sciendo Acta Marisiensis - Seria Medica 2022;68(4):145-149 DOI: 10.2478/amma-2022-0030

REVIEW

Alpha adrenergic receptors in clinical practice – Present and future

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In this review we discuss the adrenergic pathways for alpha 1 and alpha 2 receptors and the current as well as potential future medication targeting these receptors. Overall, there is ongoing research into a multitude of directions with a promising outlook for alpha 1 and alpha 2 adrenergic receptors. The alpha 1-adrenergic receptor subfamily is currently modulating only a modest number of nervous system functions due the fact, that only a relatively small number of selective commercial products are available. Chronic stress can affect the long-term depression of alpha 1 receptors. Recent studies are searching for new molecular targets which might act on these receptors. Presynaptic alpha 2 receptors play an important role in modulating release of several neurotransmitters in the central nervous system. The future of alpha 2 adrenergic receptors in clinical practice looks even more promising and versatile than that of alpha 1 adrenergic receptors. Alpha 2 adrenergic receptors show different responses, especially regarding hypertension and heart failure treatment, and current research suggests a genetic component as a cause, which is being explored further.

Keywords: alpha adrenergic receptors, molecular target, immunity, noradrenaline, pharmacotherapy

Received 28 November 2022 / Accepted 7 December 2022

Introduction

Pharmacological research is in continuous development; yet a new therapy does not necessarily require a new target. Adrenergic receptors (AR) and synapse related transporter mechanisms have been well studied and deeply understood, but new options regarding these pharmacological targets are under way [1].

The concept of adrenergic receptors was first introduced by Raymond Ahlquist in 1948 [2]. Based on our recent knowledge, two α and one β receptor families exist with a total of nine subtypes: α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, and β3. Subtypes show similar binding affinities but have different physiological effects for the same endogenous catecholamines [2].

Pharmacotherapy is using a modest number of selective agonists and antagonists and a larger number of substances are involved in research activities. Each of the nine different subtypes are expressed in different regions of the nervous system and they are now constituting direct and indirect drug targets [2].

In this review we will discuss the adrenergic pathways for α -1 and α -2 receptors and the current as well as potential future medication targeting these receptors.

Adrenergic pathways

Locus coeruleus is the originating area for the norepinephrinergic system and from here diffuse norepinephrinergic projections emerge to innervate the hippocampus, spinal cord, prefrontal cortex, cerebellum, thalamus, cortex, and amygdala [3]. The norepinephrinergic system via the α -adrenergic receptors is involved in a number of functions of the nervous system: learning and memory [4], depression, anxiety, sleep, and motor activity [5]. The most important clinical uses for α-adrenergic receptors involve the central nervous system. The pathophysiological basis of Parkinson's disease, Alzheimer's disease, depressive disorders, stress, ADHD relies of disruption of functions [6].

Alpha-adrenergic receptors

Alpha 1-adrenergic receptors

Excitatory and inhibitory functions can both be caused by α1-adrenergic receptors through pre- and postsynaptic mechanisms of action, which can involve protein kinase C, phospholipase C or calcium [7]. The latter two are also involved in presynaptic inhibitory effects. Glutamate and/or acetylcholine release can be stimulated by presynaptic α1-adrenergic receptors, leading finally to an increase of their excitatory effect [8]. On the other hand, many γ-Aminobutyric acid (GABA)-pathways are also modulated by α1-adrenergic receptors [9]. More recently, it has been established that α1-adrenergic receptors can influence non-neuronal transmission as well [10].

The α -1-adrenergic receptor subfamily is currently modulating only a modest number of nervous system functions due the fact, that only a relatively small number of selective commercial products are available [11].

Alpha 1-adrenergic receptors – therapeutic potential

The main indication for α -1 adrenergic receptor blockers is still arterial hypertension, benign prostatic hyperplasia (prazosin, doxazosin, etc.), and in cases of pheochromocytomas if needed (phenoxybenzamine, phentolamine) [12]. While often not as effective as other hypertensive drugs they are still used for mild to moderate hypertension, especially in benign prostatic hyperplasia patients. Prazosin, in

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addition, is used in the treatment of post-traumatic stress disorder (PTSD). By blocking α -1 AR in the prefrontal cortex it blocks the actions of the increased levels of noradrenaline which are found in PTSD patients [13].

Since the norepinephrine system influences the serotonin system through the α receptors, serotonin reuptake inhibitors (SRIs) and triple reuptake inhibitors (TRIs) will be mentioned here. While still not fully understood it is thought that the monoaminergic transmission plays an important role in the pathophysiology of depressive disorders. This involves not only dopamine and serotonin, but also norepinephrine. Serotonin and norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine are therefore used in depression but also in chronic pain associated with fibromyalgia and diabetic peripheral neuropathy. These drugs have been in use since the 1990s already [14] but current research continues in the direction of TRIs which will be mentioned later.

