Snca and *Bdnf* gene expression in the VTA and raphe nuclei of midbrain in chronically victorious and defeated male mice

Natalia N, Kudryavtseva[1], Natalia P. Bondar[1], Ul'yana A. Boyarskikh[2], Maxim L. Filipenko[2]

[1]Institute of Cytology and Genetics SD RAS; [2]Institute of Chemical Biology and Basic Medicine SD RAS, Novosibirsk, Russia

The study aimed to analyze the mRNA levels *of Snca* and *Bdnf genes* in the ventral tegmental area (VTA) and raphe nuclei of the midbrain in male mice that had each won or defeated 20 encounters in daily agonistic interactions. Groups of animals that had the same winning and losing track record followed by a no-fight period for 14 days were also studied. *Snca* mRNA levels were increased in the raphe nuclei in the losers and in the VTA of the winners. After fighting deprivation *Snca* mRNA levels were decreased to the control level in both groups. *Snca* mRNA levels were similar to the control level in the VTA of the losers and in the raphe nuclei of the winners. However *Snca* gene expression was increased in these areas after no-fight period in the winners and losers in comparison with respective mRNA levels in the undeprived animals. Significant positive correlations were found between the mRNA levels of *Snca* and *Bdnf* genes in the raphe nuclei. It was concluded, that social experience affects *Snca* gene expression depending on brain areas and functional activity of monoaminergic systems in chronically victorious or defeated mice.

Key words: repeated aggression, social defeats, *Snca*, *Bdnf*, mRNA

Introduction

Alpha-synuclein (α-Syn) is a small neuronal protein localized in the presynaptic compartment of neurons that has been found to be expressed throughout the brain (George, 2002; Totterdell et al., 2004). It has been shown that α-Syn regulates the homeostasis of monoamine neurotransmitters, through its trafficking, and regulation of the cell surface expression and, thereby, the activity of dopamine, serotonin and norepinephrine transporters (Yavich et al., 2004; Wersinger et al., 2006; Wersinger et al., 2006). α-Syn is involved in various degenerative disorders such as Parkinson's disease, dementia with Lewy bodies (review George, 2002; Sidhu et al., 2004; Kao et al., 2009; Wersinger et al., 2006), which are recognized as alpha-synucleinopathies. It is suggested that α-Syn may also play a pathophysiological role in depressive symptoms (Frieling et al., 2008; Jeannotte et al., 2009).

Previous data have revealed that long positive or negative fighting experience in daily agonistic interactions in male mice is accompanied by different changes in brain neurochemical activities. It has been experimentally demonstrated that repeated aggression which is accompanied by victories, leads to total activation of brain dopaminergic systems. This activation was detected in the winners as elevated DOPAC (3,4-dihydroxyphenyleacetic acid) levels or/and increased DOPAC/DA (dopamine) ratios in different brain areas (Kudriavtseva, Bakshtanovskaia, 1991; Devoino et al., 1998). Enhanced expression of the *Th*, *Dat1* and *Snca* genes (Filipenko et al., 2001; Bondar et al., 2009), which are associated with brain dopaminergic systems was shown in the ventral tegmental area (VTA) of the winners.

Corresponding author: Kudryavtseva N.N., Institute of Cytology and Genetics SD RAS; pr. Ak. Lavrentjeva, 10, Novosibirsk, 630090, Russia; e-mail – natnik@bionet.nsc.ru

Reduced activity of brain serotonergic system was suggested to be developed under repeated experience of aggression as has been shown by decreased tryptophan hydroxylase activity in some brain areas (Amstislavskaya, Kudryavtseva, 1997; Kulikov et al., 1995; review, Kudryavtseva, 2006). Daily social defeats are accompanied by activation of serotonergic system as shown by changes of serotonin and 5-hydroxyindoleacetic acid levels in different brain areas of the losers (Kudriavtseva, Bakshtanovskaia, 1991; for review, Avgustinovich et al. 2004) and enhanced expression of *Sert* and *MaoA* genes in the raphe nuclei of the midbrain (Filipenko et al., 2002). Some data gave reason to suggest reduced activity of brain dopaminergic systems in defeated animals (review, Avgustinovich et al., 2004).

