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Research report

Altered regulation of Nur77 nuclear receptor gene expression in the mesocorticolimbic regions of rat brain by amphetamine sensitization

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ABSTRACT

The mechanisms underlying psychostimulant drug-induced sensitization include long-term cellular and molecular adaptations in dopaminergic circuits. Nur77, a member of the Nur family of transcription factors, is expressed in brain regions receiving dopamine inputs and plays a role in activity-induced synaptic modification. Here we evaluated changes in Nur77 mRNA levels in the medial prefrontal cortex (mPFC), dorsal striatum (Str) and nucleus accumbens (NAc) of rats receiving a repeated, sensitizing regimen of amphetamine (AMPH). Results were compared to two groups of controls – animals receiving repeated injections of saline (Rp-SAL) or with no treatment (CON). Two weeks after the last injection, the effect of an acute challenge dose of AMPH on Nur77 expression was evaluated using in-situ hybridization. Repeated AMPH treatment (Rp-AMPH) increased the levels of Nur77 mRNA in the mPFC, NAc core and shell regions. However, the effects of an acute injection of AMPH in each of the three groups of animals was distinct. Whereas an acute AMPH led to a significant increase of Nur77 in all brain regions of the CON animals, it had no significant effect in Rp-SAL animals. Interestingly, in acute AMPH-injected Rp-AMPH animals, Nur77 mRNA levels in the mPFC, Str and NAc regions were significantly lower compared to CON and Rp-SAL animals treated with acute AMPH. There was a positive correlation between AMPH - induced locomotor activity and Nur77 mRNA expression in CON animals; however, this relationship was absent in Rp-SAL and Rp-AMPH animals. The data suggest that Nur77 is a part of neuroadaptive changes caused by either mild stress of repeated injections as well as AMPH-sensitization and may play a role in abnormal behaviors induced by the drug.

1. Introduction

Repeated administration of psychostimulant drugs such as amphetamine (AMPH) and cocaine produces a long-lasting increase in the behavioral responses to the drug at subsequent exposures, a phenomenon known as behavioral sensitization (Kalivas and Stewart, 1991; Robinson and Becker, 1986). The behavioral effects of sensitization include changes in locomotor activation (Pierce and Kalivas, 1997), stereotypies (Fowler et al., 2003), drug self-administration (Alexinsky et al., 1997) and acoustic startle response (Pierce and Kalivas, 1997; Steketee, 2003; Tenn et al., 2003; Vezina, 2004). Accordingly, psychostimulant drug-sensitized animals have often been used to understand the mechanisms associated with addictive and psychosis-related behaviors (Fletcher et al., 2007; Robinson and Berridge, 2008). Changes in synaptic plasticity in dopamine (DA)-related reward circuits are believed to underlie behavioral sensitization to AMPH and other drugs of abuse (Kalivas, 2008; Luscher, 2013). Alterations within the ventral tegmental area (VTA) DA neurons have been suggested to initiate the sensitization process, whereas enhanced DA release in the nucleus accumbens (NAc) appears necessary for the expression of a sensitized response (Kalivas and Stewart, 1991). Alterations in reward and cognitive processes, as well as neural activity within the medial prefrontal cortex (mPFC) are also reported in sensitized animals (Onn and Grace, 2000; Steketee, 2003, , 2005; Vanderschuren and Kalivas, 2000). There is also evidence of long-term molecular and synaptic adaptations in these brain regions after repeated psychostimulant drug administrations. These include alterations in transcription factors, synaptic spine density, glutamatergic receptor trafficking and long-term plasticity (Ghasemzadeh et al., 2003; Li et al., 2004; Nyberg, 2014; Robinson and Kolb, 1999; Thomas et al., 2001; Wolf et al., 2004). It is believed that at least a part of the long-term effects of psychostimulant-induced sensitization is mediated by repro-

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gramming of immediate early gene (IEG) expression (Nestler, 2004; Szumlinski et al., 2006; Valjent et al., 2006).

