Neuroscience and Biobehavioral Reviews 35 (2011) 1419–1449

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

5-HT receptors and reward-related behaviour: A review

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ARTICLE INFO

Article history:
Received 7 September 2010
Received in revised form 3 March 2011
Accepted 4 March 2011

Keywords:
5-HT
Serotonin
Reward
Receptors
Behavioural models
Human
Animal
Intracranial self-stimulation
Drug self-administration
Place conditioning

ABSTRACT

The brain's serotonin (5-HT) system is key in the regulation of reward-related behaviours, from eating and drinking to sexual activity. The complexity of studying this system is due, in part, to the fact that 5-HT acts at many receptor subtypes throughout the brain. The recent development of drugs with greater selectivity for individual receptor subtypes has allowed for rapid advancements in our understanding of this system. Use of these drugs in combination with animal models entailing selective reward measures (i.e. intracranial self-stimulation, drug self-administration, conditioned place preference) have resulted in a greater understanding of the pharmacology of reward-related processing and behaviour (particularly regarding drugs of abuse). The putative roles of each 5-HT receptor subtype in the pharmacology of reward are outlined and discussed here. It is concluded that the actions of 5-HT in reward are receptor subtype-dependent (and thus should not be generalized) and that all studied subtypes appear to have a unique profile which is determined by content (e.g. receptor function, localization – both throughout the brain and within the synapse) and context (e.g. type of behavioural paradigm, type of drug). Given evidence of altered reward-related processing and serotonergic function in numerous neuropsychiatric disorders, such as depression, schizophrenia, and addiction, a clearer understanding of the role of 5-HT receptor subtypes in this context may lead to improved drug development and therapeutic approaches.

Contents

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0149-7634/$ – see front matter.
doi:10.1016/j.neubiorev.2011.03.005

1. Introduction

1.1. Serotonin in reward-related processing

In its most basic form, a reward (an object or event, regardless of its origin) is something that an organism will expend energy to obtain or approach; in this context, it is operationally opposite to an aversive stimulus (e.g. Wise, 2004). A rich animal literature has shown that the brain neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) plays an important role in the regulation of reward-related processing. For instance, 5-HT is involved in natural reward-related physiology and behaviour, from feeding to sexual activity (for reviews, see Pfaus, 2009; Wirtshafter, 2001). Recent studies in humans have supported this notion, showing for instance that 5-HT is involved in emotional regulation (see Cools et al., 2008 for review) and experiences as varied as the pleasantness of warmth (Lowry et al., 2009) or chocolate (McCabe et al., 2010).

Given 5-HT's role in reward-related functioning (Kranz et al., 2010), and that altered reward processing has been proposed in many psychiatric disorders (as reflected, for instance, by reduced motivation to obtain rewards in depression and schizophrenia), it should not be surprising that serotonergic dysfunction has been associated with numerous neuropsychiatric pathologies and, as such, has been a main target for therapeutic drug development. Most notably, extensive research has implicated this system in depression (e.g. a typical first-line treatment is the use of selective serotonergic reuptake inhibitors) (Trivedi et al., 2006), anxiety (Hood et al., 2010), schizophrenia (Emsley, 2009) and addiction (Rothman et al., 2008). Nonetheless, there is an incomplete understanding of the pharmacological mechanisms underlying the role of 5-HT in reward-related processing; this is necessary for a full understanding of both healthy and pathological reward system functioning and for the development of future effective drug therapies for disorders that entail dysfunction of brain reward systems.

