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Elements toward novel therapeutic targeting of the adrenergic system

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ABSTRACT

Adrenergic receptors belong to the family of the G protein coupled receptors that represent important targets in the modern pharmacotherapies. Studies on different physiological and pathophysiological properties of the adrenergic system have led to novel evidences and theories that suggest novel possible targeting of such system in a variety of pathologies and disorders, even beyond the classical known therapeutic possibilities. Herein, those advances have been illustrated with selected concepts and different examples. Furthermore, we illustrated the applications and the therapeutic implications that such findings and advances might have in the contexts of experimental pharmacology, therapeutics and clinic. We hope that the content of this work will guide researches devoted to the adrenergic aspects that combine neurosciences with pharmacology.

Contents

Abbreviations: NA, noradrenaline; a-AR, alpha adrenergic receptor; a1-AR, alpha adrenergic receptor; a1A-AR, alpha 1 A adrenergic receptor; a2-AR, alpha 2 adrenergic receptor; a 2A-AR, alpha 2 A adrenergic receptor; β-AR, beta adrenergic receptor; β1-AR, beta 1 adrenergic receptor; β2-AR, beta 2 adrenergic receptor; β2a-AR, beta 2 a adrenergic receptor; β3-AR, beta 3 adrenergic receptor; AD, Alzheimer's disease; PD, Parkinson's disease; GPCR, G protein coupled receptors; CNS, central nervous system; LC, locus coeruleus.

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1. Introduction

G protein coupled receptors (GPCRs) are of crucial importance in modern pharmacotherapies and neurosciences, a fact explained by the high amount of functions, diseases and disorders that involve GPCRs or their linked pathways including enzymes, second messengers (Barreda-Gómez et al., 2005, 2014; Duttlinger et al., 2003; Ghanemi and Hu, 2014; Hibert et al., 1994; Hofmann et al., 2013; Lin et al., 2011; Moser and Klose, 1993; Shen et al., 2013; Tofighi et al., 2012; Wirz et al., 2005) which, all, constitute potential targets in pharmacology and also in experimental biology to modify, stimulate or inhibit the signal transduction with or without the receptors activation. Therefore, investigating the properties of the GPCRs will without doubt lead to more advances towards clinical applications. Classified among GPCRs, adrenergic receptors constitute promising pharmacological targets. By "Adrenergic system" we refer to the adrenergic receptors, adrenaline, noradrenaline, in addition to the enzymes and messengers of the pathways related to the signal transduction after the receptors bind to the adrenaline, noradrenalin or a pharmakon. Herein, we briefly illustrate some concepts on how to go from the description of the physiological properties and the pathophysiological roles that have been described by recent publications to a variety of pharmacologic implications and therapeutic applications via applying those new concepts toward finding out new treatments. Importantly, data related to the physiological and pathological implication of the adrenergic receptors supported by structural analytic approaches (Leioatts et al., 2014; Nguyen et al., 2014; Weichert et al., 2014; Zhu et al., 2014) will lead to the definition of new compounds (candidates) for the drug screening. Indeed, the adrenergic receptors structures has similarities with the other GPCRs (Shukla et al., 2014) which make extrapolating some data from some other GPCR, such as pharmacogenetics (Thompson et al., 2014) and signal transmission (Zalewska et al., 2014), a source of details about the structures of the receptors. Furthermore, compounds deriving from the chemical synthesis constitute strong elements toward further pharmakon development.