Nur77 [also termed nerve growth factor inducible-B (NGFI-B), or nuclear receptor subfamily 4, group A, member 1 (Nr4a1)] belongs to a family of IEGs that encode three orphan nuclear receptors (Nr4a1, Nr4a2, and Nr4a3) (Hawk and Abel, 2011). Nur77 transcription is rapidly modulated by various environmental stimuli and neurotransmitters, in particular glutamate, serotonin and DA (Benito et al., 2011; Hawk and Abel, 2011; Levesque and Rouillard, 2007; Maheux et al., 2012; Volakakis et al., 2010). Nur77 plays a critical role in activity-induced synaptic modification and affects cognitive, motivational and reward processes (Bridi et al., 2016; Hawk and Abel, 2011; Werme et al., 2000a; Zetterstrom et al., 1996). Nur77 may be involved in the expression of some schizophrenia-like behaviors. Nur77 null mice show increased locomotor activity (Bourhis et al., 2009) and Nur77 mRNA levels are reported to be reduced in the PFC of schizophrenia brains as well as in an animal model of schizophrenia (Bhardwaj et al., 2003; Xing et al., 2006). In human PFC, high levels of the transcriptionally-active Nur77 correlate with measures of synaptic loss and cognitive impairment (Jeanneteau et al., 2018). Nur77 also plays a role on synaptic plasticity and learning and memory. For example, Nur77 expression is induced by learning tasks (von Hertzen and Giese, 2005), Nur77 loss-of-function causes deficits in long-term potentiation (LTP) and long-term memory (Bridi and Abel, 2013; Hawk and Abel, 2011) and pharmacological activators of Nur77 enhance LTP (Bridi et al., 2016). Consistent with the role of Nur77 in synaptic plasticity, a recent report indicates a critical role of Nur77 in regulating the density and distribution of spines and synapses in hippocampal pyramidal neurons (Chen et al., 2014).

Nur77 is closely linked to dopaminergic transmission as it is highly expressed in brain areas receiving DAergic projections such as the mPFC, striatum and NAc, and its expression is modulated by DAergic agonists and antagonists; for example, chronic administration of haloperidol, a DA D2 receptor blocker, leads to increased Nur77 mRNA expression in the striatum and NAc (Beaudry et al., 2000; Werme et al., 2000b). The expression of Nur transcription factors in motivational and reward regions of the brain is also regulated by drugs of abuse and stress through dopaminergic and non-dopaminergic mechanisms (Campos-Melo et al., 2013). Similar to other immediate early genes, acute administration of AMPH, methamphetamine, methylphenidate and cocaine to rodents increases the expression of Nur77 in the striatal and cortical regions (Backman and Morales, 2002; Bhardwaj et al., 2003; Gonzalez-Nicolini and McGinty, 2002). However, chronic administration of methamphetamine either blunts Nur77 mRNA expression in the NAc (Akiyama et al., 2008) or reduces it in the striatal tissue (McCoy et al., 2011). Since Nur77 is known to play a critical role in motor and cognitive behaviors that are reported to be perturbed in psychostimulant-sensitized animals, we evaluated the spatiotemporal expression of Nur77 mRNA in the rat brain using a model of AMPH-sensitization established in our laboratory. We compared the effect of AMPH-sensitization with two sets of controls; repeated saline-treated and untreated animals (Bhardwaj et al., 2006). Our data show that AMPH-sensitized animals have distinct mPFC, NAc shell and dorsolateral Str Nur77 mRNA responses to an acute AMPH challenge. We report that repeated AMPH administration leads to long-term changes in the modulation of Nur77 mRNA by AMPH in brain regions associated with the expression of sensitized behaviors.

