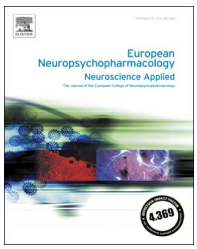
European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro



Effects of amphetamine on pro-social ultrasonic communication in juvenile rats: Implications for mania models

K.-Alexander Engelhardt[a], Eberhard Fuchs[b], Rainer K.W. Schwarting[a], Markus Wöhr[a,*]

[a]*Behavioral Neuroscience, Experimental and Biological Psychology Philipps-University of Marburg, Gutenbergstr. 18, D-35032 Marburg, Germany*
[b]*German Primate Center, Leibniz Institute for Primate Research, Kellnerweg 4, D-37077 Göttingen, Germany*

Received 8 November 2016; received in revised form 8 December 2016; accepted 5 January 2017

KEYWORDS
Ultrasonic vocalizations;
Acoustic communication;
Social behavior;
Playback;
Dopamine;
Bipolar disorder

Abstract
Communication is the act of information transfer between sender and receiver. In rats, vocal communication can be studied through ultrasonic vocalizations (USV). 50-kHz USV occur in appetitive situations, most notably juvenile play, likely expressing the sender's positive affective state. Such appetitive 50-kHz USV serve important pro-social communicative functions and elicit social exploratory and approach behavior in the receiver. Emission of 50-kHz USV can be induced pharmacologically by the administration of psychostimulant drugs, such as amphetamine. However, it is unknown whether amphetamine affects the pro-social communicative function of 50-kHz USV in the receiver. We therefore assessed dose-response effects of amphetamine (0.0 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 2.5 mg/kg, 5.0 mg/kg) on pro-social ultrasonic communication on both, sender and receiver, in juvenile rats. We found an inverted U-shaped effect of amphetamine on 50-kHz USV emission, with 50-kHz USV levels being strongly enhanced by moderate doses, yet less prominent effects were seen following the highest dose. Likewise, amphetamine exerted inverted U-shaped effects on social exploratory and approach behavior induced by playback of appetitive 50-kHz USV. Social approach was enhanced by moderate amphetamine doses, but completely abolished following the highest dose. Amphetamine further dose-dependently promoted the emission of 50-kHz USV following playback of appetitive 50-kHz USV, indicating more vigorous attempts to establish social proximity. Our results support an important role of dopamine in closing a perception-and-action-loop through linking mechanisms relevant for detection and production of social vocalizations. Moreover, our approach possibly provides a new

*Corresponding author. Fax: +6421 28 23610.
E-mail address: markus.woehr@staff.uni-marburg.de (M. Wöhr).

http://dx.doi.org/10.1016/j.euroneuro.2017.01.003

means to study mania-like aberrant social interaction and communication in animal models for bipolar disorder.

1. Introduction

Communication is the act of information transfer between sender and receiver. It constitutes an important component of the mammalian social behavioral repertoire by coordinating social interactions. In rats, vocal communication can be studied through ultrasonic vocalizations (USV), which serve as situation-dependent socio-affective signals (Brudzynski, 2013; Wöhr and Schwarting, 2013). Juvenile and adult rats emit two major call types. In aversive situations, such as predator exposure, 22-kHz USV occur, probably expressing a distressed state and serving an alarming communicative function through eliciting defensive behavior in receivers. In appetitive situations, 50-kHz USV occur, most notably during juvenile play (Burgdorf et al., 2008; Knutson et al., 1998), where they likely express the sender's positive affective state ("rat laughter"; Panksepp, 2005) and maintain playful contact between conspecifics (Kisko et al., 2015a, b).

