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Dopaminergic transmission in the midbrain ventral tegmental area in the induction of hippocampal theta rhythm

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ABSTRACT

Hippocampal rhythmic slow activity (RSA, theta) is regulated by many brainstem structures, including the midbrain ventral tegmental area (VTA). This work aimed at assessing the role of the dopaminergic (DA) transmission of the VTA in this regulation. Male Wistar rats ($n=35$) in urethane anaesthesia received an intra-VTA microinjection of either flupenthixol (FLU; doses of 5.0, 2.5, 1.25 and 0.625 μg) or amphetamine (AMPH; 2.5 and 5.0 μg) following control solvent microinjection. Peak power (P_{max}) and corresponding peak frequency (F_{max}) for delta and theta bands were extracted from EEG recording. Flupenthixol at a dose of 1.25 μg evoked long-lasting theta, continuing for 32.0 min on average, with a mean latency of 7.1 min. Other doses of FLU caused an increase of P_{max} theta and reduction of P_{max} delta without generating visually recognizable, regular theta rhythm. 5 μg of AMPH evoked theta continuing for 24.4 min on average, with a mean latency of 9.7 min. The lower dose was much less effective, with its outcome resembling the one after the less active FLU doses. During pharmacologically induced theta rhythm, both after FLU and AMPH, brief episodes of asynchronous activity appeared periodically, and they were more frequent and longer in AMPH groups. AMPH may act locally on multiple sites, inhibiting DA cells in somatodendritic region but also increasing dopamine release in target structures, and this, depending on AMPH dose, can lead to induction of theta rhythm. Locally administered DA antagonist on the other hand, when used at a proper dose, can produce theta most likely by the mechanism of inhibiting autoreceptors.

1. Background

Rhythmic slow activity (RSA), also called theta rhythm, is a high voltage and low frequency (3–12 Hz) electrical activity of the hippocampus and it constitutes the most regular EEG signal in the mammalian brain, especially in rodents. Its appearance is associated with voluntary locomotor activities (Oddie and Bland, 1998; Vanderwolf, 1969), as well as episodes of REM sleep (Kemp and Kaada, 1975; Montgomery et al., 2008; Whishaw and Vanderwolf, 1973). Theta rhythm has long been

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an object of investigations, particularly because of reports indicating presence of episodes of this rhythm in humans during cognitive and memory processes (Aguirre et al., 1996; Fell et al., 2011; Kaplan et al., 2012; Lega et al., 2012; Meador et al., 1991; Nyhus and Curran, 2010; O'Keefe and Burgess, 1999; Sammer et al., 2007; Sauseng et al., 2010) and also due to data showing the key role of theta waves in the formation of memory traces through the phenomenon of long-term potentiation of synaptic transmission (LTP) (Abel and Kandel, 1998; Bliss and Collingridge, 1993; Lynch, 2004; Stevens, 1998). It is commonly believed that the theta rhythm plays a special role in the mechanisms of spatial orientation (O'Keefe and Recce, 1993; Skaggs and McNaughton, 1996), spatial learning and navigation (Caplan et al., 2001, 2003; Cornwell et al., 2008, 2012; Ekstrom et al., 2005; Kober and Neuper, 2011; Olvera-Cortés et al., 2012; Watrous et al., 2011; White et al., 2012), verbal and spatial working memory (Hsieh et al., 2011; Masuoka et al., 2006; Poch et al., 2011; Tesche and Karhu, 2000).

Our research indicates that the brainstem-diencephalo-septohippocampal system controlling the theta rhythm (Bland and Oddie, 1998; Vertes, 1981, 1982; Vertes and Kocsis, 1997; Vertes et al., 2004; Vinogradova, 1995) can also include the midbrain ventral tegmental area (VTA). We found that unilateral, cytotoxic lesion of the VTA caused a bilateral decrease in the neocortical and hippocampal EEG power in conscious rats during behaviours (such as exploratory sniffing) which are easily elicitable by VTA stimulation and usually accompanied with hippocampal theta rhythm (Jurkowlaniec et al., 2003). We also found that procaine injections into the VTA temporarily prevent the appearance of sensory stimulated theta rhythm in urethane anaesthetised rats. Moreover, lesions of this area seriously damage synchronisation of the hippocampal signal, which is seen as diminished power of the dominating band with simultaneously increased power at other, non-dominating frequency bands (Orzeł-Gryglewska and Trojniar, 2002, Orzeł-Gryglewska et al., 2006). On the other hand, electrical stimulation of the VTA induces a regular theta rhythm in the hippocampal EEG (Orzeł-Gryglewska et al., 2012). Other authors indicate the involvement of the mesolimbic dopaminergic (DA) transmission in hippocampal activation and memory processes (Jay, 2003; Lisman and Grace, 2005; Silkis, 2009).

