Short Communication

Comparable CNS mechanisms for locomotor rhythm generation and self-consciousness expression

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Walking is a form of locomotor behavior that is essentially controlled by spinal neurons – i.e., specifically the central pattern generator (CPGs) for locomotion. The latter, localized in the lumbosacral area of the spinal cord, is capable of generating the basic neural signals underlying locomotor rhythm and pattern generation even in absence of descending signals from the brain. Pacemaker-like membrane properties and specific families of transmembrane systems including NMDA ionophores and 5-HT2A receptors were shown to underlie its activity in the spinal cord. Interestingly, increasingly evidence suggests that comparable systems are involved also with the modulation of various levels of consciousness.

Key Words: *CPG; Monoamies; 5-HT; NMDA; Oscillations; Locomotion; Brainstem; Spinal cord; Consciousness*

INTRODUCTION

Locomotor rhythm generation depends upon transmembrane voltage oscillations, NMDA ionophores and 5-HT receptors in the spinal cord. A clear demonstration of such a command center for locomotion in the lumbosacral area of the spinal cord has generally been attributed to Sten Grillner. He elegantly showed that spinal cord-transected (Tx) cats, after decerebration, can still express locomotor-like activity monitored from hindlimb nerves [1]. Although its functional organization remains incompletely understood, one of the first models has described the spinal locomotor CPG as two half-centers (flexor and extensor) reciprocally inhibiting each other rhythmically. The mutual inhibitory interactions, ensured by inhibitory neurons, would enable only one half-center to be active at a given time. The activity of the active half-center would gradually reduce due to some fatigue, allowing an activation of the antagonistic half-center which, in turn, would then inhibit the active half-center, hence switching the locomotor phase from flexion to extension and vice versa [1]. Those half-centers were found to depend upon neuromodulation and neurotransmitters for normal activity.

More recently, pharmacological approaches in Tx mice receiving no assistance or sensory stimulation revealed indeed that L-DOPA, 5-HT or DA receptor agonists such as 8-OH-DPAT or buspirone (5-HT1A/7), quipazine (5-HT2A/2C) or SKF-81297 (D1-like) can best acutely trigger short episodes of locomotor-like movements in completely paraplegic animals [2]. Using selective antagonists and genetically-engineered mice (e.g., 5-HT7KO), it has been clearly established that NMDA, 5-HT1, 5-HT2A, 5-HT7, and D1 receptors were specifically involved in mediating those effects [3,4]. Endogenous glutamate release and NMDA ionophore activation were also found to be critically important for quipazine-induced effects since a complete loss of induced-movement was found in NMDA antagonist (MK-801)-treated Tx mice [5]. Transmembrane voltage oscillations and pacemaker-like properties are also generally believed to contribute to CPG activity. Their expression is known to depend on the presence of glutamate and tetrodotoxin (TTX)-resistant NMDA ionophore activation [6]. Plateau potentials [7], when rhythmically occurring, is another intrinsic property believed by some researchers to be associated with endogenous TTX-resistant pacemaker-like activity [8].

Self-consciousness, awereness and mindfulness may depend on comparable cellular and transmembrane mechanisms in the brain. Although clear definitions are still the subject of debates, some people define consciousness as a state of mind or as a level of awareness – i.e., to be aware of an object, etc. [9]. For some experts in meditation such as Kabat-Zinn, mindfulness is the ability to focus on the present moment without any judgment which is emerging at a given moment of consciousness [10]. However, from a medical perspective, consciousness is often more globally referred to as the capacity of sensing and responding to the world [11]. According to Flohr, consciousness may thus be associated with different states that depend on the formation of transient higher-order, self-referential mental representations [12] – a loss of consciousness will occur, if the brain's representational activity falls below a critical threshold because of inhibited NMDA ionophore activity. In fact, pharmacological agents that directly inactivate the NMDA synapse necessarily have general anesthetic properties [12]. More specifically, the anterior insula and the cingular cortex were reported as potential centers of consciousness since particularly active in people practising meditation but inactive in individuals with disorders of consciousness [13]. Amantadine, a NMDA ligand was recently found to suddenly restore consciousness in a 36-year-old woman suffering from a persistent vegetative state irresponsive to other drugs [14] whereas electrical stimulation activating some of those areas (i.e., insula) was found to reversibly restore consciousness in a woman in a coma [14]. Researchers at MIT found that brain waves are neural correlates of consciousness. Indeed, they reported that when thoughts are in our minds, corresponding groups of neurons are oscillating in synchrony at around 30 Hz or higher, whereas thoughts that are no longer in our minds oscillate at lower frequencies, that is below 30 Hz [15]. Most recently, psychedelic drugs such as LSD, well known to induce altered states of consciousness, were found to be blocked in ketanserine (selective 5-HT2A receptor antagonist)-treated subjects [16,17]. Interestingly, spinal cord stimulation (SCS) has been shown to improve, via brain-mediated processes, the consciousness levels of patients with disorder of consciousness [18].

CONCLUSION

Although localized in different areas of the CNS, comparable neuronal mechanisms may be involved in mediating both biological functions that are locomotion and consciousness. An oral drug comprising some of these compounds (NMDA ionophore or 5-HT2A receptor ligands) shall thus be expected to act upon both systems simultaneously.

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