available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Role of dorsal raphe nucleus 5-HT_{1A} and 5-HT_2 receptors in tonic immobility modulation in guinea pigs

*Mateus Dalbem Ferreira, Leda Menescal-de-Oliveira**

Department of Physiology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, 14049-900 Ribeirão Preto, SP, Brazil

ARTICLE INFO

Article history:
Accepted 10 June 2009
Available online 16 June 2009

Keywords:
Dorsal raphe nucleus
Serotonin
Tonic immobility
Defensive behavior

ABSTRACT

Tonic immobility (TI) is an innate defensive behavior characterized by a state of physical inactivity and diminished responsiveness to environmental stimuli. Behavioral adaptations to changes in the external and internal milieu involve complex neuronal network activity and a large number of chemical neurotransmitters. The TI response is thought to be influenced by serotonin (5-HT) activity in the central nervous system (CNS) of vertebrates, but the neuronal groups involved in the mechanisms underlying this behavior are poorly understood. Owing to its extensive afferents and efferents, the dorsal raphe nucleus (DRN) has been implicated in a great variety of physiological and behavioral functions. In the current study, we investigated the influence of serotonergic 5-HT_{1A} and 5-HT_2 receptor activity within the DRN on the modulation of TI behavior in the guinea pig. Microinjection of a 5-HT_{1A} receptor agonist (8-OH-DPAT, 0.01 and 0.1 μg) decreased TI behavior, an effect blocked by pretreatment with WAY-100635 (0.033 μg), a 5-HT_{1A} antagonist. In contrast, activation of 5-HT_2 receptors within the DRN (α-methyl-5-HT, 0.5 μg) increased the TI duration, and this effect could be reversed by pretreatment with an ineffective dose (0.01 μg) of ketanserine. Since the 5-HT_{1A} and 5-HT_2 agonists decreased and increased, respectively, the duration of TI, different serotonin receptor subtypes may play distinct roles in the modulation of TI in the guinea pig.

1. Introduction

Tonic immobility (TI), also known as reflex immobility, animal hypnosis, catalepsy, or death feigning, can be defined as an inborn defensive response characterized by a temporary state of profound inactivity and a relative lack of responsiveness to external stimuli. The duration of TI episodes is quite variable, with the animal remaining motionless for seconds or hours depending on the species and environmental conditions (Hoagland, 1974). This response is triggered in many vertebrate and invertebrate species by different types of sensory stimuli, primarily prolonged physical contact with predators (Gilman et al., 1950; Ratner, 1967; Klemm, 1971). Tonic immobility is an inhibitory behavioral response in which the absence of movement appears to be of great adaptive value since struggling may encourage the predator to continue the attack (Thompson et al., 1981). Thus, according to the literature, the initiation of TI during a confrontation increases the chances of surviving a predatory attack by 50% (Sargent and Eberhardt, 1975). The animal's survival depends on its capacity to appear immobile, which encourages the predator to stop the attack (Rodgers and Randal, 1987).

Different experimental approaches have been used to determine the regions of the central nervous system (CNS)

* *Corresponding author*. Fax: +1 55 16 633 0017.
E-mail address: lmdolive@fmrp.usp.br (L. Menescal-de-Oliveira).

0006-8993/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2009.06.030

that control the TI response. In addition, it has been shown that brainstem structures are fundamental to the expression of this behavior (Klemm, 1976; Franchi-Vasconcelos and Hoffman, 1994; Monassi et al., 1999). Studies carried out in our laboratory have demonstrated that the periaqueductal gray matter (PAG) (Monassi et al., 1997; Ramos Coutinho et al., 2008), the amygdala (Leite-Panissi et al., 1999; Leite-Panissi and Menescal-de-Oliveira, 2002), the parabrachial region (Menescal-de-Oliveira and Hoffmann, 1993), the hypothalamus (Oliveira et al., 1997), the nucleus raphe magnus (NRM) (Silva and Menescal-de-Oliveira, 2006 and 2007) and the hippocampus (unpublished data) are involved in TI modulation.

The dorsal raphe nucleus (DRN), located in the ventral part of the periaqueductal gray matter, is the most prominent of the brainstem serotonergic nuclei. A very important mechanism of control of 5-HT neurons is self-inhibition through 5-HT1A autoreceptors. Activation of these receptors by 5-HT leads to opening of potassium channels in the cell membrane, hyperpolarization of the cell and a cessation of cell firing (Sprouse and Aghajanian, 1987). In particular, 5-HT1A autoreceptors in the DR may play a pivotal role in the physiological control of ascending 5-HT pathways, attenuating excessive activation of 5-HT neurons by excitatory afferents from the different forebrain structures. The proportion of 5-HT-containing cells in the DRN is estimated to range from 1/3 to 2/3 (Descarries et al., 1982; Jacobs and Azmitia, 1992; Baumgarten and Grozdanovic, 1997). The remaining non-serotonergic cells contain a variety of other neurotransmitters and neuromodulators (Jacobs and Azmitia, 1992).

