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α_2-Adrenoceptor subtypes—Unexpected functions for receptors and ligands derived from gene-targeted mouse models

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Abstract

α_2-Adrenoceptors belong to the group of nine adrenoceptors which mediate the biological actions of the endogenous catecholamines adrenaline and noradrenaline. Studies with gene-targeted mice carrying deletions in the genes encoding α_{2A}-, α_{2B}- or α_{2C}-adrenoceptors have provided new insight into adrenergic receptor biology: (1) In principle, all three α_2-receptor subtypes may operate as presynaptic inhibitory feedback receptors to control the release of noradrenaline and adrenaline or other transmitters from neurons. (2) Pharmacological effects of non-selective α_2-ligands could be assigned to specific receptor subtypes, e.g. hypotension, sedation and analgesia are mediated via α_{2A}-receptors. (3) α_2-Adrenoceptor deficient mice have helped to uncover novel and unexpected functions of these receptor, e.g. feedback control of catecholamine release via α_{2C}-receptors in adrenal chromaffin cells and control of angiogenesis during embryonic development. (4) Additional pharmacological targets for α_2-adrenoceptor ligands were identified, e.g. inhibition of cardiac HCN2 and HCN4 pacemaker channels by clonidine.

Keywords: Adrenoceptors; Adrenaline; Noradrenaline; Gene-targeted mice

1. Introduction

α_2-Adrenoceptors were among the first G-protein-coupled receptors (GPCR) to be cloned (Kobilka et al., 1987). Since then, >800 GPCRs were identified in the human genome and in many other species (Vassilatis et al., 2003). For many endogenous ligands, a family of receptor subtypes has been found, which mediate a variety of biological effects. In the adrenergic system, the biological signals of the catecholamines noradrenaline and adrenaline are transmitted via nine different receptor subtypes. These receptors have been divided into three groups, including three α_1-subtypes (α_{1A}, α_{1B}, α_{1D}), three α_2-subtypes (α_{2A}, α_{2B}, α_{2C}) and three β-receptors (β_1, β_2, β_3) (Bylund et al., 1994). Due to the lack of ligands with sufficient subtype-selectivity, the physiological relevance of these subtypes has not been fully resolved. Gene-targeted mouse models have greatly helped to identify subtype-specific functions for all adrenoceptor subtypes. In this short review, primarily data derived from targeted deletions of α_2-adrenoceptor genes will be discussed. For detailed reviews and further insight, the reader is referred to more detailed review articles on this topic (Hein, 2006; Scheinin et al., 2001).

2. The first decade of adrenoceptor knockout models

Mice with targeted deletions of the α_2-adrenoceptor genes were the first animal models lacking functional adrenoceptors. Deletion of the α_{2C}-receptor gene in mice has been reported in 1995 (Link et al., 1995), which was followed by α_{2B}- and α_{2A}-deficient mouse models in 1996 (Link et al., 1996) and 1999 (Altman et al., 1999; Hein et al., 1999), respectively. Using gene targeting, also ‘‘a knock-in’’ model with a point mutation in the α_{2A}-receptor gene (α_{2A}-D79N) has been generated (MacMillan et al., 1996). Initially, these mouse models were used to address two major questions: (1) which α_2-adrenoceptor subtype is the main presynaptic feedback regulator and

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(2) which subtypes mediate the known pharmacological effects of α_2-agonists?

α_2-Adrenoceptors were first proposed as presynaptic feedback inhibitors of neurotransmitter release (for reviews, see Langer, 1997; Starke, 2001). Since then, presynaptic receptors were termed "autoreceptors" if stimulated by neurotransmitter released from the same neuron. Presynaptic receptors which were activated by transmitters from neighbouring neurons were termed "heteroreceptors". Surprisingly, all three α_2-adrenoceptor subtypes contributed to presynaptic feedback inhibition of noradrenaline release from adrenergic neurons *in vitro* (Fig. 1; Trendelenburg et al., 2003). However, differences between the three α_2-subtypes and between tissues were identified. Similar to pharmacological predictions, the α_{2A}-subtype was found to be the main inhibitory presynaptic feedback receptor (Altman et al., 1999; Hein et al., 1999; Trendelenburg et al., 2003; Vonend et al., 2007). In addition to the α_{2A}-subtype, α_{2C} participated in presynaptic regulation in the central nervous system, whereas all three α_2-receptor subtypes served as feedback regulators in peripheral tissues which are innervated by sympathetic nerves (Fig. 1; Trendelenburg et al., 2003). α_{2A} and α_{2C} served as heteroreceptors to inhibit the release of dopamine an serotonin in the central nervous system (Bücheler et al., 2002; Scheibner et al., 2001a). Presynaptic inhibitory α_2-receptor subtypes may not be completely redundant in their function. In cardiac atria, α_{2A} and α_{2C} operated optimal at different frequencies of sympathetic nerve stimulation (Hein et al., 1999; Scheibner et al., 2001b).