Serotonin-containing neurons make extensive connections to other neural systems in reward-related brain areas. Clusters of serotonergic cell bodies are divided into nine nuclei or cell groups (B1–B9) (Dahlstrom and Fuxe, 1964) along the midline (or raphe) from the medulla to the midbrain. The primary ascending projections originate from the anterior (i.e. dorsal and median) raphe nuclei and account for the majority of 5-HT innervation of the forebrain (Azmitia and Segal, 1978). Innervation by these anterior raphe nuclei is extensive, diffuse, and overlapping, and includes areas known to be involved in aversion- and reward-related regulation such as the nucleus accumbens septi (NAc), ventral tegmental area (VTA), substantia nigra, hippocampus, amygdala, and prefrontal cortex (Hensler, 2006; Ikemoto, 2010; Lechin et al., 2006). In addition to having reciprocal connections with many reward-related brain areas, 5-HT regulates the transmission of all major neurotransmitters (Fink and Gothert, 2007), including the well-studied dopamine (Alex and Pehek, 2007). In a recent review by Kranz et al. (2010), the authors present converging evidence, particularly from pharmacology, electrophysiology, and human brain imaging, that the 5-HT system is as important for reward processing as dopamine. The current review focuses on the specific putative roles of individual 5-HT receptor subtypes in this processing.

1.2. The pharmacology of reward-related serotonergic mechanisms

The idea that 5-HT may be involved in the regulation of reward-related behaviours likely began with the work of James Olds and his colleagues. They showed that rats decreased their motivated responding following lateral hypothalamic microinjections of 5-HT (Olds et al., 1964), about a decade following their discovery that rats would self-administer electrical stimulation into similar regions (Olds and Milner, 1954). Indeed, many studies have since shown that stimulation of serotonin-rich nuclei of the brain (i.e. median and dorsal raphe nuclei) can sustain intracranial self-stimulation (ICSS) (e.g. Broadbent and Greenshaw, 1985; Van Der Kooy et al., 1978). At least one study has demonstrated that perfusion of 5-HT close to the ventral tegmental area (a key area of the mesolimbic system which contains the cell bodies of mesocorticolimbic dopamine-containing projections) increases rates of ICSS of the medial forebrain bundle (Redgrave and Horrell, 1976). Paradoxically, selective lesioning of serotonergic cells appears to facilitate ICSS (Poschel et al., 1974). In addition, increased reward is seen with conditioned place preference following administration of drugs that increase brain 5-HT (Subhan et al., 2000), although increases in 5-HT generally correlate with decreases in self-administration (Lyness et al., 1980; Yu et al., 1986). These conflicting, and often difficult to interpret, results are likely due to the high number of 5-HT targets (which can be located on multiple cell types within and/or across brain regions – resulting in the potential for each receptor subtype to have opposing effects on reward; for an excellent narrative review on the history of 5-HT and the discovery of its receptor subtypes, see Green, 2006). The use of behavioural models with reward-selective measures are discussed below in Section 2.4.

The rapid growth of knowledge around existing 5-HT receptor subtypes, in conjunction with improved techniques and a more collaborative environment among fields encompassing biomedical research and chemical engineering, allowed for the rapid development of numerous ligands in the 1980s and 1990s (Green, 2006). The early identification of 5-HT receptor selective ligands – such as mianserin and eltoprazine, which were originally considered antagonists for the 5-HT_2 receptor family, though eltoprazine was also known to be an agonist for the 5-HT_{1B} receptor – allowed for a more detailed investigation of 5-HT receptor subtype function (Peroutka and Snyder, 1981; Schipper et al., 1990). Although some studies using these compounds reported reward-related findings consistent with more recent studies (for instance, the finding by Risinger and Oakes (1996) showing that mianserin did not induce place conditioning alone, but did enhance alcohol-induced place preference), others had seemingly contradictory findings (Rocha et al., 1993). These were later clarified through the use of additional, more selective, ligands (e.g. Mosher et al., 2005; Hayes et al., 2009a,b), and an improved knowledge of 5-HT receptor pharmacology.

Taken together, these data underscore the need to clarify the role of 5-HT in reward-related processing and behaviour. An increase in the number and development of much more selective pharmacological agonists and antagonists, and refinement of reward-related behavioural measures, over the past two decades has been essential to this endeavour. As a result of this advancement of knowledge on many fronts (e.g. multiple, readily available, selective ligands; improved understanding of 5-HT receptor subtypes) this is perhaps