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Research report

Opposite effects of acute and chronic amphetamine on Nurr1 and NF-κB p65 in the rat ventral tegmental area

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ABSTRACT

Dopamine neurons are overstimulated by drugs of abuse and suffer molecular alterations that lead to addiction behavior. Nurr1 is a transcription factor crucial for dopamine neurons survival and dopamine production, activating the transcription of key genes like tyrosine hydroxylase (TH). Interestingly, nuclear factor-kappa B (NF-κB) has emerged as a new Nurr1 partner in response to inflammatory stimulus. In this study we evaluated the effects of single and repeated amphetamine administration in the expression of Nurr1 and the NF-κB p65 subunit in the rat ventral tegmental area (VTA). We found that acute amphetamine treatment increased Nurr1, p65 and TH protein levels in the VTA. On the other hand, chronic amphetamine treatment decreased Nurr1 and p65 protein levels, but TH was unchanged. Mammalian reporter assays in cell lines showed that p65 represses Nurr1 transcriptional activity in an artificial promoter driven by Nurr1 response elements and in the native rat TH promoter. These results indicate that Nurr1 and NF-κB p65 factors are involved in the adaptive response of dopamine neurons to psychostimulants and that both transcription factors could be regulating Nurr1-dependent transactivation in the VTA.

1. Introduction

Drug addiction is one of the most serious public health problems that remain unresolved (Koob et al., 2010). There are different drugs of abuse, but all have a common target pathway: the mesocorticolimbic dopamine system, whose neurons arises in the ventral tegmental area (VTA) and project to the nucleus accumbens (NAc) and the prefrontal cortex (PFC) (Di Chiara and Imperato, 1988; Pierce and Kumaresan, 2006; Lüscher and Malenka, 2011). The psychostimulants cocaine and amphetamine raise dopamine extracellular levels with the dopamine transporter (DAT) as the molecular target. Cocaine acts as a competitive inhibitor of DAT, displacing dopamine while amphetamine operates as substrate, reverting DAT flow (Sulzer, 2011).

The nuclear receptor Nurr1 is crucial for the origin and survival of midbrain dopaminergic neurons and its expression is required from embryo to adult stages (Zetterström et al., 1997; Saucedo-Cárdenas et al., 1998; Perlmann and Wallén-Mackenzie, 2004; Kadkhodaei et al., 2009). This transcription factor is an immediate early gene that regulates the expression of key dopaminergic genes like tyrosine hydroxylase (TH) (Sakurada et al., 1999; Kim et al., 2003) and DAT (Sacchetti et al., 2001).

Nurr1 is broadly expressed in TH-positive dopaminergic neurons in the midbrain (Bäckman et al., 1999). Bannon et al. (2002) demonstrated that Nurr1 mRNA levels are decreased in dopaminergic neurons of human cocaine abusers. Later, they also showed that cocaine abusers have lower levels of mRNA for Pitx3, another transcription factor associated with Nurr1 in dopaminergic specification (Bannon et al., 2004). Heroin, another highly addictive drug, also decreases Nurr1 level in the midbrain of human abusers (Horvath et al., 2007). The reduction in Nurr1 levels after repeated drug consumption has also been observed in animal models. Chronic cocaine (Leo et al., 2007) and methamphetamine (Krasnova et al., 2011) administration reduces Nurr1 levels in rat midbrain. On the other side, mice with reduced Nurr1 levels exhibit a different behavior in response to drugs of abuse. Mice with a heterozygous deletion of Nurr1 has decreased ethanol preference (Werme et al., 2003). In addition, Nurr1 heterozygous mice show increased vulnerability to neurodegeneration after long-term methamphetamine exposure (Luo et al., 2010) and altered dopamine neurotransmission after combined exposure to amphetamine and social isolation (Moore et al., 2008), indicating that Nurr1 levels in dopamine neurons may protect against the harmful effects of drugs of abuse.

Interestingly, Saijo et al. (2009) reported that Nurr1 interacts with the nuclear factor-kappa B (NF-κB) in microglia and astrocytes in response to lipopolysaccharides. NF-κB is widely known for its role in inflammation and immune responses, but in the nervous system it has

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roles in neuroprotection, learning and memory. NF-κB has been associated with neuronal survival and plasticity (Mattson, 2005; Nestler, 2012). Drugs of abuse with strong inflammatory effects as methamphetamine increase NF-κB activity in mice striatum (Asanuma and Cadet, 1998). Meanwhile, repeated cocaine administration raises NF-κB protein levels in the rat NAc (Ang et al., 2001). Imam et al. (2005) describe an increase in NF-κB protein levels in a dose-dependent manner in PC12 cells. Russo et al. (2009) found that NF-kB signaling pathway is activated in mouse NAc in response to chronic cocaine administration, controlling neuron morphology and cocaine reward.

