALR2 receptor agonist exerts an anxiolytic effect in mice [14]. On the other hand, SPX does stimulate intestinal peristaltic movement through GALR2-dependent activation of L-type calcium VDCC channels in the murine smooth muscle cells [15].

Escitalopram is an S-enantiomer of citalopram, a well-known highly selective serotonin reuptake inhibitor (SSRI) and a very effective treatment for depression and anxiety disorders. It has more potent allosteric affinity to the neuronal serotonin transporter (SERT) molecule than pure R-enantiomer or even isomer mixtures and therefore its pharmacological effect is especially beneficial with a satisfactory tolerance profile [16]. Escitalopram does not bind to serotonin, dopamine (D1 and D2), muscarinic and histamine receptors, which minimize the range of its potential side effects. SSRI-related changes in energy homeostasis and weight gain are often clinically observed [17,18], however little is known about peptidergic neuronal pathways which could be additional targets for these medications. Serotonin neurons located in the midline raphe nuclei send numerous long afferents to almost all brain structures including the hypothalamus, thalamus, hippocampus and neocortex.

There are many suggestions that SSRI treatment may affect the hypothalamic corticotropin-releasing factor (CRF) pathway [19,20] and hypothalamo-pituitary adrenal (HPA) axis [21]. Interestingly, 2 h after escitalopram administration the level of TRH-like peptides was increased in the rat nucleus accumbens, striatum, cerebellum and medulla oblongata, while TRH concentration was decreased in the nucleus accumbens. It should not be therefore excluded that SSRI action is mediated by modulation of TRH and TRH-like neuropeptides [22]. Potential direct or indirect action of SSRIs at the level of brain spexin signalling are so far completely unknown.

The present experimental paradigm aims to shed light on this area by determining if and how long-term treatment with escitalopram influences the expression of SPX in the rat brain. In the current study we evaluated for the first time the level of SPX mRNA and protein in the selected brain structures; hippocampus, hypothalamus and striatum after drug administration. The results cautiously indicate that extended escitalopram administration may significantly modulate SPX regulatory activity (Figs. 1 and 2).

Materials and methods

Animals

The studies were carried out on adult (2–3 months old, 185–220 g) male Sprague-Dawley rats housed at 22 °C with a regular 12/12 light-dark cycle with access to standard Murigran chow and water *ad libitum*. All experimental procedures were approved by the local bioethic committee (agreement no 36/2012).

Drug administration and tissue collection

Two groups of rats (n = 4) received intraperitoneal injections with respectively physiological saline and escitalopram at dose 10 mg/kg/day every day for 4 weeks (28 injections). The dose used at the experiment were taken from the publications where authors examine the influence of the escitalopram on the neuropeptide expression in the rat brain [19,23]. 24 h after the last drug administration, animals were anaesthetized with isoflurane and quickly sacrificed. Samples of hypothalamus, hippocampus and striatum were microsurgically excised from the brain halves for RNA isolation. Remaining tissues were fixed (with 4% paraformaldehyde in PBS, pH 7.2–7.4) for immunohistochemistry.

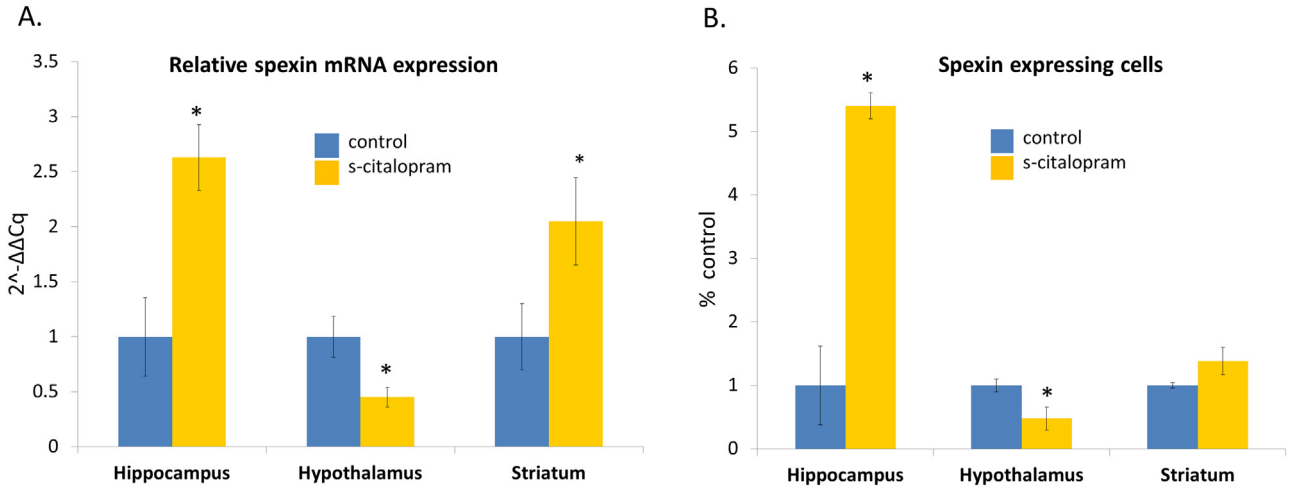

Fig. 1. Quantitative PCR results of relative spexin mRNA expression levels in the rat hypothalamus, hippocampus and striatum. (A). Obtained results were normalized to beta-2-microglobulin reference gene. The number of spexin immunopositive cells in the examined brain structures (B). Data are presented as multiples/decimals of control (1) ± SEM. Differences were considered statistically significant at $p \leq 0.01$ (asterisks).

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