Tricyclic antidepressants such as imipramine and amitriptyline also block serotonin and norepinephrine reuptake and therefore help in the treatment of depression, similar to SNRIs, their use is discouraged in clinical practice due to their high side effect profile and the availability of better treatment options [15]. Monoamine oxidase inhibitors (MAOIs) such as phenelzine and tranylcypromine - introduced after Hugh Blascho's work in Oxford around 1960 - were formerly used as antidepressants as well but the strict dietary restrictions for the patient kept patient compliance low [16,17]. Today, the MAO-A selective inhibitor moclobemide is used in clinical practice.

For reasons of completeness, α -1 agonists midodrine (for orthostatic hypotension), naphazoline (for nasal mucosa and ocular vasoconstriction), phenylephrine (for nasal congestion, hypotension) and xylometazoline (for mucosal congestion) can be mentioned as well [18].

Future perspectives

Chronic stress and depression seem to be side effects of our modern way of living, inducing the long-term depression of α1-ARs which ultimately decreases synaptic strength and plasticity in the dorsal raphe nucleus. With its increased incidence rate the search for better treatment options, pharmacological or otherwise, continues. This shows that stress itself can influence the adrenergic system and might make it a potential future target to battle chronic stress induced negative effects [19]. As mentioned before, research towards triple reuptake inhibitors continues as well. By influencing the norepinephrine system, the serotonin system is indirectly influenced as well, through α1 receptors; this in part may be a reason for TRIs potential effectiveness. New tetrazoles have been found that can achieve triple monoamine neurotransmitter reuptake inhibition. Dopamine is included, as it is believed to be a strategy to develop not only more effective but also safer medication for use in depression [20]. Safety is a big issue, the main downside with TRIs being the high side effect profile caused by the wide blockage. Due to this, researchers are trying to find new molecular targets which might either improve TRIs or identify the need for a new drug altogether [21].

For future developments of potential α1 adrenergic medication it should be kept in mind that α -receptors are involved in the modulation of a variety of other neurotransmitters. In the ventral tegmental area, which is involved in motivation and reward, for example, presynaptic α1-Rs modulate the release of GABA for ventral tegmental area dopaminergic neurons [22]. This increases possible effects of α 1 adrenergic medication.

Besides the fairly well-known involvement of adrenergic receptors in neurotransmitter release, there have been new findings showing involvement also in the immune system: muscarinic, nicotinic and adrenergic receptors can all be found on immune cells [10]. Additionally, neurotransmitter release can also adjust innate, as well as adaptive immune responses by up-or downregulating inflammatory pathways. When adrenergic receptors located on immune cells are activated, it can regulate its development, proliferation, circulation in the body and recruitment. AR stimulation is also involved in cytokine production and therefore cell-to-cell contacts [10]. Sepsis, a commonly feared complication in hospital settings, could potentially be treated by adjustments in the adrenergic system according to a study performed in 2004 [23]. Further research is required though because AR stimulation effects depend on a multitude of factors that need to be explored more. This includes factors such as the pattern of the AR expression on the immune cell, neurotransmitter concentration and also the age of the patient [24].

Alpha 2-adrenergic receptors

The presynaptic α2 receptors were first described by Klaus Starke in the eighties [25]. From the total of nine adrenergic-receptor subtypes, three belong to the α2-adrenergic receptors: α2A, α2B, α2C. These show similar binding affinities and signaling selectivity is achieved in both temporal and spatial environment and play an important role in modulating release of several neurotransmitters in the central nervous system [26].

The primary α2-adrenergic receptor subtypes which are involved in central nervous system function are α2A- and α2C-adrenoceptors. The α2-adrenergic receptors exhibit presynaptic and postsynaptic activities [27]. The presynaptic α2-adrenergic auto-receptor's major role is in the negative feed-back in the synthesis and release of catecholamines, while the presynaptic hetero-receptors have been implicated in the regulation of the synthesis and release of dopamine, serotonin, and glutamate. The stimulation of postsynaptic α2-adrenergic-receptors will have effect on neuronal excitability modulation, through the direct effect on potassium channels and indirect effect on hyperpolarization-activated channels [28].

Alpha 2-adrenergic receptors – therapeutic potential

The most commonly known α2 adrenoreceptor agonists are clonidine and the indirectly acting methyldopa. Both can be used in the treatment of hypertension. In antihypertensive therapy in pregnancy, methyldopa is still a first-line agent. Clonidine is not used in mainstay treatment of hypertension anymore but is used in hypertensive crisis, as well as ADHD and opioid and alcohol withdrawal [18]. In case of hyperreactivity syndromes the mechanism by which clonidine plays a beneficiary role is related to stimulation of alpha-2 adrenoceptors in the brain stem activating inhibitory neurons, resulting in reduced sympathetic outflow from the central nervous system. Lofexidine, a structural analogue to clonidine, has been approved for mitigation of opioid withdrawal symptoms by the Food and Drug Administration (FDA) in 2018 (although it had been used in the UK since 1992); the advantage being a much better side effect profile than with clonidine [29]. Guanfacine can also be used in ADHD and hypertensive treatment, but while it is still FDA approved, it is rarely used clinically. Dexmedetomidine, mainly used for sedation in anesthesiology, brimonidine (glaucoma) and tizanidine (spasticity treatment) are α2 agonists with increasing importance [18].