The paper aimed to study the possible changes of *Snca* gene expression in animals with different brain monoaminergic activity. We focused on the VTA containing the cell bodies of mesolimbic dopaminergic neurons, because mesolimbic dopaminergic projections from the VTA play an important role in the mediation of rewarding processes (review, Cooper, 1991). Also we studied the raphe nuclei containing the cell bodies of serotonergic neurons whose projections are involved into regulation of stress, depression, anxiety and in many kinds of social behaviors. Expression of *Bdnf* gene, whose protein is associated with many psychiatric disorders (Groves, 2007; Greenberg et al., 2009) by participating in differentiation, growth and maintenance of neuronal cells, was also studied in the VTA and raphe nuclei of midbrain.

Materials and Methods

Animals and housing. Adult male mice of the C57BL/6J strain from a stock maintained in the Animal Facility of the Institute of Cytology and Genetics, SD RAS, (Novosibirsk, Russia) were used. The animals were housed under standard conditions (12:12 h light/dark regime, switch-on at 8.00 a.m.; food (pellets) and water available *ad libitum*). Mice were weaned at one month of age and housed in groups of 8-10 in plastic cages (36 x 23 x 12 cm). Experiments were performed on mice 10-12 weeks of age. All procedures were in compliance with the European Communities Council Directive of November 24, 1986 (86/609/EEC).

Chronic agonistic interactions (winners and losers). Aggressive or submissive behaviors in male mice was induced using the sensory contact model (Kudryavtseva, 1991). Pairs of weight-matched animals were each placed in a steel cage (28 x 14 x 10 cm) bisected by a perforated transparent partition allowing the animals to see, hear and smell each other, but preventing physical contact. The animals were left undisturbed for three days to adapt to new housing conditions and sensory contact before they were exposed to encounters. In the second half of the light period, the lid was replaced by a transparent one and five minutes later the partition was removed for 10 minutes to encourage agonistic interactions. The superiority of one of the mice was firmly established within two or three encounters (three days) with the same opponent. The superior mouse would be attacking, biting and chasing another, who would be displaying only defensive behavior (sideways postures, upright postures, withdrawal, lying on the back or freezing). As a rule, in our experiments, aggressive confrontations between males are discontinued by lowering the partition if the aggression has lasted more then 3 min or less. Each defeated mouse (loser) was exposed to the same winner for three days, while afterwards each loser was placed, once a day after the fight, in an unfamiliar cage with an unfamiliar winner behind the partition. Each victorious mouse

(winner) remained in its original cage. This procedure was performed for 20 days and yielded an equal number of winners and losers.

Five groups of animals were used. (1) Fight-undeprived winners: a group of mice that had each won 20 encounters in succession (2) Fight-deprived winners: a group of 20-time winners who were allowed to live for 14 days after the last encounter without agonistic interactions; (3) Fight-undeprived losers: a group of mice that had each defeated 20 encounters; (4) Fight-deprived losers: a group of 20-time losers who were allowed to live for 14 days after the last encounter without agonistic interactions. During period of fighting deprivation animals shared a cage with a partner (losers or winners); the partition between their compartments being down at all times, to prevent encounters. (5) Controls: the mice that had been housed individually for five days. The rationale for this choice is that it gives the best trade-off between group housing and social isolation: five days is sufficient for group housing to no longer be a factor and insufficient for social isolation to become a factor. Special investigations confirmed strong rationality of this control in the sensory contact model (Avgustinovich et al., 2005). Each experimental group contained 7-13 animals.

To measure mRNA levels in the brain areas, all the mice were decapitated simultaneously: "undeprived" winners and "undeprived" losers, 24 hours after the last agonistic interaction; "deprived" winners and "deprived" losers, immediately after 14-day fighting deprivation; and the controls, on day 6 of individual housing. The mouse brains were removed and chilled rapidly on ice. The VTA and raphe nuclei were dissected according to the Mouse Brain Atlas (Rosen et al., 2000). Obtained tissue was rapidly frozen in liquid nitrogen and stored at -70° C until used.

Total RNA extraction and reverse transcription. Total RNA was extracted from each individual brain tissue sample using the Chomczynski and Sacchi method (Chomczynski, Sacchi, 1987) with modifications. Total RNA was quantified by measuring the absorbance at 260 nm. The integrity of total RNA was assessed by agarose gel electrophoresis. 1 μg of total RNA was used for cDNA synthesis by MoMLV reverse transcriptase (Biosan, Novosibirsk, Russia).

