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Effects of amphetamine administration on neurogenesis in adult rats

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Abstract

In our study expression of phospho-(Ser-10)-histone H3 ($pH3S_{10}$), a marker for the early stage of neurogenesis, and cellular early response genes were investigated using c-Fos protein as an example of a transcription factor in the neurogenic process in rats. Neurogenesis in the adult brain is regulated by endo- and exogenous factors, which influence the proliferation potential of progenitor cells and accelerate the dendritic development of newborn neurons. D-amphetamine, a psychoactive substance, is one of the exogenous factors able to influence the process of neurogenesis. The rats were injected with D-amphetamine at a dose of 1.5 mg/kg/body weight (b.w.) under one administration scheme. Analysis of the $pH3S_{10}$ and c-Fos expression levels in the group of D-amphetamine administered rats provided evidence of enhanced expression of these proteins in the regions of neurogenesis occurrence in rats. However, conclusions concerning stimulant effects of amphetamine on neurogenesis should be formulated with great caution, taking into account amphetamine dosage and the administration scheme. It should also be remembered that doses of psychoactive substances used in animal models can be lethal to humans.

Key words: *neurogenesis, neural stem cells, neuronal progenitor cells, DG, SVZ.*

Introduction

Neurogenesis in the adult brain is not a simple continuation of embryonic neurogenesis. During adulthood neurons are not born in such a huge number and do not migrate over such long distances in different directions. Groundbreaking animal investigations carried out in the 1960s resulted in the identification of undifferentiated neural stem cells (NSCs) [3]. Two locations, the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ), in which neurogenesis takes place, have been identified in the adult mammalian brain. During the neurogenic process in the adult brain neurons newly born in the subventricular zone migrate to the olfactory bulb, while those born in the dentate gyrus migrate locally [14]. Some studies also indicate the presence of neural stem cells (NSCs) in other regions of the brain, the frontal and temporal cortex, tonsillar body and the subcortical white body [20,26].

In neurogenesis in the adult brain with NSCs, apart from neurons, glial astrocytes and oligodendrocytes are also generated. New neurons generated from NSCs undergo consecutive developmental stages. Firstly, they become neuronal progenitor cells (NPCs) and neuroblasts, then immature neurons and finally they take the form of neurons. In the DG granular layer

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three types of transcription active cells have been identified: radial glia-like matrix cells with expression of glial fibrillary acidic protein (GFAP) and Sox 2 (type I); non-process bearing cells with nestin and Tis-21 expression (type II), also known as transiently active progenitor cells; and neuroblasts (type III) with DCX protein (doublecortin) and Ki67 expression, and immature neurons with expression of DCX, PSA-NCAM protein, marker of migrating neurons (polysialylated neuronal cell adhesion molecule) and neuron-specific protein (NeuN) [5,12]. Also in the subventricular zone three types of cells have been identified: type B cells, GFAP-positive neural stem cells (NSCs); type C cells with expression of Mash1 protein; and neuroblasts (type A) with expression of DCX protein [24].

Neurogenesis in the adult brain is regulated by endo- and exogenous factors, which influence the proliferation potential of progenitor cells and accelerate the dendritic development of newborn neurons [41]. D-amphetamine, a psychoactive substance, is one of the exogenous factors able to influence the process of neurogenesis. The results of individual studies in this area, published so far, have been conflicting. Some of them indicate that D-amphetamine administration does not exert an effect on proliferation and/or survival of newborn neurons in the dentate gyrus in the mammalian model [6], while others reveal that psychostimulants diminish the level of neurogenesis in the adult brain [19,40,43].

Phosphorylation of the *N*-terminal H3 histone domain in the Ser-10 position ($pH3S_{10}$) and/or Ser-28 position destabilises chromatin, directly preceding replication and transcription. Histone H3 is a very widespread marker of early stages of neurogenesis. Unlike DCX, $pH3S_{10}$ expression takes place only in newborn cells [23,28]. Due to the external factor activity, gene activation of early cellular response occur in parallel with histone H3 phosphorylation, e.g., *c-fos* genes. The same kinase, mitogen-activated protein kinase (MAPK), is responsible for both processes [7,9,18]. The product of the c-fos gene is a good marker for neuron activation in the mechanism of neuroadaptation [21,25].

