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Research Report

Lesion of the ventral tegmental area amplifies stimulation-induced Fos expression in the rat brain

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ABSTRACT

Unilateral lesions of the ventral tegmental area (VTA), the key structure of the mesolimbic system, facilitate behavioral responses induced by electrical stimulation of the VTA in the contralateral hemisphere. In search of the neuronal mechanism behind this phenomenon, Fos expression was used to measure neuronal activation of the target mesolimbic structures in rats subjected to unilateral electrocoagulation and simultaneously to contralateral electrical stimulation of the VTA (L/S group). These were compared to the level of mesolimbic activation after unilateral electrocoagulation of the VTA (L group), unilateral electrical stimulation of the VTA (S group) and bilateral electrode implantation into the VTA in the sham (Sh) group. We found that unilateral stimulation of the VTA alone increased the density of Fos containing neurons in the ipsilateral mesolimbic target structures: nucleus accumbens, lateral septum and amygdala in comparison with the sham group. However, unilateral lesion of the VTA was devoid of effect in non-stimulated (L) rats and it significantly amplified the stimulation-induced Fos-immunoreactivity (L/S *vs* S group). Stimulation of the VTA performed after contralateral lesion (L/S) evoked strong bilateral induction of Fos expression in the mesolimbic structures involved in motivation and reward (nucleus accumbens and lateral septum) and the processing of the reinforcing properties of olfactory stimuli (anterior cortical amygdaloid nucleus) in parallel with facilitation of behavioral function measured as shortened latency of eating or exploration. Our data suggest that VTA lesion sensitizes mesolimbic system to stimuli by suppressing an inhibitory influence of brain areas afferenting the VTA.

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Abbreviations: Acb, accumbens nucleus; AcbC, accumbens nucleus, part core; AcbS, accumbens nucleus, part shell; ACo, anterior cortical amygdaloid nucleus; BLA, basolateral amygdaloid nucleus, anterior part; BST, bed nucleus of the stria terminalis; Ce, central amygdaloid nucleus; EC, entorhinal cortex; GABA, gamma-aminobutyric acid; L, unilateral lesion of the ventral tegmental area; LS, lateral septal nucleus; L/S, unilateral lesion and contralateral stimulation of the ventral tegmental area; Me, medial amygdaloid nucleus; MFB, medial forebrain bundle; MS, medial septal nucleus; NMDA, *N*-methyl-D-aspartate; PBS, phosphate buffered saline; S, unilateral stimulation of the ventral tegmental area; Sh, sham; VP, ventral pallidum; VTA, ventral tegmental area

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1. Introduction

The ventral tegmental area (VTA) is the key structure of the mesolimbic system (Oades and Halliday, 1987) which is engaged in the emotional and motivational aspect of various behaviors of biological significance i.e. food intake, sex or exploration (e.g. Le Moal and Simon, 1991). The mesolimbic system, begins in the A10 dopaminergic cells in the VTA and the most posterior part of the lateral hypothalamus and terminates in several forebrain limbic structures e.g. nucleus accumbens, septum, amygdala and prefrontal cortex (Oades and Halliday, 1987).

Unilateral electrolytic lesions of the VTA facilitate behavioral responses induced by electrical stimulation of the VTA in the contralateral hemisphere (Trojniar and Staszewska, 1994; Maliszewska-Scislo and Trojniar, 2000). This "contralateral facilitation of function" manifests itself in the shortening of latency of stimulation-elicited feeding and exploratory locomotion. We found this effect after electrolytic (Trojniar and Staszewska, 1994; Maliszewska-Scislo and Trojniar, 2000) and chemical (6-hydroxydopamine) (Klejbor et al., 1995) lesions of the dopaminergic A10 neurons in the VTA as well as after a unilateral blockade of its dopaminergic D1 and D2 (Klejbor and Trojniar, 1997), $GABA_A$ (Trojniar and Klejbor, 1999) and glutamatergic NMDA (Maliszewska-Scislo and Trojniar, 2000) receptors. The facilitatory effect of the unilateral electrolytic lesion of the VTA appeared replicable by administration of pharmacological agents decreasing dopaminergic transmission in the VTA (see Kalivas, 1993).