Real-time quantitative PCR. Amplification was performed using an iQ5 iCycler (Bio-Rad, Hercules, CA, USA). *Bdnf*, β-actin (*Actb*), and cyclophilin (*Cphn*) mRNA levels were quantified by TaqMan real-time PCR. PCR was performed in a total volume of 25 μl containing an aliquot of the RT mixture, dNTPs, the appropriate concentrations of sense and anti-sense primers, a TaqMan probe, PCR buffer, and hot-start Taq DNA polymerase (Biosan, Novosibirsk, Russia). Amplification was run for 2 min at 96°C, followed by 37 cycles of 15 s at 96°C, 45 s at 61°C. Fluorescence was monitored for 10 s after the last cycle.

Snca mRNA levels were quantified by SybrGreenI real-time PCR in a total volume of 25 μl containing an aliquot of the RT mixture, dNTPs, the appropriate concentrations of the sense and anti-sense primers, Sybr Green I (Invitrogen), PCR buffer, and hot-start Taq DNA polymerase. Amplification was run for 3 min at 95°C, followed by 40 cycles of 10 s at 92°C, 6 s at 60°C, 6 s at 72°C and 10 s at 85°C. Fluorescence was monitored for 10 s after the last cycle. To check for the presence of non-specific PCR products or primer-dimers, a melting curve analysis was performed after the final PCR cycle.

Amplification efficiencies were calculated a relative standard curve derived from fourfold serial dilutions of pooled cDNA. In all cases, the amplification efficiency was higher than 85%. Each sample was PCR-amplified twice. RT-PCR results were quantified using the relative standard curve method. The level of expression of each gene was normalized to the mean level of expression of the *Actb* and *Cphn* genes. The oligonucleotide primers and probes were designed using Beacon Designer 5.0 (PREMIER Biosoft International, USA). The PCR primer and probe sequences are shown in Table.

Table . Primer and probe sequences

Genes	Primer and probe sequences	
Bdnf	Sense	5'-ACTATGGTTATTTCATACTTCGGTT-3'
	anti-sense	5'-CCATTCACGCTCTCCAGA-3'
	Probe	5'-FAM-CGTCCACGGACAAGGCAACTT-BHQ1-3'
Snca	Sense	5'-TGACAGCAGTCGCTCAGA-3'
	anti-sense	5'-CATGTCTTCCAGGATTCCTTC-3'
Cphn	Sense	5'-GAGAACTTCATCCTAAAGCATACAG-3'
	anti-sense	5'-TCACCTTCCCAAAGACCA-3'
	Probe	5'- TAMRA -CGTTGCCATCCAGCCATTCAG-BHQ2-3'
Actb	Sense	5'- TCTTTGCAGCTCCTTCGTT -3'
	anti-sense	5'-CGATGGAGGGGAATACAG-3'
	Probe	5'- ROX-CACACCCGCCACCAGTTCGC-BHQ2-3'

Statistical analysis. The data are reported as mean ± SEM. Two-way ANOVA of ranked data was used to reveal effect of factors social status and fighting deprivation effects and its interactions. Statistical analysis of data was also performed using the Kruskal-Wallis one-way analysis of variance (ANOVA) with factor groups in consideration – the control, "undeprived" winners, "undeprived" losers, "deprived" winners and "deprived" losers. A post-hoc pair-wise comparison of the groups was made with the Mann-Whitney *U* test. Correlations were assessed using Spearman's rank correlation coefficient. We searched for correlations between the *Bdnf* and *Snca* mRNA levels in each experimental group separately and in combination. The statistical significance was set at $P \leq 0.05$; the tendency level was set at $0.05 < P < 0.1$.

Results

For the *Snca* mRNA levels, two-way ANOVA reports a significant interaction for social status and deprivation effect in the raphe nuclei ($F(1,47) = 15,57$, $p < 0.0003$) and in the VTA ($F(1,33) = 15.87$, $p < 0.0003$). For the *Bdnf* mRNA levels no significant interactions were found between social status and deprivation effects in the raphe nuclei ($F(1,47) = 1.023$, NS) and in the VTA ($F(1,31) = 0.440$, NS).

