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## Research Report

# Induction of hippocampal theta rhythm by electrical stimulation of the ventral tegmental area and its loss after septum inactivation

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## ABSTRACT

The ventral tegmental area (VTA), which may be one of the structures involved in regulation of hippocampal theta rhythm, sends direct projections to the hippocampus and also to the forebrain septum, the key centres involved in theta generation. In the present study we aimed at assessing which projections from the VTA (direct or through the septum) participate in regulation of hippocampal electric activity. Experiments were conducted on 3 groups of urethanised male Wistar rats. In the first group (n=6) electrical stimulation of the VTA was used to evoke theta rhythm episodes in hippocampus. Stimulation was repeatedly applied in control conditions and after procainic blockade of the septum. The second group (n=6), subjected to unilateral electrical stimulation of the VTA (30-s stimulation at 10-min intervals during 2 h) and to subsequent detection of Fos expression, served to measure neuronal activation of the target mesolimbic structures. Activation levels of selected structures were compared to data from analogous stimulation of the zona incerta (ZI, the third group, n=6). Stimulation of the VTA immediately generated regular theta rhythm in both hippocampi. Inactivation of the septum with procaine temporarily abolished this effect. VTA stimulation increased the density of Fos in the ipsilateral nucleus accumbens. Stimulation of the ZI never generated theta but evoked significant induction of Fos expression in the hippocampus. Our data suggest that the projection through which the VTA enhances theta rhythm is not direct but is incorporated into the main route of theta generation, which involves septum as the main relay node.

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## 1. Introduction

The hippocampal theta rhythm, in rodents known as rhythmic slow activity (RSA), is a regular 3–12 Hz oscillation present not only in the hippocampus but also in other related structures.

Appearance of theta rhythm is associated with active wakefulness and paradoxical sleep (Kemp and Kaada, 1975; Whishaw and Vanderwolf, 1973). This rhythm has been also related to different functions, e.g. voluntary movements during wakefulness (Vanderwolf, 1969), sensory stimulation (Nunez et al.,

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Abbreviations: ANOVA, analysis of variance; RSA, rhythmic slow activity; VTA, ventral tegmental area; ZI, zona incerta.

1991), spatial learning and navigation (Caplan et al., 2001, 2003), and memory processes (Teschke and Karhu, 2000).

Projections that are involved in the generation of theta rhythm origin in the nuclei of the brainstem reticular formation such as the nucleus reticularis pontis oralis (Klemm, 1972; Macadar et al., 1974; Nunez et al., 1991; Vertes, 1979, 1981; Vertes et al., 1993) and the pedunculo-pontine tegmental nucleus (Kinney et al., 1998; Nowacka et al., 2002; Vertes et al., 1993). These structures send nerve impulses to the medial and lateral mammillary nuclei (Alonso and Llinas, 1992; Kocsis and Vertes, 1994; Llinas and Alonso, 1992), supramammillary nucleus (Kirk and McNaughton, 1993; Kirk et al., 1996; Pan and McNaughton, 2002; Woodnorth and McNaughton, 2002a), posterior hypothalamic area (Bland and Oddie, 1998; Kirk, 1998; Kirk et al., 1996; Oddie et al., 1994; Woodnorth and McNaughton, 2002b; Woodnorth et al., 2003), dorsomedial hypothalamus (Destrade and Ott, 1982; Woodnorth et al., 2003) and subsequently, via the medial septum, these projections reach the hippocampus.

There are other structures that have also been found to regulate theta rhythm: they include the raphe nuclei (Kinney et al., 1996; Nitz and McNaughton, 1999; Vanderwolf and Baker, 1986), fasciculus retroflexus (Valjakka et al., 1998), ventral tegmental nucleus of Gudden (Bassant and Poindessous-Jazat, 2001; Kocsis et al., 2001; Tortorolo et al., 2002) and nucleus incertus (Nunez et al., 2006; Olucha-Bordonau et al., 2003; Teruel-Marti et al., 2008).

The ventral tegmental area (VTA), consisting mainly of dopaminergic neurons constituting the A10 group and of GABAergic interneurons (Dahlstrom and Fuxe, 1964; Oades and Halliday, 1987), sends projections to the hippocampal formation as well as to the septum (Gasbarri et al., 1994, 1997; Haghdoost-Yazdi et al., 2009) and data can be found implying that the VTA is involved in regulation of theta types characteristic for certain behaviours. All the types of dopaminergic receptors have been detected both in the septum and in the hippocampus (Huang and Kandel, 1995; Meador-Woodruff et al., 1997; Yokoyama et al., 1994). D1/D5 receptor agonists injected directly into the dorsal hippocampus induced an increase in release of acetylcholine in this region and this neurotransmitter is known to play a crucial role in the generation of theta activity (Hersi et al., 1995, 2000; Imperato et al., 1993; Laplante et al., 2004). D1/D5 agonists injection into the septal area intensified neuronal activity in this region and generated an increase in hippocampal signal power at 3–7 Hz band, while dopaminergic antagonists applied to the septum suppressed spontaneous hippocampal theta bursts (Fitch et al., 2006; Miura et al., 1987).