Future perspectives

The future of α2 AR in clinical practice looks even more promising and versatile than that of α1 AR. Severe pain for patients can be caused by gastrointestinal inflammation, coupled with nausea and potential vomiting. New drug targets to battle this inflammation include 5-hydroxytryptamine (5-HT) and glutamate, but also α2 ARs [30]. Gastric and colorectal inflammation causes distension that triggers nociceptive signals. These signals can be inhibited by activating pre-synaptic α2 AR on sensory nerve terminals. This inhibition is normally done by noradrenaline but clonidine and dexmedetomidine have a similar action, when administered intrathecally [30]. As mentioned before, clonidine and lofexidine are used in opioid withdrawal, working through their anti-adrenergic effect in locus coeruleus neurons. A study showed that while side effects are increased, α2 agonists might be the better treatment choice when the goal is opioid dose reduction compared to opioid discontinuation. α2 agonists can also be administered if buprenorphine, which is far superior in opioid withdrawal control, is ineffective [29]. Additionally, due to their sedative, analgesic and also opioid-sparing effects, α2 adrenergic agonists can be administered during surgery or postoperatively not only to reduce the postoperative pain but also decrease opioid consumption. While a meta-analysis from 2020 had trouble to increase the evidence of this, they are still suggesting further large randomized controlled studies for the problem [31].

Another major area of investigation is pain management. Dexmedetomidine, so far used for sedation and mainstay treatment for anesthesia in animals, has shown to have also analgesic effects. By mixing it with local anesthetics, the effectiveness of the anesthetics is greatly improved. Unfortunately, clinical trials for chronic pain and hyperalgesia are still missing [32,33]. The advantage of dexmedetomidine is no respiratory suppression and no effect on carbon dioxide clearance. When compared with propofol and benzodiazepines, the mainly used sedatives, dexmedetomidine shows less days that the patient has to stay in the intensive care unit due to delirium or coma [32]. The main reason why dexmedetomidine is not used as much clinically is the fact that a lot of clinicians don't know about it according to the paper by Spieth et al. [32].

Immunity

The main two systems involved in immune responses are the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system (SNS). Sympathetic innervation is found widely in the human body, including lymphoid tissues such as bone marrow and thymus. The actual effects of the SNS in immune responses are not well understood, and little is known for example about its effect on "hematopoiesis, thymocyte development, and mucosal immunity" [34].

A large variety of immune cells have adrenergic lymphocyte receptors, including macrophages, monocytes, dendritic cells, natural killer cells, and T & B lymphocytes, therefore adrenergic drugs are considered potential modifiers of these cells and their action in the immune system. While β-2 AR are considered the dominant adrenergic receptor type on immune cells, α receptors are not excluded [35,36,37]. Primary and secondary lymphoid organs are innervated by nerves releasing neurotransmitters such as norepinephrine [35]. The lymphocytes, having adrenergic receptors, are then exposed to norepinephrine in the blood or tissue, or, when entering the central nervous system (CNS) at the neurotransmitter release sites of the neurons [38]. α2 AR agonists and antagonists are currently under investigation for use in autoimmune diseases, like inflammatory bowel disease, irritative colon, systemic lupus erythematosus; fibromyalgia and chronic fatigue syndrome [34].

Following renal injury, norepinephrine release spikes due to sympathetic stimulation by the CNS. Norepinephrine mediates the fibrosis and further loss of kidney function. Interestingly, α2-AR inhibition might inhibit this fibrogenesis and is therefore implicated in multiple kidney diseases, including chronic kidney disease. α2-AR antagonist might become an important tool in clinical scenarios involving fibrogenic response in the kidney, and maybe even in liver, lung and heart [39]. Overreactive sympathetic stimulation is also the basis of sepsis and α2 agonists can influence "inflammatory regulation, coagulopathy, dynamic flow, as well as vascular responsiveness and integrity". While they remain controversial and cannot be used reliably yet, their use in sepsis is still considered further [40, 41].

The direction of new research does not only continue towards new medication and sub-targets, but also towards optimizing existing therapy methods. α2-AR show different responses, especially regarding hypertension and heart failure treatment, and current research suggests this is due to a genetic component which is being explored further. One study goes as far as linking nucleotide polymorphisms of α2-AR to increased heart failure in black patients [42].

Discussion

Compounds influencing α-AR has kept its place in clinical medicine since its discovery for good reasons. While the applications are rather narrow now and are mostly focused on depression, hypertension, benign prostatic hyperplasia and few others, the potential is much larger. Research continues into lots of different areas of clinical practice and seems promising. One of the major disadvantages with AR targeting medication being the wide array of side effects that needs to be mitigated or "worth the risk".

Acknowledgments

This work was supported by the George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, Research Grant number NR. 224/4.

Authors' contribution

PL - Identification of the subject for the review, Identification of search key words, Performing the systematic literature research, Selecting studies to be included, Data-charting, Summarizing the results, Reporting discussion and conclusion.

EGB - Identification of the subject for the review, Identification of search key words, Selecting studies to be included, Reporting discussion and conclusion.

Conflict of interest

None to declare.

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