It has remained unknown whether Nurr1 and NF-κB functionally interact in midbrain dopamine neurons during adaptive response to addictive drugs. Our main goal is to find a relationship between Nurr1 and NF-kB in dopaminergic neurons of the VTA area during acute and chronic exposure to amphetamine. Here, we report that Nurr1 and the NF-κB subunit p65 are basally expressed in dopamine neurons of VTA in adult male rats. Acute amphetamine administration increased Nurr1, p65 and TH protein levels in the VTA meanwhile repeated amphetamine treatment decreased Nurr1 and p65 protein levels, leaving TH unchanged compared to saline controls. Mammalian reporter gene assays in PC12 cells showed that p65 represses Nurr1-induced transcription in the TH promoter. Our results suggest that Nurr1 and p65 could mediate a common adaptive pathway of dopamine neurons to psychostimulants.

2. Results

2.1. Nurr1 and p65 are expressed in dopaminergic neurons of rat VTA

In our interest to learn about Nurr1 and p65 localization in the rat

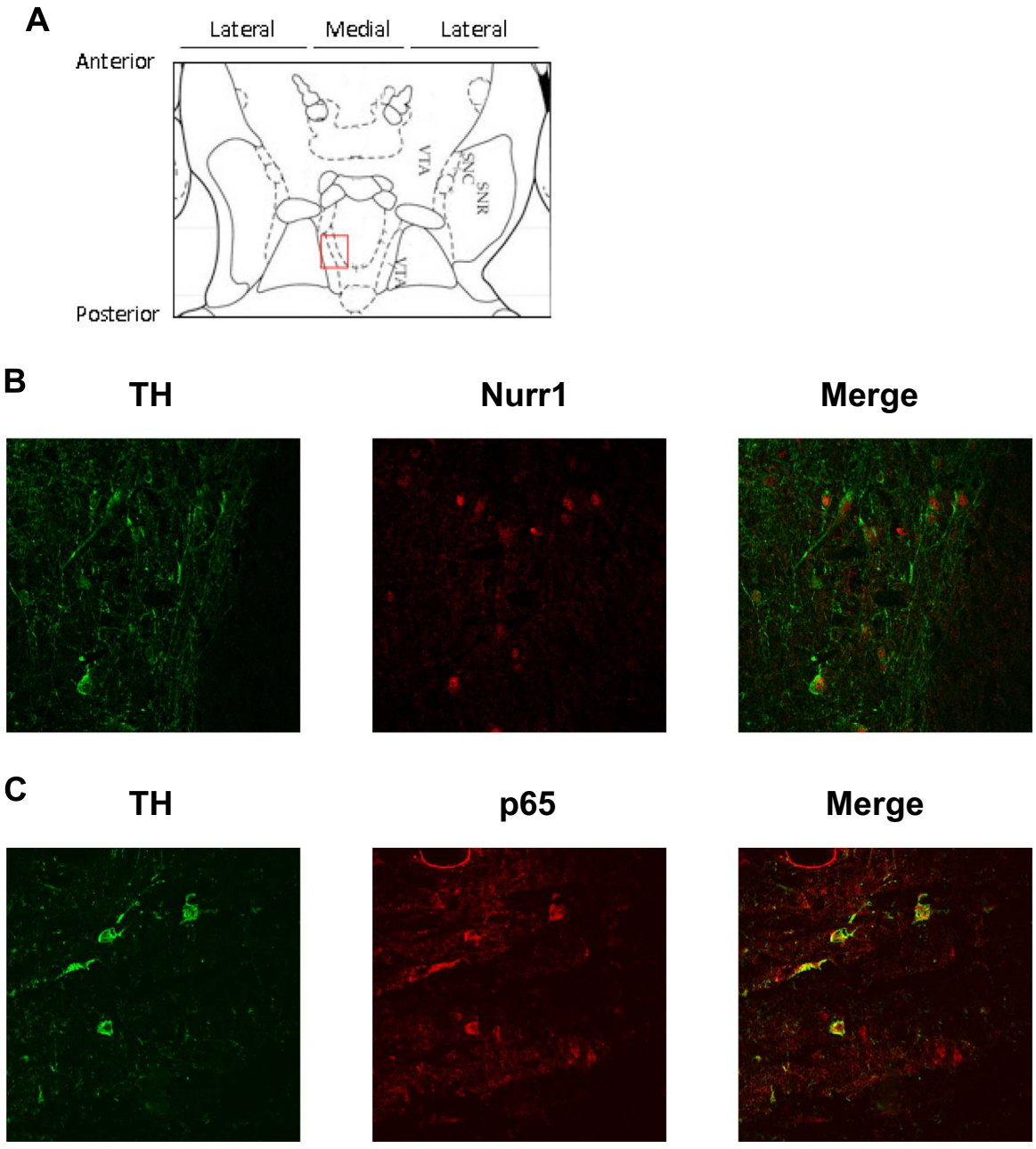

Fig. 1. Nurr1 and p65 are expressed in rat VTA TH+ cells. (**A**) Schematic diagram of VTA with the region showed in (**B**) and (**C**) (red box), adapted from the rat brain atlas (Paxinos and Watson, 2007). Adult rat brain horizontal slices were incubated with (**B**) mouse anti-TH and rabbit anti-Nurr1 or (**C**) mouse anti-TH and rabbit anti-p65 antibodies. Twenty four hours later, slices were incubated with fluorescent secondary antibodies. Labeling was visualized by indirect immunofluorescence. The images show the area in a 40× magnification.