The aim of our study was to establish the levels of $pH3S_{10}$ expression and the early cellular response of genes as markers for transcription, using c-Fos protein as an example in the process of neurogenesis in a group of rats administered D-amphetamine by injection.

Material and methods

In our research we used two groups: the study group composed of 8 rats receiving amphetamine according to a two-injection sensitisation protocol with a booster dose (TIPS), and the control group of 6 rats not exposed to amphetamine. The rats received a single dose of amphetamine (1.5 mg/kg/day). After a 6-day interval, the same dose of D-amphetamine was given once a day for 7 days. Following a 14-day interval after amphetamine administration the rats were given a single booster dose (1.5 mg/kg/day) of amphetamine, 2 h before decapitation. Under this scheme a single dose of amphetamine initiates the process of permanent neuroadaptation changes. These changes become apparent at the behavioural and biochemical level in response to a second dose [35,39]. D-amphetamine sulfate (Sigma, St. Louis, MO, USA) was dissolved (1.5 mg/ml) in sterile aqueous 0.9% NaCl solution (Sal; Polpharma, Starogard Gdański, Poland) and injected intraperitoneally (i.p.) at a dose of 1.5 mg/kg body weight (b.w.).

All animal use procedures were performed in accordance with both the European Communities Council Directive of November 24, 1986 on the protection of laboratory animals (86/609/EEC), and with the current laws of Poland, and were approved by the Bioethical Committee of the Medical University of Warsaw (Certificate of Approval No. 47/2012).

Immunochemistry

The rats were decapitated and the brains were fixed in 10% buffered formalin. The material was washed in 70% ethanol for 2 h, then in 96% ethanol for 12 h, twice in 100% ethanol for 12 h and twice in xylene for 12 h. After fixing the brains were embedded in paraffin for 48 h. The material was then cut serially in 5 µm slices on the rotary microtome onto silane-coated glass slides (Silan Sigma A36648), deparaffinized in xylene 3x10 min, released in a decreasing ethyl alcohol series, 100%, 96% and 70%, for 10 min and rinsed in distilled water for 10 min. Epitopes were exposed to a temperature of 100°C 3 × 5 min in citrate buffer (pH 6.0), cooled at room temperature for 10 min and rinsed in distilled water for 10 min. This was followed by blocking endogenous peroxidase in 0.3% TRIS+H_2O_2 (TrisBase T1503, pH 7.4-7.6) for 10 min. Then they were rinsed in TRIS for 10 min and blocked with serum NORMAL HORSE SERUM 2.5% (VECTOR PK-7200) for 1 h. Specimens