Kruskal-Wallis analysis revealed a significant influence of the factor groups for the *Snca* mRNA level in the VTA ($H(4, N=44)=14.41$, $p = 0.0061$) and in the raphe nuclei ($H(4, N= 64)=13.69$, $p = 0.0084$) as well as for the *Bdnf* mRNA level in the raphe nuclei ($H(4, N=64)=10.58$, $p = 0.0317$). There was no significant influence of the factor groups on the *Bdnf* mRNA level in the VTA ($H(4, N=42)= 2.96$, NS).

Based on the Mann-Whitney *U* test (Figure), in the VTA, "undeprived" winners and "deprived" losers had increased *Snca* mRNA levels as compared to the control ($U = 16$; $p < 0.028$ and $U = 7$; $p < 0.025$, respectively). Groups of the "undeprived" winners and "undeprived" losers as well as groups of the "deprived" winners and "deprived" losers differed significantly ($U = 31$; $p < 0.031$ and $U = 8$; $p < 0.035$, respectively). "Deprived"

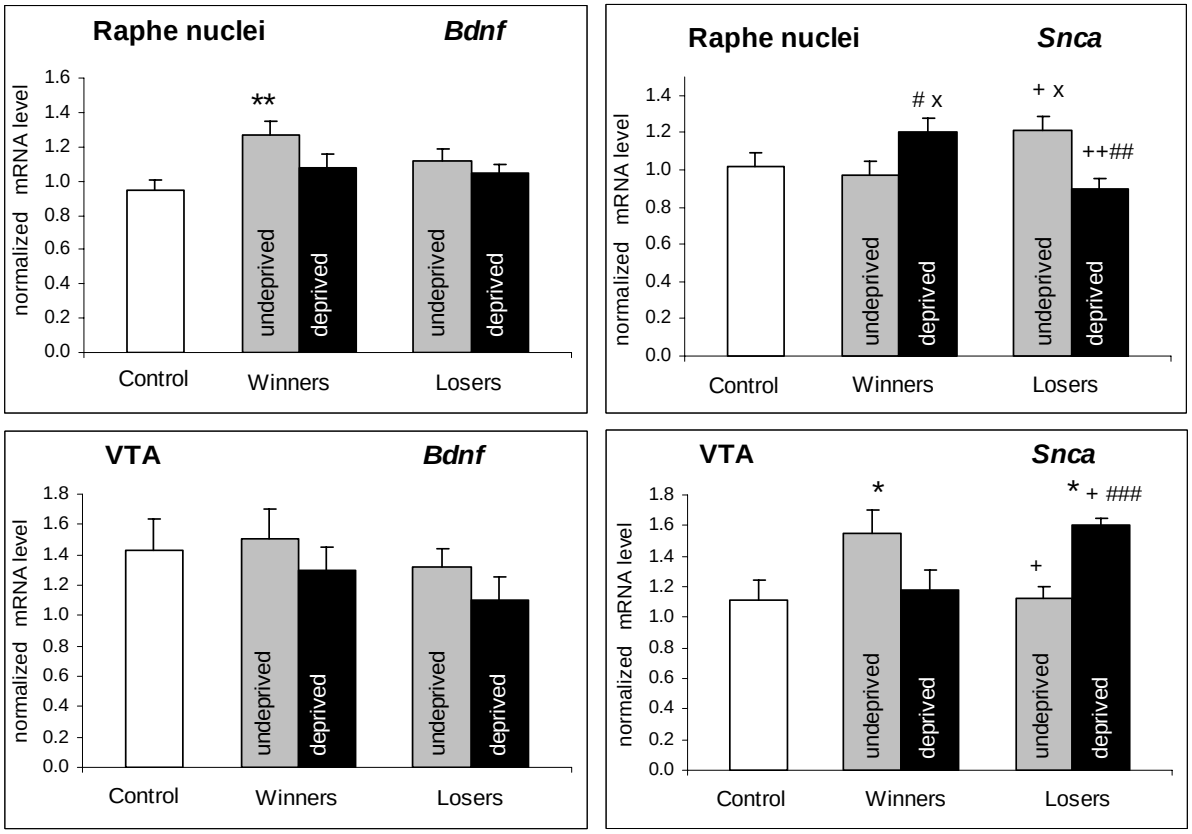

Figure. The normalized *Snca* and *Bdnf* mRNA levels in the VTA and raphe nuclei of midbrain of the controls, fight-undeprived and fight-deprived winners and losers.
* $p < 0.05$; ** $p < 0.01$; ^{X}- ($0.05 < p < 0.1$) *vs* the controls; # $p < 0.05$; ## $p < 0.01$; ### $p < 0.001$ *vs* "undeprived" mice in respective group; + $p < 0.05$ *vs* respective level in the "undeprived" or "deprived" winners.

losers had increased *Snca* mRNA levels as compared to the "undeprived" losers ($U = 2$; $p < 0.0009$).