VTA, we explored whether Nurr1 and p65 are expressed in TH+ cells by indirect immunofluorescence. As shown in Fig. 1, TH is appropriately expressed in the VTA region. Nurr1 is expressed in TH+ cells, with a nuclear localization (Fig. 1B). p65 also is expressed in TH+ cells but present preferentially a cytoplasmic localization (Fig. 1C)..

2.2. Acute amphetamine treatment upregulated VTA Nurr1 and p65 expression

Total protein extracts from VTA and NAc of rats treated with a single dose of saline or amphetamine were analyzed by western blot. According with previous reports, Nurr1 was practically undetectable in the NAc fraction (Ojeda et al., 2003). Nurr1 protein expression was significantly increased about three times in the VTA (t_6=4.380; p < 0.01) (Fig. 2A). Interestingly, p65 expression was also significantly increased (t_6=4.241; p < 0.01) (Fig. 2B). TH, the Nurr1 target gene, displayed an increase in expression of about two times (t_4=7.377; p < 0.01) (Fig. 2C). No significant change was observed in NAc p65 and TH..

2.3. Chronic amphetamine treatment downregulated VTA Nurr1 and p65 expression

Rats were injected with saline or amphetamine for 14 consecutive days. Western blots from total protein extracts of VTA show that Nurr1 expression decreased by half in the VTA (t_6=5.207; p < 0.01) (Fig. 3A).