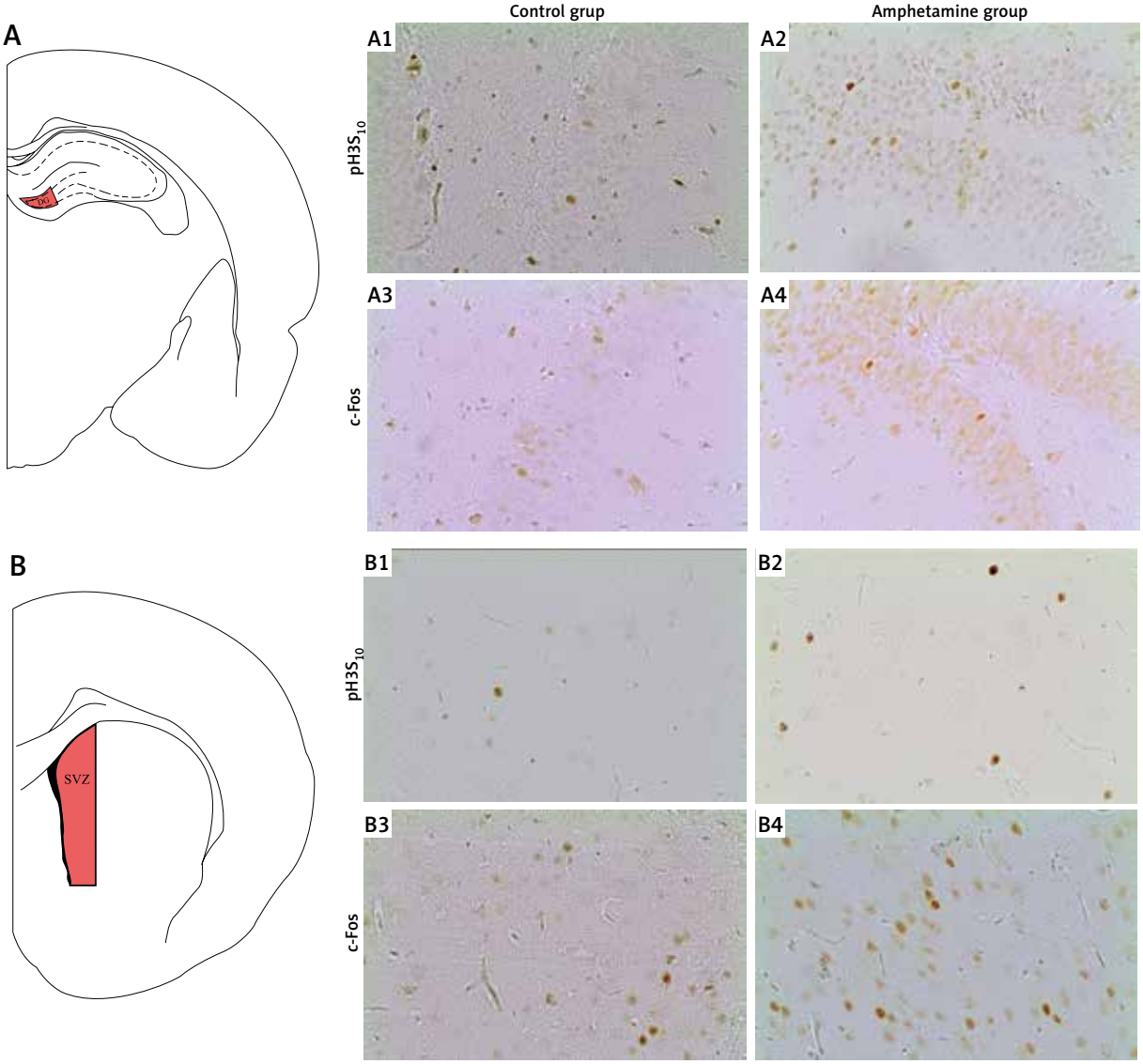

Fig. 1. Quantitative analysis of c-Fos and $pH3S_{10}$ proteins in immunopositive cells. **A)** Scheme of analysed dentate gyrus (DG). **A1-A2** show $pH3S_{10}$ expression in DG in control and amphetamine groups. **A3-A4** show c-Fos expression in DG in control and amphetamine groups. **B)** Scheme of analysed subventricular zone (SVZ). **B1-B2** show expression of $pH3S_{10}$ in SVZ in control and amphetamine groups. **B3-B4** show expression of c-Fos in SVZ in control and amphetamine groups.

were incubated with c-Fos antibody (1 : 700) (sc-253, Santa Cruz Biotechnology) or with phospho-(Ser-10)-histone H3 ($pH3S_{10}$) antibody (1 : 50) (sc-8656-R, Santa Cruz Biotechnology) for 50 min in 2% serum NORMAL HORSE SERUM. Then the following procedures were applied: rinsing in TRIS for minimum 40 min, incubation in biotinylated anti-rabbit IgG (Victor PK-7200) for at least 25 min, rinsing in TRIS for minimum 40 min, incubation in Vectastain RTV Elite ABC Reagent (PK-7200) for minimum 25 min, incubation in chromogen DAB (Sigma, D5637-5G) for 0-3 min, rinsing in distilled water for 10 min, dehydration in two ethyl alcohols, 96% and 100%, respectively, for 10 min, rinsing in xylene 2 × 10 min and sizing of Histokitt specimens (MarFour 1025/500).