Some reports have shown that the serotonergic system is an important neuromodulator of central nervous system activity, and TI is a behavior that seems to be highly influenced by cerebral levels of serotonin (5-HT) (Wallnau and Gallup, 1977). Systemic studies have demonstrated that different doses of serotonin could produce an increase or decrease in the IT duration in chickens (Henning, 1980). In the same way, intraventricular administration of 5-HT produced opposing results in chickens and rabbits (Harston et al., 1976; Hatton et al., 1978). These different results have been attributed to differences in the route of drug administration or the species used. Moreover, systemic injections of 5-HT could alter the levels of 5-HT in the entire CNS.

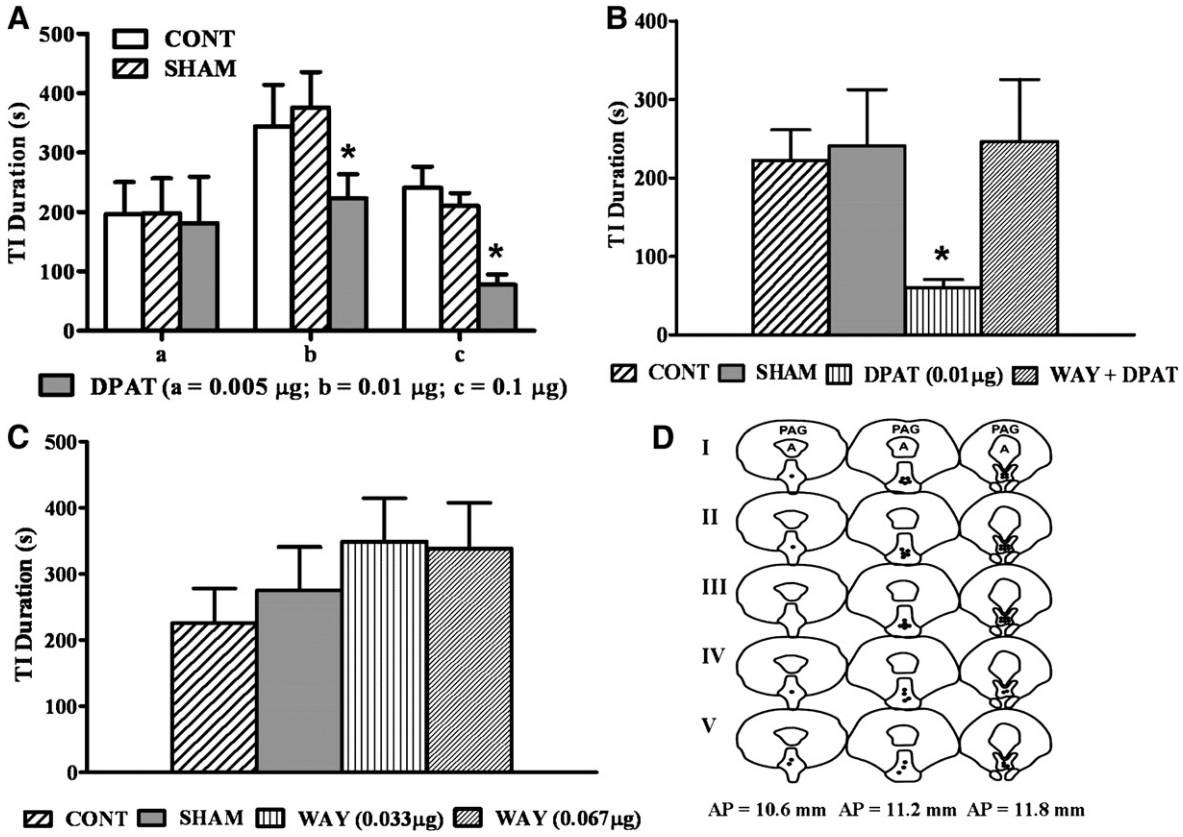

Fig. 1 – Duration of tonic immobility (TI) episodes. Mean ± S.E.M. (A) TI duration under control conditions (CONT), after surgery (SHAM) and after 5-HT$_{1A}$ agonist 8-OH-DPAT [DPAT; Aa (0.005 μg; $n=12$), Ab (0.01 μg; $n=10$), Ac (0.1 μg; $n=11$)]; (B) TI duration after WAY-100635 (WAY; 0.033 μg) followed 10 min later by DPAT (0.01 μg; $n=7$). $^{*}p<0.05$ compared with CONT and SHAM; (C) TI duration after two different doses of WAY (0.033 μg and 0.067 μg) injection into the DRN on consecutive days ($n=8$); (D) Schematic drawings of frontal sections obtained at representative levels of the guinea pig DRN indicating the site of microinjection (filled circles, •) of DPAT (0.005 μg, DI), DPAT (0.01 μg, DII), DPAT (0.1 μg, DIII), WAY (0.033 μg) followed by DPAT (0.01 μg, DIV) and WAY (0.033 μg and 0.067 μg, DV). Abbreviations: PAG, periaqueductal gray matter; A, brain aqueduct.