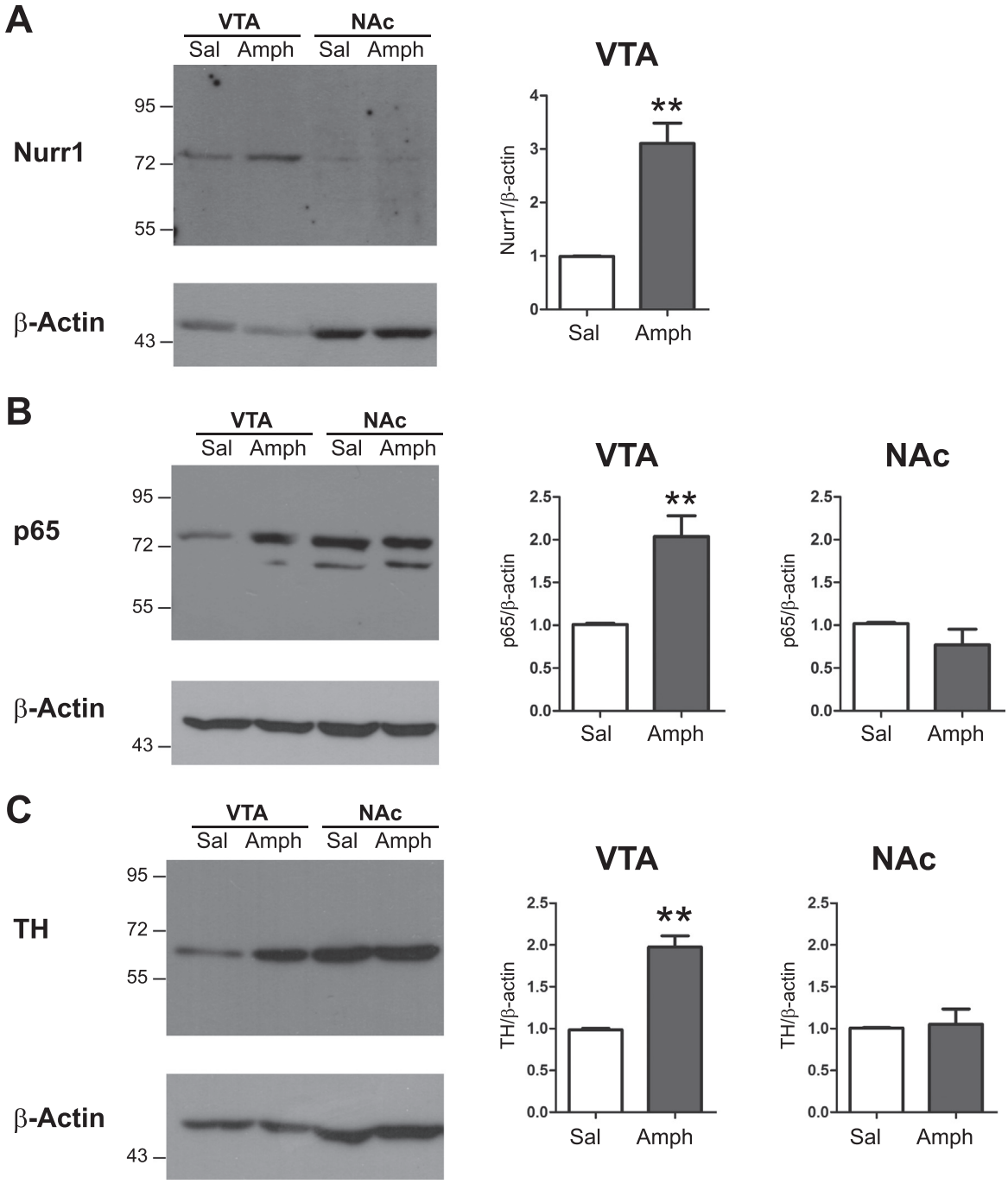

Fig. 2. Acute amphetamine treatment increases Nurr1, p65 and TH protein levels in rat VTA. Representative western blots with protein extracts from saline or acute amphetamine treated rats. (**A**) Nurr1 (**B**) p65 (**C**) TH. Quantitative densitometric analysis was made using ImageJ software. Data correspond to the mean ± S.E.M. of 3 or 4 independent experiments from three or four different set of rats. Statistical significance was estimated by the unpaired Student's t test. ** p < 0.01.