In the raphe nuclei, the "deprived" winners had increased *Snca* mRNA levels as compared to the "undeprived" winners ($U = 41$; $p < 0.044$). "Deprived" losers had decreased *Snca* mRNA levels as compared to the levels in "undeprived" losers ($U = 30$; $p < 0.005$). There were significant differences in the *Snca* mRNA levels between the "undeprived" winners and "undeprived" losers ($U = 38$; $p < 0.030$) as well as the "deprived" winners and "deprived" losers ($U = 29$; $p < 0.004$). Differences in mRNA levels between the control and "deprived" winners and between the control and "undeprived" losers were not definitely significant, but strongly suggestive ($p = 0.086$ and $p = 0.061$, respectively). The "undeprived" winners had increased *Bdnf* mRNA level as compared to the control ($U = 22$; $p < 0.002$). Other pair comparisons failed to reach significance.

Based on Spearman's rank correlation coefficient, there were significant positive correlations in the raphe nuclei between the mRNA levels of *Bdnf* and *Snca* genes in the groups of the "undeprived" and "deprived" winners ($R = 0.643$, $p < 0.018$ and $R = 0.734$, $p < 0.007$, respectively); in the group of the "undeprived" losers ($R = 0.560$, $p < 0.046$); and in all groups in combination using pooled data from all the groups ($R = 0.397$, $p < 0.001$). There was one significant positive correlations in the VTA between the mRNA levels of *Bdnf* and *Snca* genes in the control ($R = 0.893$, $p < 0.007$).

Discussion

It has been shown that long positive fighting experience in daily agonistic interactions is accompanied by activation of brain dopaminergic systems and reduced serotonergic activity in male mice (review, Kudryavtseva, 2006). Chronic social defeat stress is accompanied by activation of the brain serotonergic system and, presumably, decreased dopaminergic activities (review, Avgustinovich et al., 2004). Our neurochemical observations in the aggressive mice (winners) are in agreement with other studies in animals and humans (Cocarro, 1992; reviews, Miczek et al., 2007, De Boer et al., 2009).

Two-way ANOVA for the *Snca* mRNA levels in the raphe nuclei and VTA showed significant interaction effects for social status and fight-deprivation period. This means that expression of the *Snca* gene in brain areas changes differently in animals with positive or negative fighting experience and that the changed monoaminergic activity influences gene expression during fight-deprivation period. Increased mRNA levels of the *Snca* gene were found in the "undeprived" winners' VTA and in the "undeprived" losers' raphe nuclei in comparison with respective level in opposite social group. On the contrary, decreased *Snca* mRNA level was found in "deprived" winners' VTA and in "deprived" losers' raphe nuclei in similar comparisons.

Data analysis allows concluding: the changes in *Snca* gene expression are a consequence of the functional state of the brain dopaminergic and serotonergic systems. Enhanced expression of the *Snca* gene due to repeated aggression or defeats is associated with activation of the leading monoaminergic systems: mesolimbic dopaminergic system in the VTA of the "undeprived" winners and serotonergic system in the raphe nuclei of the "undeprived" losers. After no-fight period increased *Snca* gene expression in both areas reverts to the control level. On the contrary, when reduced activity of dopaminergic systems in the "undeprived" losers' VTA or serotonergic system in the "undeprived" winners' raphe nuclei is suggested, no changes in *Snca* gene expression were found under repeated agonistic interactions. After no-fight period the *Snca* mRNA levels are increased in these areas. Since similar changes in *Snca* gene expression were found in different brain areas, *Snca* may act as a common regulator of monoaminergic activity as shown earlier (Wersinger et al., 2006).

