European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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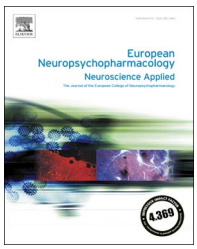

Nicotine and caffeine modulate haloperidol-induced changes in postsynaptic density transcripts expression: Translational insights in psychosis therapy and treatment resistance

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Received 4 May 2017; received in revised form 30 October 2017; accepted 26 January 2018

KEYWORDS
Schizophrenia;
Homer1;
Arc;
Haloperidol;
Gene expression;
PSD proteins

Abstract
Caffeine and nicotine are widely used by schizophrenia patients and may worsen psychosis and affect antipsychotic therapies. However, they have also been accounted as augmentation strategies in treatment-resistant schizophrenia. Despite both substances are known to modulate dopamine and glutamate transmission, little is known about the molecular changes induced by these compounds in association to antipsychotics, mostly at the level of the postsynaptic density (PSD), a site of dopamine-glutamate interplay. Here we investigated whether caffeine and nicotine, alone or combined with haloperidol, elicited significant changes in the levels of both transcripts and proteins of the PSD members Homer1 and Arc, which have been implicated in synaptic plasticity, schizophrenia pathophysiology, and antipsychotics molecular action. *Homer1a* mRNA expression was significantly reduced by caffeine and nicotine, alone or combined with haloperidol, compared to haloperidol. Haloperidol induced significantly higher *Arc* mRNA levels than both caffeine and caffeine plus haloperidol in the striatum. *Arc* mRNA expression was significantly higher by nicotine plus haloperidol vs. haloperidol in the cortex, while in striatum gene expression by nicotine was significantly lower than that by both haloperidol and nicotine plus haloperidol. Both Homer1a and Arc protein levels were significantly increased by caffeine, nicotine, and nicotine plus haloperidol. *Homer1b* mRNA expression was significantly increased by nicotine and nicotine plus haloperidol, while protein levels were unaffected. Locomotor activity was not significantly affected by caffeine, while it was reduced by nicotine. These data indicate that both caffeine and nicotine

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https://doi.org/10.1016/j.euroneuro.2018.01.006

Please cite this article as: de Bartolomeis, A., et al., Nicotine and caffeine modulate haloperidol-induced changes in postsynaptic density transcripts.... European Neuropsychopharmacology (2018), https://doi.org/10.1016/j.euroneuro.2018.01.006

trigger relevant molecular changes in PSD sites when given in association with haloperidol.

1. Introduction

Schizophrenia has been conceptualized as a disorder of synaptic plasticity and of aberrant dopamine- glutamate neurotransmission (Howes et al., 2015; Iasevoli et al., 2014). Recent evidence has pointed to the postsynaptic density (PSD) as a major synaptic structure associated to schizophrenia (Focking et al., 2015; Network and Pathway Analysis Subgroup of Psychiatric Genomics, 2015), and as a target of acute and chronic antipsychotic treatment (Buonaguro et al., 2017a; de Bartolomeis et al., 2014b). In clinical practice, however, antipsychotic therapy may be complicated by the exposure to unnecessary and potentially addictive substances, e.g. caffeine and nicotine, which are among the most used ones by schizophrenia patients (Thoma and Daum, 2013). Despite the relevance of the issue and the potential interest for the influence on treatment response, no information is available to date on the concomitant effect of antipsychotics and nicotine or caffeine on PSD.

