Effect of the selective activation of serotonin 5-HT$_3$ receptors on sleep and waking

Luc Staner, Caroline Graff, Remy Luthrhinger and Nadine Noel

Abstract

The 5-HT$_3$ receptor is a ligand-gated ion channel that belongs to the Cys-loop family, which also includes receptors such as the nicotinic acetylcholine receptor. As other 5-HT receptors subtypes, the 5-HT$_3$ receptor seems to be involved in a large range of physiological processes, among of them sleep. Its role in the sleep-wake physiology has not been clearly established until now, but several pieces of evidence show its activation effect on wakefulness and inhibitory effect on slow-wave sleep. In addition, the 5-HT$_3$ receptors seem to be implicated in circadian rhythm regulation and in REM sleep propensity. Many studies highlight its role in sleep disorders and more precisely in obstructive sleep apnea (OSA) and in fibromyalgia. Its effects in OSA are double. Indeed, 5-HT$_3$ receptor antagonists increase respiration both at the central and the peripheral levels, and thus are potential therapeutic drugs for OSA. Drugs acting on 5-HT transmission have brought interesting results in animal models of apnea syndrome, as well as in patients with OSA. However, results are still disappointing since, in contrast to nasal continuous positive airway pressure that suppress nearly all respiratory events, drugs only lower the respiratory disturbance index by about 20–50%. Chronic pain that relates to inflammatory processes implicates 5-HT$_3$ neurotransmission, and there is some evidence that the 5-HT$_3$ receptor antagonist tropisetron had beneficial effects on pain intensity and sleep disturbance in patients with fibromyalgia.

Introduction

The serotonin (5-hydroxytryptamine, 5-HT) neurons in the brainstem raphe nuclei form the largest and most complex efferent system in the brain. As a consequence, 5-HT is involved in many physiological and behavioral systems, and this is reflected by the use of numerous 5-HT-related drugs applied as treat-
ments across a wide variety of very different clinical conditions. Indeed, 5-HT mediates cardiovascular and respiratory activity, sleep, nutrient intake, sexual activity, anxiety, mood, aggression and nociception. 5-HT produces its effects through a variety of membrane-bound receptors. Among them, the 5-HT$_3$ receptor takes up a particular place since it is the only ligand-gated ion channel and it mediates fast 5-HT synaptic transmission. Indeed, the 5-HT$_3$ receptor belongs to the Cys-loop family of ligand-gated ion channel, which include nicotinic acetylcholine receptors (n-AchR), GABA$_A$ receptors and glycine receptors.

The physiological role of 5-HT$_3$ receptors remains elusive. In contrast to the huge interest in the pharmacology of 5-HT$_3$ receptor antagonists (such as ondansetron, tropisetron and granisetron) that are considered as a tremendous step forward in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting, progress in understanding central 5-HT$_3$ receptor physiology has lagged behind. Over the last few years, a renewed interest in 5-HT$_3$ receptors has emerged since 5-HT$_3$ antagonists have been found to be clinically relevant in different pain syndromes such as chronic neuropathic pain, migraine, rheumatoid arthritis, tendinopathies, fibromyalgia and irritable bowel syndrome [1], but also in psychiatric disorders such as anxiety, depression and schizophrenia [2, 3]. Other new perspectives in clinical use of 5-HT$_3$ ligands are drug addiction, cognitive functions, and satiety control [1].

Although 5-HT has been implicated in the regulation of sleep for more than 40 years [4–8], the specific role of 5-HT$_3$ in sleep physiology has been addressed by very few studies. Adrien et al. [9] and Ponzoni et al. [10, 11] reported divergent effects of 5-HT$_3$ ligands on rat REM and slow-wave sleep (SWS) that could be accounted by dosage ranges and by route or site of administration. In humans, two studies in healthy subjects suggested a role of 5-HT$_3$ receptors in REM sleep regulation [12, 13]. During the last decade, interest in 5-HT$_3$ receptors ligands as potential treatment in the field of sleep medicine has grown, with results of animal and human studies suggesting that drugs antagonizing 5-HT$_3$ receptors could be effective in the treatment of sleep apnea [14] and of fibromyalgia syndrome [1].

The present review focuses on investigations on the pharmacology of the 5-HT$_3$ receptor, including structural, functional and anatomical aspects that relate to sleep-wake physiology and sleep medicine.

**General description of the 5-HT$_3$ receptor**

5-HT$_3$ receptors are pentamers [15] and members of the superfamily of ligand-gated ion channels [16]. Each subunit is composed of four transmembrane domains, the second of which delineates the ion channel pore [17] (Fig. 1). The extracellular N-terminal domain contains the agonist recognition site [18–20]. There are two 5-HT$_3$ subtypes: the 5-HT$_{3a}$ and the 5-HT$_{3b}$ subtypes. The