Our previous studies showed that inactivation of the VTA, both temporary by procaine microinjection or permanent by lesion, caused disruptions in generation of hippocampal theta rhythm (Jurkowlanec et al., 2003; Orzeł-Gryglewska et al., 2006). Le Moal and Cardo (1975) recorded bursts at theta frequency from the part of the ventral tegmentum that is located in the vicinity of the nucleus interpeduncularis, and during paradoxical sleep these bursts were correlated with hippocampal theta rhythm. The VTA itself also exhibits rhythms at theta frequency in the field potential activity, particularly during episodes of paradoxical sleep and exploration (Orzeł-Gryglewska and Trojnar, 2004). Electric stimulation of the VTA was found to induce rhythmic bursts of theta frequency in the

neurons of the medial septum (Fitch et al., 2006) and also to elicit feeding and exploratory reactions (Maliszewska-Ścisło and Trojnar, 2000; Trojnar and Klejbor, 1999) and these two types of behaviour in natural conditions are accompanied by theta rhythm. On the other hand, after VTA stimulation, theta rhythm recorded from this area during subsequent paradoxical sleep showed decreased power (Orzeł-Gryglewska and Trojnar, 2004). We proved in our previous study in urethanised rats that the VTA may be a site of elicitation of theta rhythm in the hippocampus. Blocking GABA<sub>A</sub> receptors within the VTA by bicuculline microinjection immediately induced regular theta rhythm lasting for circa 30 min, whereas activation of these receptors by muscimol microinjection caused long-lasting deterioration of theta rhythm, which in those experiments was induced by sensory stimulation (Orzeł-Gryglewska et al., 2007, 2010). According to the data from the literature, it is justified to assume that the pharmacological manipulations that we performed with those agents resulted mainly in disinhibition of the A10 group of dopaminergic cells that are located in the VTA (Ikemoto et al., 1997). Moreover, blockade of dopaminergic autoreceptors within the VTA by flupenthixol elicits theta rhythm (Orzeł-Gryglewska et al., 2008). Thus, our lines of evidence, together with other published data, confirm that the VTA belongs to theta regulating system, however, many issues connected to this idea still need investigation. Electric stimulation of different parts of the midbrain reticular formation, including its ventral part, was used in the past as a method of RSA induction (Klemm, 1972; Klemm and Douglass, 1974; Kramis and Vanderwolf, 1980; Macadar et al., 1974; McNaughton and Sedgwick, 1978; Oswald and Emmerich, 1980; Robinson and Vanderwolf, 1978; Vorobev et al., 1988). However, with the exception of one publication (Fitch et al., 2006), the VTA was never mentioned as a separate site whose stimulation could elicit theta rhythm. Routtenberg (1970) obtained theta rhythm in waking rats after stimulation of ventral tegmental nuclei, however, the author described this site as neutral in respect to rewarding or aversive conditioning. This inconsistency between anatomy and function might be due to long existing vagueness pertaining to morphological boundaries of the VTA and to the lack of clarity regarding the relationship between the VTA and the localisation of the A10 dopaminergic cells group (Ikemoto, 2007). However, there are data indicating that RSA can be induced by the means of electric stimulation of the dopaminergic substantia nigra pars compacta (Hallworth and Bland, 2004; Sabatino et al., 1986). Another unclear point is what could be the neuronal pathway that originates in the VTA and participates in the elicitation of hippocampal theta rhythm. So far no data have been found as to projections from the VTA that would directly reach the supramammillary nucleus, although connection in the opposite direction is documented (Vertes, 1992). Connection between the VTA and the posterior hypothalamus, which belongs to the theta generation system, has not been found either (Abrahamson and Moore, 2001; Oades and Halliday, 1987). On the other hand, there is a direct pathway from the VTA to the septum, particularly to its lateral part (Asaumi et al., 2006; Fallon, 1981; Haghdoost-Yazdi et al., 2009) and to the hippocampus (Gasbarri et al., 1994, 1997; Winship et al., 2006), although the VTA's contribution to the total of projections reaching those structures is not more than 10–18%. Dopaminergic receptors are found both in the septum and hippocampus (Berlanga et al., 2005; Huang and Kandel, 1995; Yokoyama et al., 1994). The

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