The emission of appetitive 50-kHz USV can be induced pharmacologically by the administration of various compounds, most notably psychostimulant drugs, such as amphetamine (Ahrens et al., 2009; Brudzynski et al., 2012; Natusch and Schwarting, 2010; Simola and Morelli, 2015; Taracha et al., 2012, 2014). Amphetamine leads to a massive increase in extracellular dopamine and noradrenaline through its direct interaction with monoamine transporters (Hutson et al., 2014), and several studies indicate that 50-kHz USV emission is critically dependent on dopamine signaling in mesolimbic reward pathways, such as the nucleus accumbens (Nacc; Brudzynski et al., 2011; Burgdorf et al., 2000, 2001, 2007; Thompson et al., 2006; Scardochio et al., 2015). Besides increased 50-kHz USV rates, the euphorigenic properties of amphetamine are probably best reflected by shifts in the call profile towards a larger proportion of frequency-modulated (FM) calls, particularly the trill subtype, under acute testing conditions (Pereira et al., 2014; Simola et al., 2010, 2012, 2014; Wöhr et al., 2015; Wright et al., 2010, 2012, 2013). The trill subtype is most closely associated with positive affect (Burgdorf et al., 2011). Importantly, amphetamine exposure is an established model of mania (Van Eukhuizen et al., 2015). In line with this, we found that amphetamine effects on 50-kHz USV can be reversed by antimanic drugs, such as the "mood stabilizer" lithium used for the treatment of bipolar disorder, suggesting that amphetamine-induced 50-kHz USV can serve as a translational marker for euphoria-like positive affect in animal models of mania (Pereira et al., 2014; Wendler et al., 2016).

By means of playback studies, we demonstrated that appetitive 50-kHz USV serve important pro-social communicative functions and induce social exploratory and approach behavior in receivers, likely by eliciting the anticipation of rewarding social contact (Brenes et al., 2016; Seffer et al., 2015; Wöhr and Schwarting, 2007, 2009, 2012). Social approach is particularly prominent in juvenile rats (Wöhr and Schwarting, 2007), which are characterized by high levels of social motivation (Douglas et al., 2004), suggesting that it can be used as a behavioral readout for the incentive salience of social contact. We further showed that playback of appetitive 50-kHz USV evokes phasic Nacc dopamine release (Willuhn et al., 2014), indicating that dopamine serves as a neurochemical nexus linking mechanisms relevant for detection and production of pro-social ultrasonic communication. However, this notion is challenged by studies showing that amphetamine disrupts social interaction in rats (Campbell and Randall, 1977; Achterberg et al., 2014; Manduca et al., 2014; Sams-Dodd, 1995). Such findings raise the question as to whether amphetamine-induced 50-kHz USV only reflect vocal outbursts of positive affect dissociated from any communicative function. It is currently unknown whether amphetamine affects the pro-social communicative function of appetitive 50-kHz USV in receivers.

In the present study, we therefore assessed dose-response effects of amphetamine on both, detection and production of appetitive 50-kHz USV, in juvenile rats. We used juvenile rats since the suppressing effects of amphetamine on social interaction have most consistently been reported for juvenile play behavior (Trezza et al., 2010), while amphetamine-induced 50-kHz USV have only been systematically assessed in adult rats (Rippberger et al., 2015), despite the abundant occurrence and important role of appetitive 50-kHz USV during juvenile play (Burgdorf et al., 2008; Kisko et al., 2015a, b; Knutson et al., 1998). The emission of amphetamine-induced 50-kHz USV by the sender was assessed in an open field, with behavioral hyperactivity serving as positive control for amphetamine effects. To probe the effects of amphetamine on the pro-social communicative function of 50-kHz USV in receivers, we exposed rats to playback of appetitive 50-kHz USV and assessed social exploratory and approach behavior using our established radial maze playback paradigm (Seffer et al., 2014). Because disturbances in social interaction and communication reflect core symptoms of mania (American Psychiatric Association, 2013), our experimental approach may provide important insights into neurochemical mechanisms of socio-affective communication and information processing, with possible implications for animal models of mania.

2. Experimental procedures

2.1. Animals

Drug-naïve juvenile male Wistar rats (Harlan Laboratories, The Netherlands) were housed in groups of 4–6 in Macrolon Type IV cages (L × W × H: 55 × 33 × 20 cm) under controlled laboratory conditions

Please cite this article as: Engelhardt, K.-A., et al., Effects of amphetamine on pro-social ultrasonic communication in juvenile rats: Implications for mania models. European Neuropsychopharmacology (2017), http://dx.doi.org/10.1016/j.euroneuro.2017.01.003