The VTA is composed mainly (almost 70%) of the A10 dopaminergic cells group (Dahlstrom and Fuxe, 1964; Oades and Halliday, 1987) with widespread projections to forebrain structures, and GABA cells, which mostly play the role of interneurons and they represent approximately 25% of the total population of neurons in this area (Adell and Artigas, 2004; Kalivas, 1993; Oades and Halliday, 1987; Swanson, 1982). Blockade of $GABA_A$ receptors in the VTA, that releases DA neurons from the tonic inhibition provided by interneurons, proved to be a method of induction of hippocampal theta rhythm, whereas strengthening of GABAergic tonus in the VTA by muscimol microinjection and thereby reducing the secretion of dopamine on the VTA projection terminals deteriorates parameters of stimulated theta (Orzeł-Gryglewska et al., 2010). The activity of the mesolimbic DA system is regulated via two independent dopaminergic mechanisms: (1) a transient or "phasic" DA release that is mediated mainly through DA neuron burst firing, and (2) a "tonic" dopamine state, which is composed of spontaneous firing of dopamine neurons population and which is responsible for maintaining stable extrasynaptic baseline level of dopamine. The DA neuron burst firing induces a large transient increase in synaptic DA in target regions and is considered to be the temporally relevant signal sent to post-synaptic sites. In contrast, tonic DA transmission occurs over a much slower time scale and has been proposed to regulate the responsivity of the DA system through pre- and post-synaptic mechanisms (Grace, 1991; Grace et al., 2007; Lodge and Grace, 2008). There is a notion of an intrinsic pacemaker in the dopaminergic system that drives single-spike or 'tonic' firing (Grace and Bunney, 1984) and some DA cells were found to be firing spontaneously in both anaesthetised and non-anaesthetised conditions (Freeman et al., 1985). Tonic dopamine release is thought to set the background level of dopaminergic receptor stimulation (postsynaptic as well as autoreceptors) and, through homoeostatic mechanisms, it also generates the responsivity of the system to dopamine (Grace, 1991).

Dopamine release in the VTA is partly of somatodendritic nature and D2 autoreceptors tonically limit the local release of dopamine (Adell and Artigas, 2004; Kalivas, 1993; Momiyama et al., 1993). Blockade of these receptors should therefore result in increased dopamine release in target structures, including the septum and hippocampus and may contribute to signal changes in the hippocampal EEG. It has been shown, however, that some subpopulations of VTA DA neurons are not regulated by autoreceptors. In mice, mesoprefrontal dopaminergic neurons do not possess functional somatodendritic Girk2-coupled dopamine D2 autoreceptors (Lammel et al., 2008). In rats, DA neurons projecting to the prefrontal cortex and nucleus accumbens express D2-like receptors, while the cells that project to the amygdala do not (Margolis et al., 2008). However, connexions between the VTA, septum and hippocampus are relatively sparse and despite a large number of studies in this area, these connexions are usually not analysed. If indeed blockade of D2 receptors can generate hippocampal theta rhythm, it can be speculated that the pool of neurons that participate in theta induction belongs to the group of DA cells that are regulated via autoreceptors.

Another way to interfere with local regulatory mechanisms can be possibly achieved by amphetamine, a dopaminergic agonist of indirect activity, which enhances DA release from presynaptic endings, blocks its reuptake and metabolism by inhibiting monoamine oxidase type A (Fleckenstein et al., 2007; Raiteri et al., 1975; Sulzer et al., 2005). Simultaneously, amphetamine stimulates autoreceptors of the somatodendritic region and (when it is given systemically) activates striatal loop of feedback inhibition of DA neurons (Bunney and Aghajanian, 1975, 1976; Bunney et al., 1984; Schmitz et al., 2001; Sulzer et al., 1993, 2005). It can be assumed that with the proper dose of amphetamine administered into the VTA, an increase of the somatodendritic DA secretion can be obtained, which activates D2 receptors and thus reduces the secretion of DA in the target structures. This pharmacological manipulation could be of particular importance, as it potentially could pertain mainly to the dopaminergic system of the VTA without affecting GABAergic interneurons, as D2 receptors are sparse or not present at all in the latter group (Adell and Artigas, 2004; Pickel et al., 2002).