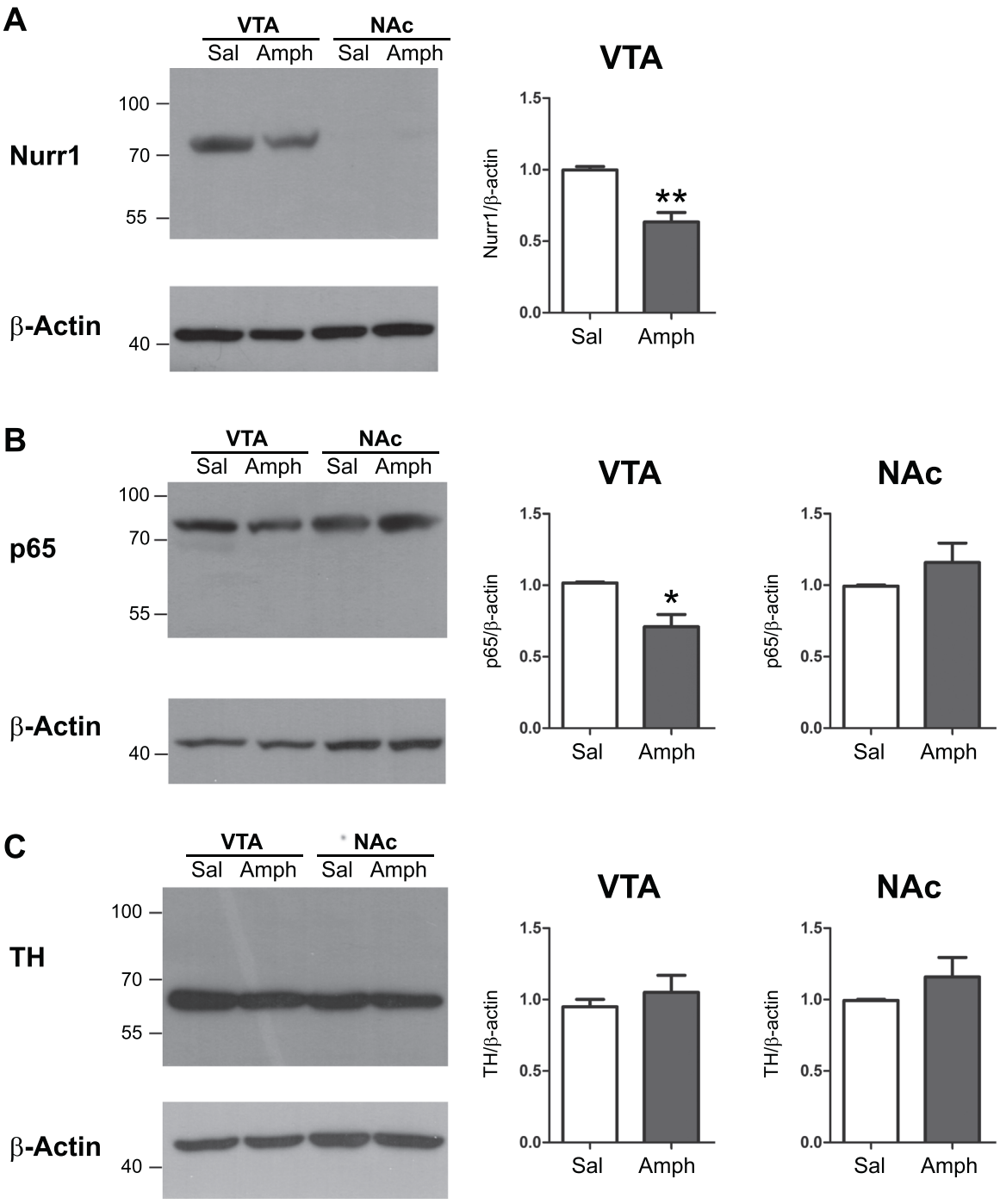

Fig. 3. Chronic amphetamine treatment decreases Nurr1 and p65 protein levels, but maintains unchanged TH protein levels in rat VTA. Representative western blots with protein extracts from saline or chronic amphetamine treated rats. (**A**) Nurr1 (**B**) p65 (**C**) TH. Quantitative densitometric analysis was made using ImageJ software. Data correspond to the mean ± S.E.M. of 4 independent experiments from four different set of rats. Statistical significance was estimated by the unpaired Student´s *t* test. * $p < 0.05$; ** $p < 0.01$.

p65 expression was also decreased by half (t_6=3.521; $p < 0.05$) (Fig. 3B). Unexpectedly, TH expression was preserved (Fig. 3C)..

2.4. p65 decreased Nurr1 transcriptional activity in mammalian cells

We observed that acute amphetamine treatment increased TH expression (Fig. 2C) and that chronic treatment did not have any significant effect in TH expression (Fig. 3C). In a mammalian reporter assay with 1.0-kb of the rat TH promoter in PC12 cells, p65 was able to repress Nurr1 transcriptional activity [F(5,23)=10.27; $p < 0.0001$] (Fig. 4A). At the same time the presence of NF-κB subunit p50 had no effect on Nurr1 transcriptional activity. p65 repression was reversed when we added the NF-κB inhibitor Iκ-Bα to the system. The same assay was performed with the NBRE-3X-Tk-Luc artificial reporter system in HEK293T cells. This artificial promoter has three Nurr1 response elements (Fig. 4B). Once more, p65 repressed Nurr1 transcriptional activity [F(5,23)=47.11; $p < 0.0001$] and this repression was annulled in the presence of Iκ-Bα..