Quantitative analysis

The cells were counted in the hippocampal dentate gyrus (DG, Bregma –3.3 mm) and the subventricular zone (SVZ, Bregma +1.00 mm). c-Fos and $pH3S_{10}$ immu-

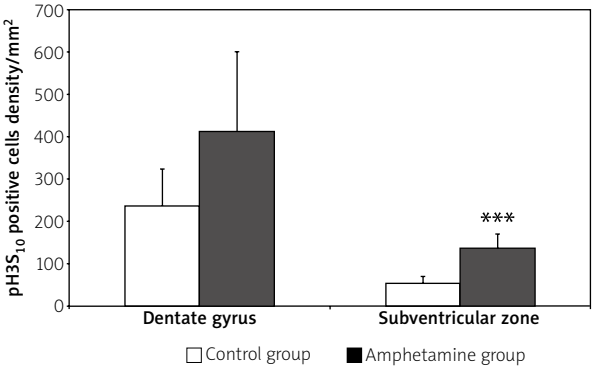

Fig. 2. Density of phospho-(Ser-10)-histone H3 ($pH3S_{10}$) immunoreactivity in cells in dentate gyrus and subventricular zone after amphetamine administration. ***$p < 0.001$.

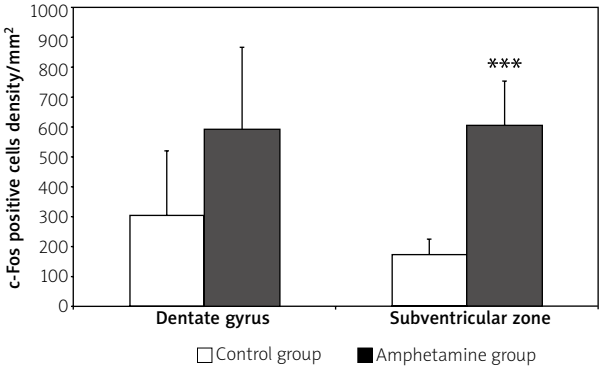

Fig. 3. Density of c-Fos immunoreactivity in cells in dentate gyrus and subventricular zone after amphetamine administration. ***$p < 0.001$.

nostaining was quantified at × 100 magnification, using an Olympus BX-51 microscope with a DP-70 (Olympus) camera and CellSens Dimension imaging software (Olympus Soft Imaging Solutions GmbH, Munster, Germany). Positive nuclei were counted and averaged for the two serial slices for statistical analysis.

Statistical analysis

In the statistical analysis of the results the Mann-Whitney *U* test was used. A value of $p \leq 0.05$ was considered to indicate statistical significance. The results were analyzed using STATISTICA 12 software.

Results

Expression of c-Fos and $pH3S_{10}$ proteins in cells of the subventricular zone and hippocampal dentate gyrus in the left cerebral hemisphere was analyzed. We observed transcription active cells with marked nuclei. The analysis of c-Fos protein expression (605.31 ± 147.39, $p < 0.00002$) and $pH3S_{10}$ (134.61 ± 4.32, $p < 0.0002$) in the SVZ cells showed a statistically significantly higher number of transcription active cells in the D-amphetamine administered rats compared to the control group, while the quantitative analysis of cells in the DG revealed an upward tendency in the number of transcription active cells in rats given D-amphetamine (Table I).

Discussion

In our experiment rats were given D-amphetamine at a dose of 1.5 mg/kg/b.w. In the study group the results showed a significantly higher density of newborn cells (NSCs, NPCs) in the subventricular zone. However, there were no significant differences in the density of NSCs and NPCs between the study and control groups in the hippocampal dentate gyrus. Neurogenesis in adult brain is regulated by numerous factors which affect the proliferation potential in progenitor cells and accelerate the dendritic development of newborn neurons [41]. Two markers, c-Fos and $pH3S_{10}$ proteins, were used to identify transcription active cells. Animal studies show that a stimulant-rich environment stimulates the process of neurogenesis and enhances c-Fos expression in the hippocampal dentate gyrus [34,36]. The highest level of $pH3S_{10}$ was observed 30 min after amphetamine injection, while increased mRNA encoding c-Fos was found after 30-90 min [30]. Expression of $pH3S_{10}$ was observed only in newborn cells (NSCs, NPCs) in phases G2 and M [1,28,38]. Stress, eating habits, physical activity, alcohol and drugs are listed among factors affecting the dynamics of neurogenesis and total amount of neurons [13,32].