2. Overview of the central adrenergic system

The adrenergic system, due to the diverse roles it plays in neurophysiology, represents a very important part of the nervous system. Thus, the neuropharmacology of the adrenergic system is promising. The two adrenergic neurotransmitters, adrenaline and noradrenaline (NA), act on both subtypes α (alpha) adrenergic receptor (a-AR) and β (beta) adrenergic receptor (β-AR) and govern a variety of functions (Bylund, 2013). Indeed, whereas both neurotransmitters regulate cell differentiation in the developing brain (Berger-Sweeney and Hohmann, 1997; Lauder, 1993; Lidow and Rakic, 1995; Lipton and Kater, 1989), NA is involved in developmental processes (Felten et al., 1982; Parnavelas and Blue, 1982; Sanders et al., 2008) and nervous system development regulation (Landis, 1990; Lauder, 1993; Lipton and Kater, 1989; Whitaker-Azmitia, 1991) particularly in the cortex (Blue and Parnavelas, 1982; Loeb et al., 1987; Maeda et al., 1974; Wendlandt et al., 1977). More importantly, NA directs a2-AR development (Landis, 1990; Lauder, 1993; Lipton and Kater, 1989; Whitaker-Azmitia, 1991) which confirms adrenergic receptors' (ARs) involvement in brain development (Blue and Parnavelas, 1982; Rowe et al., 1993; Soto-Moyano et al., 1994). Additionally, a2A-ARs were linked to neuronal differentiation, growth and neurotrophy of the developing brain (Bylund, 1988). Furthermore, a2A-ARs involve Protein kinase A (Chadzinska et al., 2012a) that regulates microtubule-associated protein 2 (MAP2) which mediates dendrite growth of cortical neurons (Song et al., 2004). Also, a2-ARs play an important role in the maturation of dendritic spines within the medial prefrontal cortex (mPFC) (Ren et al., 2012). In addition to evidences concerning the age-related differences, novel a2-AR properties became know. a2-AR expression periods within the white matter show the role of a2-AR in brain development. Indeed, after a2-ARs are highly expressed in the developing brain of rat they disappear in adulthood (Sanders et al., 2005). Further neurotrophic properties have also been attributed to β2-ARs. β2-ARs activation by clenbuterol is among the properties than could be exploited in further drug development. This results, in the rat brain, in the synthesis of three growth factors; nerve growth factors (NGF), basic fibroblast growth factor (bFGF) and transforming growth factor-beta 1 (TGF-b1) (Culmsee et al., 1999; Follesa and Mocchetti, 1993). Therefore, support the important role the adrenergic system plays during brain development indicated also by other publications and thus, such elements highlight the possible pharmacological exploitation of such properties in neurodegenerative diseases treatment. Indeed, numerous publications have indicated that for neuropathologic disorders including AD, PD, epilepsy, brain trauma and stroke, therapies aiming to enhance the synthesis of endogenous growth factors could provide novel therapeutic arsenals to treat such disorders (Carswell, 1993; Semkova and Krieglstein, 1999), especially that agents that interact with β-AR are interesting including propranolol, a non-specific β-ARs antagonist that could prevent some memory impairment (Debiec and Ledoux, 2004; Ferry and McGaugh, 2000), whereas β-ARs agonists constitute cognitive enhancing molecules (Ferry and McGaugh, 1999; Friedman et al., 1999; Gibbs and Summers, 2000; LaLumiere et al., 2003; Zarrindast et al., 2004) and regulators of both amyloid and neurotrophin production (Counts and Mufson, 2010) indicating further the role elements targeting the adrenergic system might have in memory loss that is seen in some neurodegenerative diseases.

The wide distribution of a2-ARs within the central nervous system (CNS) (Nicholas et al., 1993; Unnerstall et al., 1984; Wamsley et al., 1992) indicates the physiological importance they have in different brain regions. The cognitive functions constitute illustrative examples. Learning and memory have been linked to dendritic spine morphology (Kasai et al., 2003; Ren et al., 2012) and transplantation of norepinephrine neurons into aged rats improved certain types of learning paradigms (Collier et al., 1988). In addition, the prefrontal cortex (PFC) is linked to both behavior-related neurophysiology (Goldman-Rakic, 1996) and cognitive functions (Avery et al., 2000; Ramos and Arnsten, 2007). Furthermore, several papers have shown that improving memory and other cognitive functions can be obtained via a2-ARs stimulation in some species (Arnsten and Cai, 1993; Brennan and Arnsten, 2008; Franowicz et al., 2002; Ramos et al., 2006; Wang et al., 2007) including humans (Jakala et al., 1999). Moreover, a2-ARs appear to play a role in emotional memory (de Quervain et al., 2007). Importantly, within the amygdala and hippocampus, β-ARs have been linked to memory function processes (Bush et al., 2010; Gibbs and Summers, 2005; Murchison et al., 2011). Indeed, β-ARs are implicated in emotional memory (Cahill et al., 1996) and learning process (Roullet and Sara, 1998; Rutecki, 1995; Sternberg et al., 1985). β-AR expression in the hippocampus is well documented (Hillman et al., 2005). Furthermore, noradrenergic signaling through a1-AR has also been linked to behavioral effects (Smiałowska et al., 1994) and also prefrontal cortical function regulation (Ramos and Arnsten, 2007) which further illustrates a1-AR's implication in cognition and the possibility of its targeting in disease in which loss of cognitive functions is observed such as AD (Ghanemi, 2014a; Mufson et al., 2005).

On the other hand, ARs have been linked to some metabolic and cellular processes including glycogen formation, oxidative metabolism (stimulation of a2-ARs), glutamate uptake (a1-ARs stimulation), glycogenolysis and increased Na+, K+ ATPase activity (β- ARs activation) (Hertz et al., 2010). NA has also been shown to have anti-inflammatory properties (Dello Russo et al., 2004; Feinstein et al., 2002) which might turn out to be beneficial if therapeutically