3. Discussion

In drug addiction, the initial voluntary intake of a drug turns into a continuous involuntary consumption. Addictive drugs alter the expression of genes leading to long-term adaptations (Volkow and Morales,

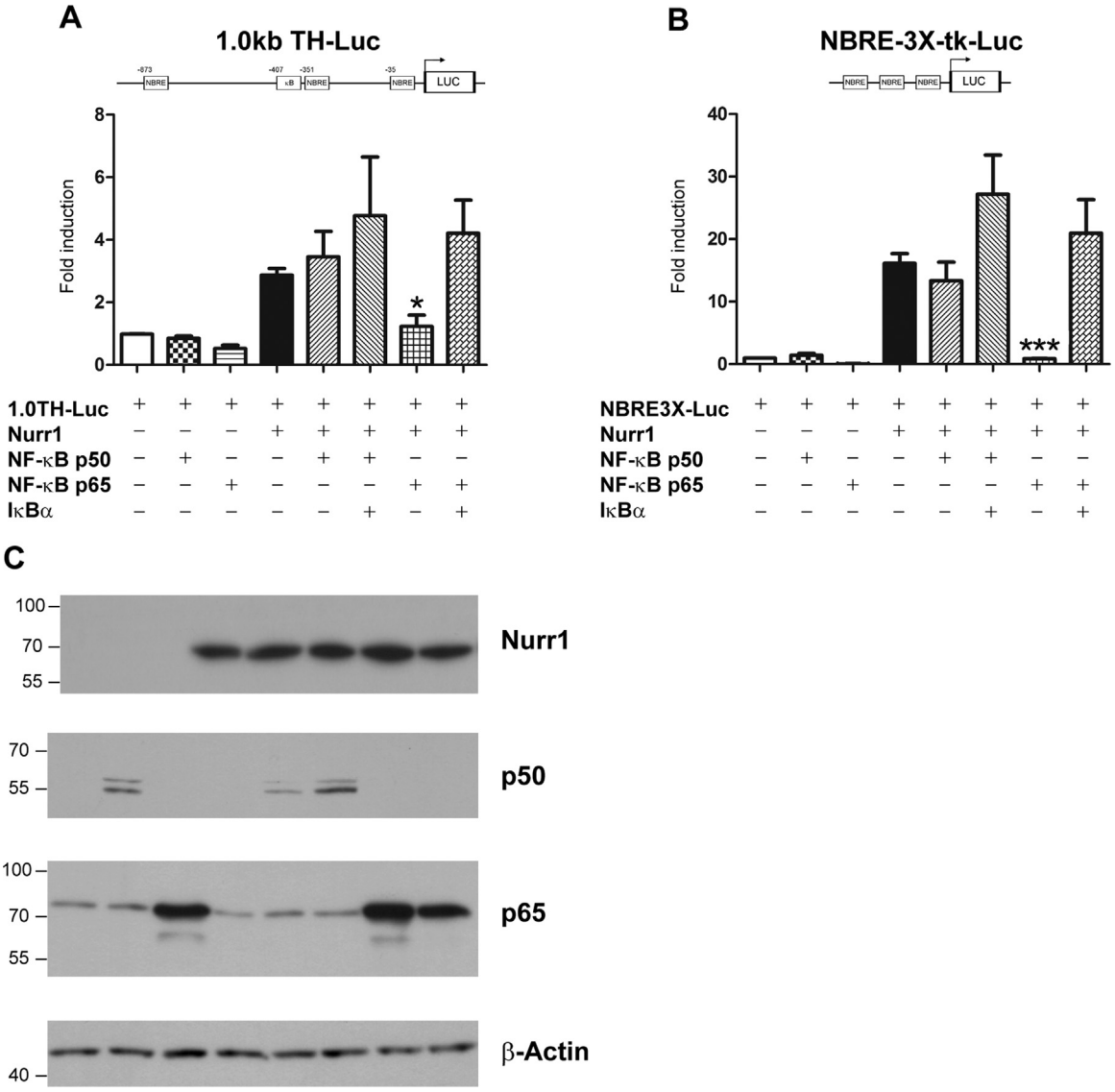

Fig. 4. p65 decreases Nurr1 transcriptional activity in a NBRE3X and a 1.0 kb TH promoter. (**A**) PC12 cells were transfected with 1.0kbTH-Luc, HA-Nurr1, p50, p65, the NF-κB inhibitor Iκ-Bα, the empty vectors and pBluescript. Error bars show the S.E.M. of 4 independent experiments performed each one in triplicate. $*p < 0.05$ (Nurr1 v/s Nurr1+p65) according with one-way analysis of variance (ANOVA), followed by Tukey´s post-test. (**B**) HEK293T cells were transfected with NBRE3X-tk-Luc, HA-Nurr1, p50, p65, Iκ-Bα, the empty vectors and pBluescript. $***p < 0.001$ (Nurr1 v/s Nurr1+p65) according with one-way analysis of variance (ANOVA), followed by Tukey´s post-test. In all cases (A) and (B), 48 h post-transfection cells were harvested and assayed for luciferase activity. Results are expressed as fold induction related to control (empty vectors). For statistical analysis Iκ-Bα columns were not considered. **(C)** Representative western blot analysis of whole extracts from mammalian reporter gene assays in A and B.

2015). Here, we report that an acute amphetamine dose increases Nurr1, p65 and TH protein levels in the rat VTA. On the other hand, chronic amphetamine treatment decreases Nurr1 and p65, but TH expression was unchanged.

It has been reported that in humans and animal models, drugs of abuse decrease Nurr1 mRNA or protein levels in the midbrain after prolonged use. Heroin and cocaine decrease Nurr1 mRNA levels in human midbrain (Horvath et al., 2007; Bannon et al., 2002, 2004). Chronic cocaine administration down-regulates Nurr1 transcript levels in rat ventral midbrain (Leo et al., 2007). Our results are in accordance with a reduction of Nurr1 levels during a continued administration of drugs. Interestingly, we found that a single dose of amphetamine increased Nurr1 and p65 protein levels. Similarly, Akiyama and cols (Akiyama et al., 2008) showed that an acute methamphetamine administration increase Nurr1 mRNA levels in the rat VTA.