In the mammalian model D-amphetamine, as a psychoactive agent, affects proliferation and/or survival of newborn neurons in the hippocampal dentate gyrus [6]. The results of the experiment indicate that psychostimulants can reduce the level of neurogenesis in the brains of adult rats [19,40,43]. Experimental data revealed a destructive effect of high D-amphetamine doses on dopaminergic nerve endings and apoptosis stimulation [4,10]. However, little is known about the effect of small D-amphetamine doses on the brain functions. It is suggest-

Table I. Comparison of c-Fos and $pH3S_{10}$ cell density between control and amphetamine groups in dentate gyrus (DG) and subventricular zone (SVZ). ***$p < 0.001$ (Mann-Whitney *U* test)

	Mean – control group	Mean – amphetamine group	*t*	*df*	*p*	SD – control group	SD – amphetamine group	Qquotient *F* variance	*p* variance
DG pH3S10	236.17	410.76	–1.89	10	0.0867	87.24	189.72	4.73	0.15
SVZ pH3S10	53.22	134.61***	–5.20	12	0.0002	16.89	35.12	4.32	0.13
SVZ c-Fos	173.99	605.31***	–6.81	12	0.00002	50.62	147.39	8.48	0.03
DG c-Fos	305.48	592.05	–2.10	12	0.0571	215.19	275.49	1.64	0.61

ed that D-amphetamine stimulates the activity of newborn neurons and dynamics of neurogenesis [11,29].

The mechanism by which D-amphetamine exerts its effect on the development and differentiation of new neurons includes the neurotrophin activation pathway. Neurotrophins regulate proliferation, differentiation and neuroplasticity. They are also responsible for the release of neurotransmitters and expression of their receptors. Trophic factors exert a major effect on neuronal survival, differentiation and maturation [2,15]. Neurotrophins comprise nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), neurotrophin 3 (NT3) and neurotrophin 4/5 (NT 4/5). Neurotrophins react with cells via receptors p75 and Trk. Reaction of neurotrophins with receptor p75 leads to cellular apoptosis, while neurotrophin-Trk receptor binding stimulates neuronal survival and differentiation [8]. BDNF plays a key role in the regulation of neuroplasticity in the adult human brain [17]. It has been evidenced that BDNF infusion into the hippocampus promotes neurogenesis [33]. There are numerous data underlying the crucial role of BDNF in the regulation of neurogenesis in the dentate gyrus of the adult brain. BDNF binds multiple receptors, e.g., p75 or Trk. The mechanism by which BDNF stimulates TrkB expression in precursor cells still remains unclear [31,42].

These findings correspond to those obtained for even higher doses of amphetamine. D-amphetamine administered to Sprague-Dawley rats at a dose of 2.5 mg/kg for 14 days did not affect the proliferation and survival of newborn neurons in the dentate gyrus [6]. It is likely that this result is influenced by the fact that amphetamine can contribute to the diminished volume of the hippocampus [38]. The studies evidenced that administration of methamphetamine enhances the proliferation of neuronal progenitor cells and their survival in the hippocampal dentate gyrus [22]. On the other hand, several *in vivo* models of METH exposure have demonstrated decreases in hippocampal neurogenesis [16,19,37]. METH-induced oxidative stress and nitrosylation have also been shown to increase apoptosis and decrease neural progenitor cell proliferation in the dentate gyrus of the hippocampus [40]. The comparison of different results supports the conclusion that the effect of amphetamine depends on the dosage and administration scheme [19]. Experiments on methamphetamine self-administration in a mammalian model show that short episodes of administration (for 1 h twice weekly (intermittent short access, I-ShA) and 1 h daily (short access ShA)) increase the number of cells in S phase, c-Fos positive in the DG [27].

This may suggest that our protocol of amphetamine administration falls within the definition of a short exposure to amphetamine. An analysis of $pH3S_{10}$ and c-Fos expression levels in D-amphetamine administered rats provides evidence of enhanced expression of these proteins in the regions in which neurogenesis occurs. Conclusions on the stimulating effect of amphetamine on neurogenesis should be formulated with great caution, having also in mind that doses of psychoactive substances applied in the animal model may be lethal to humans.

Acknowledgments

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Disclosure

Author reports no conflict of interest.

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