The phenomenon of facilitation of the intact VTA function appears immediately (1st post-lesion day), stabilizes during 8–10 days and is long-lasting (no decrement was found after 2 months). Common post-damage plasticity processes in the central nervous system e.g. receptor supersensitivity and collateral sprouting usually need at least two weeks, often a few months to appear, and do not assure the restitution of the lost function (Gerfen, 2003; Nikolaus et al., 2003; Deller et al., 2006). For this reason these post-damage processes cannot be engaged in the mechanism of instant facilitation of the VTA function after contralateral lesion. It seems essential to try to understand the neuronal mechanisms behind this quick and long-lasting effect. Besides, the combination of unilateral lesion and contralateral stimulation of the extrapyramidal structures appeared beneficial in the treatment of parkinsonian symptoms (Merello et al., 2001), so this phenomenon may be of clinical importance.

In search of the neuronal mechanism underlying the post-damage facilitation of the behavioral responses induced by the VTA stimulation observed in previous (Trojniar and Staszewska, 1994; Maliszewska-Scislo and Trojniar, 2000) and the present studies, the level of activation of target subcortical mesolimbic structures (receiving dopaminergic fibers from A10 cells) was measured by neuronal expression of Fos protein — the inducible transcription factor which is a product of immediate early gene *c-fos*. The basal neuronal level of *c-fos* gene expression is very low, even undetectable, but it can be induced rapidly and transiently by a diverse range of extracellular stimuli: e.g. neurotransmitters and growth factors, sensory stimuli, stress, depolarization, electrical stimulation or lesions (Morgan and Curran, 1989; Herdegen and Leah, 1998).

The structures which would show particularly high Fos expression during the present experiment could be engaged in the mechanism responsible for this phenomenon of post-damage facilitation of the behavioral responses induced by the VTA stimulation. The density (number per 1 mm^2) of neurons containing Fos was assessed in rats subjected to both unilateral electrocoagulation and contralateral electrical stimulation of the VTA (*L/S* group) in comparison to the unilaterally stimulated (*S*), unilaterally lesioned (*L*) and sham (*Sh*) groups.

2. Results

2.1. Behavior

Unilateral stimulation of the VTA performed in the L/S ($n=6$) and S ($n=5$) groups evoked eating or exploration (locomotor activity with sniffing response) in 78–96% of all trials. Each rat showed both reactions, however in 6 animals (3 of L/S and 3 of S group) exploration was prevalent (60–87% of all reactions), in four rats eating prevailed (63–90%), and in one rat (of S group) reactions were balanced. All reactions were observed during trials of stimulation, not in the breaks between trials and expired after switching off current.

The latencies of stimulation-induced behavioral reactions were reduced after contralateral lesion of the VTA (in the L/S group) ($F(27,153)=9.94$, $P<0.001$) and the tendency to stabilization during 10 post-lesion days was observed (Fig. 1). Post hoc comparisons showed that on the 1st, 3rd and 6th post-lesion stimulation days, latencies of the reactions in the L/S rats were shorter than on the –1st, –3rd and –4th days of screening. On remaining days (2, 4, 5, 7–10) the latencies of the reactions were reduced in relation to both screening (days –4 to –1) and S group. As shown in Fig. 1, there were no significant

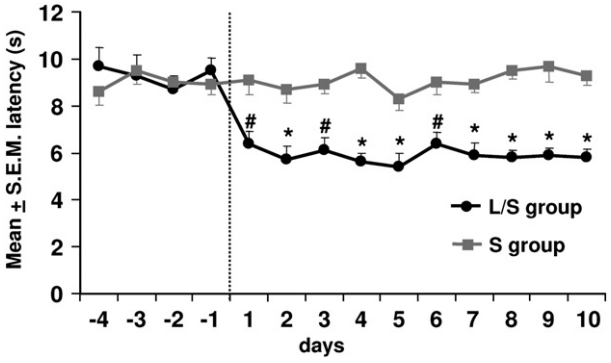

Fig. 1 – Mean latencies of ventral tegmental area (VTA) stimulation-induced behavioral reactions (eating and exploration) of rats subjected to the lesion of the contralateral VTA (L/S group, $n=6$) and control, non-lesioned rats (S group, $n=5$) before or after the VTA lesion. Explanations: In each rat latencies of both reactions obtained during each day (in 30 trials of stimulation) were averaged. #$P<0.05$ in comparison with –4, –3 and –1 days, *$P<0.05$ in comparison with all pre-lesion days and with control S group.