p65 has recently been identified as an interacting partner for Nurr1 in an inflammatory context in astrocytes and microglia (Saijo et al., 2009; De Miranda et al., 2015). As well, the other Nur family members: Nur77 and Nor-1 have common pathways with p65 in several cell types (Hong et al., 2004; Calvayrac el al., 2015; Murphy and Crean, 2015), showing that Nur and NF-κB are closely related in different cell phenotypes. NF-κB levels are changed in response to cocaine administration in rat NAc and PC12 cells (Ang et al., 2001; Imam et al., 2005). In addition, NF-κB signaling is directly involved in mediating the appetite suppressing effect of amphetamine (Kuo et al., 2012). Our results show that Nurr1 and p65 protein levels changed in the same direction during acute or chronic amphetamine treatment, suggesting that both transcription factors may be involved in the response to amphetamine in VTA dopaminergic neurons. But, which could be the role of p65 in VTA during drug intake? Mammalian reporter gene assays suggest that p65 can potentially regulate TH gene expression. In this case, p65 is a repressor for Nurr1 transcriptional activity. *In silico* analysis of the 1.0 kb TH promoter indicates that there is one putative NF-κB site and three putative Nurr1 sites in this promoter. Nurr1 and p65 can be binding on their own response elements in the DNA or inhibiting each other in a trans-repression model. According to Saijo

et al. (2009), Nurr1 is recruited to p65 target gen promoters and downregulates p65 transcriptional activity by a trans-repression model. Our results are consistent with a p65-driven trans-repression model because in a mammalian reporter assay driven by three consecutive Nurr1 response elements, p65 also strongly repressed Nurr1 transcriptional activity. In addition, it has been reported that p65 regulates the expression of Nurr1 by directly binding to consensus binding sites in Nurr1 promoter as McEvoy et al. (2002) showed that p65 activates Nurr1 promoter in synoviocytes, in a model of Rheumatoid Arthritis. This NF-kB consensus site in the Nurr1 promoter is well conserved between human and murine. Although we observed a well-defined amphetamine effect in the VTA region, many question remains unanswered regarding other cell types and other transcription factors which may be also affected and the relationship between them to generate the final response to an acute or chronic drug administration. We must take into consideration that drug intake triggers an innate immune response with change in inflammatory mediator levels (Crews et al., 2011). Nurr1 and p65 may be responsible for this response and could be mediating interactions between dopaminergic neurons and astrocytes or another cell type in the VTA. Revealing the pathways and molecular interactions between Nurrr1 and NF-κB transcription factors should help us to understand and prevent brain disorders such as drug abuse, stress and Parkinson disease.