Our data provide evidence that the *Snca* gene may be part of a feedback mechanism in regulation of neurotransmitters' metabolism. It has been shown, that the presynaptic protein α-Syn negatively modulate DAT and SERT activity (Wersinger & Sidhu, 2003; Sidhu et al., 2004; Wersinger et al., 2006). Increase of the *Snca* mRNA levels may be a response to the increase of *Dat1* mRNA level in the winners' VTA and *Sert* mRNA level in the losers' raphe nuclei shown earlier (Filipenko et al., 2001; Filipenko et al., 2002; Bondar et al., 2009). After no-fight period mRNA level of *Snca* gene reverts to the control level. Noteworthy, over-expression of the *Snca* gene in the VTA was found in the "undeprived" winners after 20 day agonistic interactions and in the "deprived" losers in comparison with the control. Some authors suggest (Sidhu et al., 2004) that over-expression of the *Snca* gene may block its neuroprotective properties. Our observations are in agreement with those of Mash and co-workers (2003) who have demonstrated over-expression of *Snca* gene in the VTA in people who abuse cocaine, which was shown to activate the brain dopaminergic systems (Kreek, 1996). Increased mRNA level of *Snca* gene was also found after amphetamine injections (Mauceli et al., 2006).

Two-way ANOVA for *Bdnf* mRNA levels did not reveal significant interaction effects for social status and deprivation in both areas. However, we cannot completely exclude the involvement of *Bdnf* gene in the mechanisms underlying repeated aggression or defeats. This expectation is supported by increased *Bdnf* mRNA level in the "undeprived" winners' raphe

nuclei in comparison with the controls and by the presence of positive functional correlations between the *Bdnf* and *Snca* mRNA levels in the raphe nuclei. These data allows suggesting that BDNF may play an important role in regulation of serotonergic activity. In the VTA, positive correlation between the *Bdnf* and *Snca* mRNA levels was found only in the control mice. However, the intrinsic molecular mechanisms responsible for the functional association have yet to be revealed. The reason for this correlative relationship might be the common molecular mechanisms of transcriptional regulation of these genes.

Thus, chronic manifestation of aggression, which leads to activation of dopaminergic metabolism in the brain areas, enhances in the VTA the expression of the *Th, Dat1 and Snca* genes, whose proteins are responsible for the DA functioning. Mesolimbic dopaminergic projections from the VTA play an important role in the mediation of rewarding processes. It is therefore possible that the observed changes of the *Snca* genes expression display the dopaminergic mechanisms from experiencing positive emotions over social victories in the winners. Because social defeats lead to the activation of the serotonergic system (Kudryavtseva, Avgustinovich, 1998; Avgustinovich et al., 2004), the changes in the *Snca* mRNA levels in the losers' raphe nuclei lend support to the involvement of a-Syn in the consequence of chronic negative emotions.

It has been shown earlier that long positive fighting history leads to development of behavioral psychopathology, which includes the demonstration of abnormal aggression, malignancy, strong hostility, pronounced anxiety, disturbances in social recognition, hyperactivity, stereotypic and hyperkinetic reactions etc (Kudryavtseva, 2006). Male mice with long defeat history developed a psychoemotional disorder similar to anxious depression in accordance with symptomatics, etiology factors, brain neurochemical changes and sensitivity to antidepressants and anxiolytics similar to those in depressive persons (reviews, Kudryavtseva, Avgustinovich, 1998; Avgustinovich et al., 2004). It may be concluded that *Snca* gene may be involved in pathogenesis of these disorders. In this context our assumption is in agreement with earlier reports (Frieling et al., 2008; Heinz et al., 2001; Hahn & Blakely, 2002) which have demonstrated that the ability of a-Syn to modulate SERT and DAT functions may be of pathological significance, particularly with regard to psychiatric disorders such as depression, suicide, and impulsive violence.

It must be noted that the activities of all neurotransmitter systems may be dynamically changed as for metabolism, receptors and enzyme activities in male mice in response to chronic activation or inhibition of neurotransmitter' systems depending on social status and/or duration of repeated agonistic interactions (reviews, Avgustinovich et al., 2004; Kudryavtseva, 2006). In the context of the fundamental problem of investigating molecular regulation from behavior to gene (Kudriavtseva et al., 2004), our behavioral approach makes it possible to track changes in gene functioning during development of behavioral pathologies and to study the transcriptional state of a set of genes, which may be involved in the pathological process.

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