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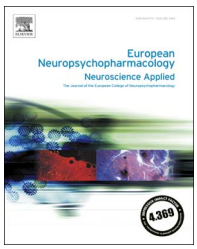

Pleiotrophin overexpression regulates amphetamine-induced reward and striatal dopaminergic denervation without changing the expression of dopamine D1 and D2 receptors: Implications for neuroinflammation

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Abstract
It was previously shown that mice with genetic deletion of the neurotrophic factor pleiotrophin (PTN-/-) show enhanced amphetamine neurotoxicity and impair extinction of amphetamine conditioned place preference (CPP), suggesting a modulatory role of PTN in amphetamine neurotoxicity and reward. We have now studied the effects of amphetamine (10 mg/kg, 4 times, every 2 h) in the striatum of mice with transgenic PTN overexpression (PTN-Tg) in the brain and in wild type (WT) mice. Amphetamine caused an enhanced loss of striatal dopaminergic terminals, together with a highly significant aggravation of amphetamine-induced increase in the number of GFAP-positive astrocytes, in the striatum of PTN-Tg mice

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compared to WT mice. Given the known contribution of D1 and D2 dopamine receptors to the neurotoxic effects of amphetamine, we also performed quantitative receptor autoradiography of both receptors in the brains of PTN-Tg and WT mice. D1 and D2 receptors binding in the striatum and other regions of interest was not altered by genotype or treatment. Finally, we found that amphetamine CPP was significantly reduced in PTN-Tg mice. The data demonstrate that PTN overexpression in the brain blocks the conditioning effects of amphetamine and enhances the characteristic striatal dopaminergic denervation caused by this drug. These results indicate for the first time deleterious effects of PTN in vivo by mechanisms that are probably independent of changes in the expression of D1 and D2 dopamine receptors. The data also suggest that PTN-induced neuroinflammation could be involved in the enhanced neurotoxic effects of amphetamine in the striatum of PTN-Tg mice.

1. Introduction

According to the European Monitoring Centre for Drugs and Drug Addiction, it is estimated that more than 2% of young people (15–34) used amphetamines in 2010 in different European countries including Czech Republic (3.2%), Denmark (3.1%), and the United Kingdom (2.3%). Ever in lifetime use of amphetamines among young people in those countries varies considerably, with levels of 30–70%. Despite widespread use of amphetamine-type stimulants, the long-term medical consequences of these drugs abuse and dependence have not been addressed until recently. During the past two decades, preclinical studies have demonstrated that this type of psychostimulants damages dopaminergic neurons, causing striatal dopaminergic denervation and dopaminergic cell death in the substantia nigra among other effects (Moratalla et al., 2015). However, clinical correlation was not studied until Callaghan et al. (2012) probed a ~77% increased risk of Parkinson's disease (PD) in amphetamine-type drug abusers (Callaghan et al., 2012). Similarly, a recent report indicates a 3-fold increased risk of PD in these drugs users (Curtin et al., 2015). Existence of genetic factors underlying individual vulnerability to the rewarding effects of amphetamine and dopaminergic neurotoxicity after consumption of this type of psychostimulants is known. Uncovering those genetic factors is not only clinically relevant but will also help to develop new therapeutic strategies for substance use disorders.

Pleiotrophin (PTN) is a neurotrophic factor known to play a role in amphetamine-induced neurotoxicity (Alguacil and Herradon, 2015). A single amphetamine administration causes a significant upregulation of PTN mRNA levels in the rat brain (Le Greves, 2005) suggesting that PTN takes part in a modulatory mechanism against the effects of amphetamine in the brain. Accordingly, extinction of amphetamine-induced conditioned place preference (CPP) is impaired in PTN genetically deficient (PTN-/-) mice (Gramage et al., 2010a). Furthermore, a periadolescent amphetamine treatment was found to produce transient cognitive deficits only in PTN-/- mice, not in wild type (WT) mice (Gramage et al., 2013a). Interestingly, amphetamine-induced neurotoxic effects in the nigrostriatal pathway are enhanced in PTN-/- mice compared to WT mice (Gramage et al., 2010b; Soto-Montenegro et al., 2015). Also, it has to be noted that amphetamine-induced increase of GFAP-positive astrocytes, a hallmark of the neuroinflammation induced by this type of psychostimulants, was slightly increased in the striatum of PTN-/- mice (Gramage et al., 2010a). Overall, the data clearly suggest a modulatory role of PTN on amphetamine effects (Herradon and Perez-Garcia, 2014). However, the knockout mouse models, although invaluable as screening tools in research, have intrinsic limitations including ubiquitous absence of the targeted gene and possible developmentally-related mechanisms of compensation. To overcome these limitations, we have now studied the rewarding and neurotoxic effects of amphetamine in mice with transgenic neuronal PTN overexpression in the brain (PTN-Tg mice). In addition, it is interesting to note that overstimulation of dopamine D1 (D1R) and D2 receptors (D2R) significantly contributes to the neurotoxic effects of amphetamine (Moratalla et al., 2015). Furthermore, dopamine is a crucial transmitter in the neuroimmune network (Kustrimovic et al., 2014) and D2R is identified as an important component controlling innate immunity and inflammatory response in central nervous system (Shao et al., 2013). To test the possibility that differences in these receptors could underlie the different genotypic susceptibility to the neurotoxic and neuroinflammatory effects of amphetamine, we carried out quantitative receptor autoradiography of D1, D2 receptors in the brains of PTN-Tg and WT mice.

2. Experimental procedures

2.1. Animals

PTN-Tg mice on a C57BL/6 J background were generated by pronuclear injection as recently described (Ferrer-Alcón et al., 2012; Vicente-Rodriguez et al., 2014a). The acceptor vector used was pTSC-a2 and contained the regulatory regions responsible for tissue specific expression of Thy-1 gene, which drives neuron-specific expression of transgenes (Aigner et al., 1995; Caroni, 1997). PTN specific overexpression in different brain areas, including a 20% increase of PTN protein levels in striatum, was established by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR), in situ hybridization, and by Western blot (Ferrer-Alcón et al., 2012; Vicente-Rodriguez et al., 2015, 2014b). Relevant to the behavioral study presented here, there were no differences in motor activity and exploration between both genotypes at baseline (Ferrer-Alcón et al., 2012).

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