In summary, we show opposite effects of acute and chronic amphetamine on Nurr1 and p65 in rat VTA. We postulate p65 as a modulator of a potential common adaptive signaling pathway together with Nurr1 of dopamine neurons in response to psychostimulants.

4. Experimental procedure

4.1. Animals

Adult male Sprague-Dawley rats weighing about 220–250 g at the beginning of the experiments were used. Rats were housed in pairs and maintained in a 12 h light/dark cycle at 22–25 °C room temperature with food and water *ad libitum*. A total of 36 rats were used in all experiments. All procedures were performed in strict accordance with the guidelines and policies established in the Chilean Institutional Bioethical guide (Comisión Nacional de Investigación Científica y Tecnológica, Conicyt) and were approved by the Ethics Committee of the Faculty of Biological Sciences, Pontificia Universidad Católica de Chile and the Ethics Boards of the Science Council of Chile (FONDECYT).

4.2. Reagents

D/L-amphetamine was donated by Laboratorio Chile S.A.

4.3. Drug administration

Previous to amphetamine treatments, rats had 5 days of handling. For the acute amphetamine treatment, rats were injected with amphetamine (1.5 mg/kg, intraperitoneally, i.p.) or equal volume of saline solution. In chronic amphetamine treatments, rats were injected with amphetamine (1.5 mg/kg, i.p.) or saline solution every day during 14 days. In both, acute and chronic amphetamine treatments, rats were euthanized by decapitation with a guillotine 24 h after the last injection, and the VTA and NAc were quickly dissected. The amphetamine dose of 1.5 mg/kg was chosen according to previous studies showing appropriate behavioral sensitization (Magendzo and Bustos, 2003).

4.4. Cell culture and transfections

HEK293T cells (ATCC) were cultured in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% fetal bovine serum (FBS). PC12 cells (ATCC) were cultured in DMEM supplemented with 5% FBS and 10% horse serum. All cell lines media were additionally supplemented with 1% penicillin/streptomycin, and maintained at 37 °C and 5% CO_2. Transfections were made using Lipofectamine2000 reagent (Invitrogen).

4.5. Western blots

Protein extracts were obtained through four punches from rat VTA and NAc. The tissue was homogenized in RIPA lysis buffer (supplemented with protease inhibitors), sonicated and then centrifuged. Supernatants were collected and quantified by the Bio-Rad Protein Assay method. Proteins were separated by SDS-PAGE and Western blotting was performed using a polyclonal anti-p65 antibody (C-20, Santa Cruz) or a monoclonal anti-Nurr1 antibody (F5, Santa Cruz or 447C2a, Santa Cruz).

4.6. Immunofluorescence

Brain horizontal slices from rats transcardially fixed with 3% paraformaldehyde were permeabilized in 0,4% Triton-X-100 and incubated with rabbit anti-p65 (C-20, Santa Cruz), rabbit anti-Nurr1 (M-196, Santa Cruz) or mouse anti-TH (T1299, Sigma) antibodies. 24 h later, slices were incubated with fluorescent secondary antibodies. Immunofluorescence images were captured by indirect immunofluorescence.

4.7. Mammalian reporter gene assay

Cells were grown in 24-well plates and transfected with the reporter plasmid (1.0 TH-Luc or NBRE-3X-tk-Luc) and equivalent molar amount of expression plasmids or empty vectors. Total amount of DNA (450 ng) was kept constant by adding pBluescript SR (Stratagene). A reporter gene expressing the β-galactosidase cDNA driven by cytomegalovirus promoter was cotransfected (20 ng) in all experiments as an internal control for transfection efficiency. Cells were harvested 48 h after transfection. Luciferase activity was normalized to the activity of the internal control β-galactosidase and protein content. Each set of experiments was performed in triplicate and repeated at least four times. Luciferase assays were performed as described previously (Galleguillos et al., 2004).

4.8. Statistical Analysis

Results are expressed as mean ± S.E.M. from at least three independent assays. Quantification analyses were performed using the ImageJ software. Statistical analyses were performed by means of the unpaired Student's *t* test (for two groups analyses) or one-way analysis of variance (ANOVA) followed by Tukey's post-test (for multiple group analyses), using the GraphPad Prism v5.0 software (San Diego, CA). A value of $p < 0.05$ was considered significant.

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