The PSD is a specialized ultrastructure at glutamatergic synapse where dopamine and glutamate transduction pathways have been described to interact (see: Tomasetti et al., 2017), and that acts as a molecular switchboard for multiple intracellular signaling pathways (de Bartolomeis et al., 2014a; de Bartolomeis et al., 2014b; Iasevoli et al., 2014). Among PSD elements, Homer1 proteins have been implicated in preclinical models of schizophrenia (Iasevoli et al., 2014; Powell et al., 2009) and demonstrated to play a potential role in antipsychotic-induced synaptic changes (de Bartolomeis et al., 2015b), since they participate in dendritic spines architecture dynamics and axon pathfinding (Foa et al., 2001; Frese et al., 2017). Homer proteins belong to a scaffolding and adaptor proteins family involved in mGluR5 signaling pathway, and they contribute to dopamine-glutamate interplay. The dominant negative truncated Homer1a isoform is induced in an immediate-early gene fashion by different behavioral and pharmacological manipulations, including dopamine D2 receptor (D2R) blocking agents, such as antipsychotics (Buonaguro et al., 2017a; de Bartolomeis et al., 2016). Another relevant effector of dopamine-glutamate interplay within PSD is the activity-regulated cytoskeleton-associated protein (Arc), which is a highly expressed dendritic protein involved in synaptic plasticity (Shepherd and Bear, 2011), implicated in schizophrenia pathophysiology (Manago et al., 2016), and demonstrated to be responsive to antipsychotic administration (Buonaguro et al., 2017b). Homer1 and Arc appear relevant candidates to study molecular modifications of the dopamine-glutamate interplay and synaptic changes in the context of antipsychotic treatments as well as in paradigms recapitulating real-world conditions, i.e. concomitant exposure to drugs putatively interfering on antipsychotic action, such as caffeine and nicotine.

The abuse of coffee drinking and tobacco smoking is a common addictive conduct in schizophrenia patients, above all those taking antipsychotics (Thoma and Daum, 2013). Besides their addictive potential, both caffeine and nicotine may be used by schizophrenia patients to alleviate antipsychotics side effects and/or psychotic symptoms (Acuna-Lizama et al., 2013; Featherstone and Siegel, 2015; Iasevoli et al., 2013; Misiak et al., 2015; Varty et al., 2008). Notably, nicotine and caffeine have been included among possible therapeutic strategies for Parkinson's disease (PD) and may counteract the PD-like extrapyramidal side effects of antipsychotics (Oertel and Schulz, 2016). Moreover, both adenosine receptors (which are directly modulated by caffeine) and nicotine receptors have been suggested as potential targets of pharmacological strategies to address residual symptoms not responding or responding poorly to conventional antipsychotics (Marcus et al., 2016; Rial et al., 2014). Despite this body of evidence, however, little is known about the molecular changes induced in synaptic sites by these compounds when given in association to antipsychotics.

Caffeine pharmacological effects are mainly mediated by its antagonist action at adenosine A1 (A1R) and A2A (A2AR) receptors (Chen et al., 2001). A2ARs are the most diffused subtypes in striatum, where they form heteromers with postsynaptic D2Rs (Ferre, 2016). Adenosine has been found to decrease D2R-mediated neurotransmission and A2AR agonists may decrease D2R binding (Ferre, 2010). As an A2AR antagonist, caffeine is considered to enhance D2R-mediated neurotransmission (De Luca et al., 2007), which may counteract antipsychotic action.

Nicotine acts as an agonist at nicotinic acetylcholine receptors (nAChRs), which are sparsely located among midbrain, striatum, and cerebral cortex. Nicotine has been described to increase dopamine neurons firing by its agonist action on distinct nAChRs subtypes located on midbrain dopamine and GABAergic neurons (Dani and Bertrand, 2007; Pidoplichko et al., 1997).

Here, we evaluated whether and to what extent molecular (i.e. PSD gene expression and protein levels) and behavioral (i.e. open field locomotor activity) phenotypes were affected by acute systemic administration of caffeine or nicotine, alone or in association with the prototype antipsychotic haloperidol or the indirect dopamine agonist GBR-12909.

2. Experimental procedures

2.1. Animals

Male Sprague-Dawley rats (mean weight 250 g) were obtained from Charles-River Labs (Lecco, Italy), housed and let to adapt to human handling in a temperature and humidity controlled colony room with 12/12 h light-dark cycle with ad libitum access to laboratory

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