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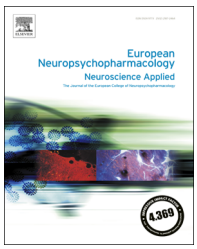

Chronic variable stress prevents amphetamine-elicited 50-kHz calls in rats with low positive affectivity

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Abstract
The relationship between stress response and positive affective states is thought to be bidirectional: whilst stress can lead to a blunted hedonic response, positive affect reduces the negative effects of stress. We have previously shown that persistently high positive affectivity as measured by 50-kHz ultrasonic vocalizations (USVs) is protective against chronic variable stress (CVS). The present study examined the effect of CVS on 50-kHz USVs elicited by amphetamine administration, simultaneously considering the stable inter-individual differences in positive affectivity. Forty juvenile male Wistar rats were categorised as of high (HC) or low (LC) positive affectivity based on their 50-kHz USV response to imitation of rough-and-tumble play ('tickling'). As adults, the rats were subjected to four weeks of CVS, after which D-amphetamine was administered in five daily doses followed by a challenge dose (all 1 mg/kg IP) nine days later. CVS reduced sucrose preference in LC-rats only. After CVS, amphetamine-elicited 50-kHz USVs were significantly reduced in LC-rats, the effect of stress in HC-rats being smaller and less consistent. In previously stressed and amphetamine-treated LC-rats, locomotor response to amphetamine was attenuated. In stressed LC-rats, DOPAC levels and dopamine turnover were increased in striatum after amphetamine treatment, and dopamine D_1 receptor levels were upregulated in nucleus accumbens. LC-rats had lower isoleucine levels in frontal cortex. These results show that stress-related changes in response to amphetamine are

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dependent on inter-individual differences in positive affectivity both at neurochemical and behavioural levels, and further support the notion of higher vulnerability of animals with low positive affect.

1. Introduction

Positive affectivity has a protective effect against the consequences of adverse life events in humans (for a review, see Lyubomirsky et al., 2005). Also in animal models, experimentally induced positive emotional states can protect against the negative effects of stress (Wöhr et al., 2009; Rygula et al., 2012; Yamamuro et al., 2010; Hori et al., 2013). In turn, stress can modify the response to positive hedonic stimuli by reducing their value (Moreau et al., 1992; Papp et al., 1993; Popik et al., 2012; Shimamoto et al., 2011). Anhedonia and deficiencies in motivational processes are the core clinical symptoms of major depression. In parallel to humans, chronic mild/variable stress causes anhedonia-like behaviour in animals, usually measured as a reduction in sucrose preference or food consumption, an effect that can be reversed by antidepressants (for review, see Hill et al. (2012)).

Rats communicate by means of ultrasonic vocalizations (USVs). Long 22-kHz USVs are emitted when subjected to aversive conditions, such as predatory exposure, social defeat in inter-male fighting, negative drug experience and initial handling (Blanchard et al., 1991; Brudzynski and Ociepa, 1992; Burgdorf et al., 2001; Kroes et al., 2007), but 50-kHz USVs, sometimes referred to as chirps, are mostly produced in rewarding situations, such as rough-and-tumble play, electrical brain stimulation of areas that can sustain self-stimulatory behaviour, access to psychostimulant drugs, and in imitated rough-and-tumble play (tickling) (Burgdorf et al., 2007, 2008; Panksepp and Burgdorf, 2000). Furthermore, 50-kHz USVs are emitted in situations that elicit a state of reward expectancy (seeking), such as access to an environment paired with a positive previous affective experience (Brenes and Schwarting, 2015; Maier et al., 2010; Simola et al., 2014). At least 14 subtypes of 50-kHz USVs have been described, of which 12 display frequency modulation (FM) (Wright et al., 2010). In contrast to 22-kHz USVs, 50-kHz vocalization is reduced by aversive stimuli (Burgdorf et al., 2001, 2008; Mällo et al., 2009; Popik et al., 2012, 2014).

Several laboratories including ours have shown that rats exhibit stable inter-individual differences in the level of 50-kHz USVs during hedonic situations, such as rough and tumble play imitation by an experimenter (Mällo et al., 2007) and amphetamine administration (Taracha et al., 2012). The trait-like nature of the 50-kHz vocalization level is also corroborated by the finding that rats can be bred for high and low levels of 50-kHz USVs (Harmon et al., 2008). High 50-kHz USV/chirping/calling (HC) and low 50-kHz USV (LC) rats display some differences in behavioural tests used in anxiety and depression studies (Mällo et al., 2007), and male LC-rats are more sensitive to chronic variable stress (CVS) as reflected in behaviour, neurochemical changes, and corticosterone response (Mällo et al., 2009; Raudkivi et al., 2012).

The brain systems relating to 22-kHz and 50-kHz vocalizations are different (for review, see Brudzynski, 2013). Vocalization at 22-kHz is dependent on signalling in the laterodorsal tegmental cholinergic projections (Brudzynski et al., 2011), while 50-kHz USVs are strongly related to mesolimbic dopaminergic circuit activity that comprises axon projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), which also intervene the lateral part of the hypothalamus (Burgdorf et al., 2007). Psychostimulant drugs such as cocaine and amphetamine administered either centrally or peripherally activate mesolimbic dopaminergic neurotransmission and concurrently increase 50-kHz USVs (Ahrens et al., 2009; Burgdorf et al., 2007; Mu et al., 2009; Simola et al., 2012).

The effect of amphetamine to induce 50-kHz USVs is dependent on dopamine D_1 and D_2 receptor (Wright et al., 2013), α- and β-adrenoceptor (Wright et al., 2012), serotonin 5-HT_{2C} receptor (Wöhr et al., 2014) and NMDA (Costa et al., 2015) receptor function. Changes in the mesolimbic reward circuit have been shown to underlie the behavioural effects of chronic psychostimulant treatment, including sensitization and tolerance (Robinson and Kolb, 2004). Repeated treatment with amphetamine (Ahrens et al., 2009; Simola and Morelli, 2015) or cocaine (Mu et al., 2009) can induce sensitization - augmentation of drug effects with repeated dosing on 50-kHz USVs (however, see also Simola et al. (2014) and Taracha et al. (2012)). On the other hand, stress can augment the response to psychostimulant drugs (Antelman et al., 1980; de Jong et al., 2005; Haile et al., 2001) and *vice versa* (Antelman et al., 1980; Barr, 2002) - an effect termed cross-sensitization. Various stressors impact on the mesolimbic reward circuit at neurochemical (for review, see Nestler and Carlezon, 2006; Shirayama and Chaki, 2006) and neuromorphological level (Bessa et al., 2013), and some of these effects of stress are reversible by antidepressants (Bessa et al., 2013).

To our knowledge, none of the previous works that have used repeated psychostimulant treatment in chronic stress regimen have made use of USV measurement. Neither the stable inter-individual differences in positive affectivity have been taken into account in stress research that examines cross-senitization with stimulant drugs. The present investigation aims to test the effects of CVS on the vocalization response elicited by repeated amphetamine treatment in rats with high *vs.* low positive affectivity. We also probed some candidate neurochemical mechanisms to shed light on the underlying neurobiological mechanisms.