2. Results

2.1. Establishment of behavioral sensitization

We employed our previously reported paradigm for the behavioral sensitization in rats (Fig. 1) (Bhardwaj et al., 2006). Adult male Sprague–Dawley rats were given repeated intermittent AMPH (1.5 mg/kg, i.p. for 5 alternate days, Rp-AMPH), saline (Rp-SAL) or no treatment (CON). After 14 days, all animals received a challenge dose of AMPH (0.5 mg/kg, i.p.) or saline. The analysis of locomotor activity during the pre-treatment phase by two-way repeated-measure ANOVA (Fig. 2A) showed a significant main effect of treatment ($F(2,45) = 52.84$, $p < 0.001$) and treatment x days interaction ($F(8,45) = 2.72$, $p = 0.007$), but no significant effect of days ($F(4,45) = 2.21$, $p = 0.07$). Tukey's post hoc analysis confirmed that Rp-AMPH animals displayed significantly higher activity compared to CON and Rp-SAL animals on all treatment days. The Rp-AMPH group displayed a significantly higher locomotor activity from pre-treatment day 3 to day 9 compared to day 1. Two-way ANOVA from the locomotor scores in the three groups after saline or acute AMPH challenge indicated a significant effect of the challenge treatment ($F_{(1,42)} = 49.41$, $p < 0.001$), pretreatment ($F_{(2,42)} = 58.46$, $p < 0.001$) and challenge x pretreatment interactions ($F_{(2,42)} = 30.82$, $p < 0.001$). Post-hoc analysis revealed that animals pre-treated with AMPH (Rp-AMPH group) displayed significantly higher locomotor activity after AMPH challenge compared to both non-treated CON ($p < 0.001$) and Rp-SAL ($p < 0.001$) animals. AMPH challenge -induced locomotor activity of the Rp-SAL-group was also significantly higher than that of controls ($p < 0.05$)

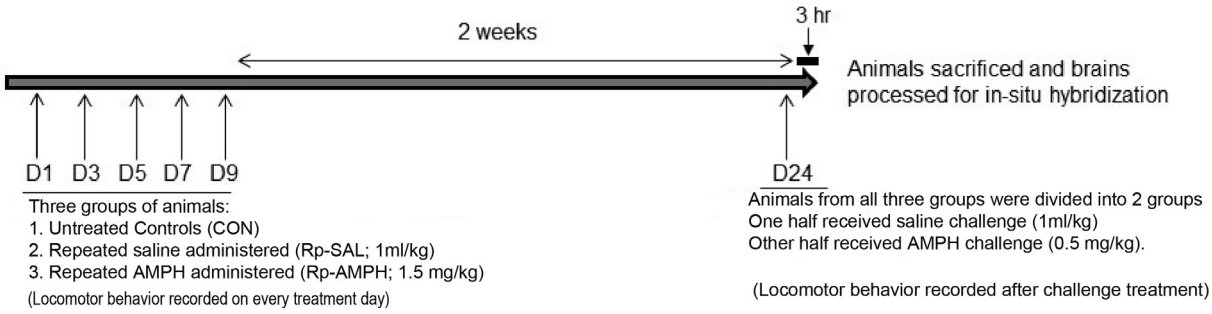

Fig. 1. Experimental design. Adult male Sprague-Dawley rats were divided into three groups (n = 16 each). The control (CON) group, animals received no treatment, the repeated saline (Rp-SAL) group received five i.p. injection of sterilized saline, once a day every alternate day and the repeated amphetamine (AMPH) sensitized (Rp-AMPH) group received five i.p. injections of d-AMPH in saline (1.5 mg/kg, i.p.) once a day every alternate day. The drug and saline treatments were given in a novel environment where their beam break activity behavior was measured for 3 h after each treatment. After the treatment regimen, the animals were left undisturbed in their home cages for a period of 2 weeks, following which animals in each group were randomly subdivided into two groups. The first subgroup of each group received a challenge of saline and the other subgroup received an acute, challenge dose of AMPH (0.5 mg/kg, i.p.) thus making a total of six group of animals. Animals' locomotor activities were recorded again for 3 h, at the end of which they were sacrificed for in-situ hybridization study.