3. Pharmacological relevance of α_2-adrenoceptor subtypes

α_{2A}-Adrenoceptors were identified as the main presynaptic inhibitory feedback receptors controlling exocytosis from adrenergic neurons (Altman et al., 1999). Thus the genetic deletion of the gene encoding α_{2A}-receptors led to increased blood pressure, heart rate and susceptibility to develop cardiac hypertrophy and failure (Brede et al., 2002; Brum et al., 2002; Hein et al., 1999; Makaritsis et al., 1999a). Interestingly, the antihypertensive and bradycardic effects of the α_2-agonists clonidine, dexmedetomidine, moxonidine and rilmenidine, were entirely dependent on the α_{2A}-receptor subtype (Altman et al., 1999; MacMillan et al., 1996; Zhu et al., 1999). Moreover, α_{2A}-receptors were required for baroreflex control (Niederhoffer et al., 2004) as well as for the hypnotic, analgesic, seizure-modulating and platelet aggregating effects of α_2-agonists (Fig. 1; Lakhlani et al., 1997; Fairbanks and Wilcox, 1999; Janumpalli et al., 1998; Pozgajova et al., 2006; Szot et al., 2004).

α_{2B}-Adrenoceptors serve functions in peripheral tissues as well as in the central nervous system. In the cardiovascular system, activation of α_{2B} elicited a transient hypertensive response (Link et al., 1996; Paris et al., 2003) and they participated in the development of chronic salt-dependent hypertension after nephrectomy (Makaritsis et al., 1999b). In the spinal cord, α_{2B}-receptors were identified as essential components of descending noradrenergic neurons mediating the analgesic effect of nitrous oxide (Fig. 1; Sawamura et al., 2000).

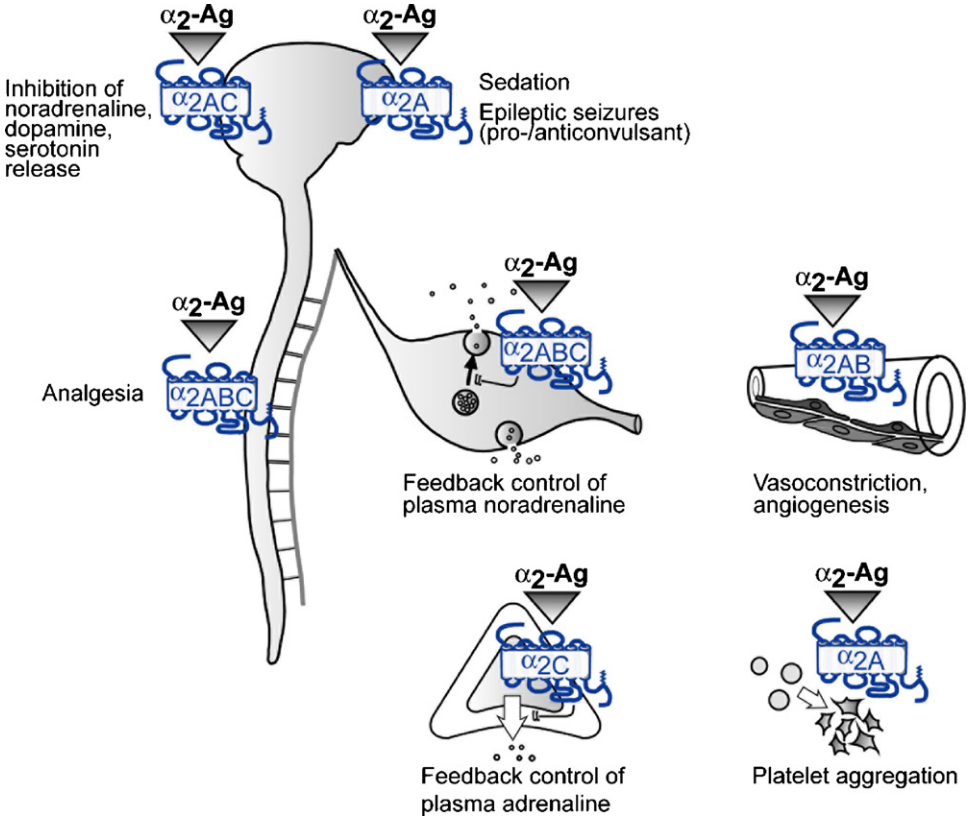

Fig. 1. Overview of subtype-specific functions of α_2-adrenoceptor subtypes derived from gene-targeted mouse models. *Abbreviations*: α_2-Ag, α_2-agonist; α_{2A}, α_{2B}, α_{2C}, α_2-adrenoceptor subtypes. For references, see text.