Case Report

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Role Of Presynaptic Alfa Receptors.

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INTRODUCTION

This review provides a comprehensive overview of what is known so far about the role of presynaptic receptors and transporters in the mode of action of some drugs used in medical practice. We will try to provide a synopsis of the pharmacological substances approved to be utilized with a mechanism of action on the presynaptic alpha-receptors as well as the presynaptic modulation of catecholamines via the uptake mechanism.

Adrenergic effect on the alpha receptors is different according to the type of receptor: alpha-1 or alpha-2, respectively also by the fact if we exert effect on presynaptic or postsynaptic subtype of the receptor. Beside that we can induce agonistic or antagonistic effect [1] [2].

We examined the different types of alpha receptors and the active substances that can act on these receptors and modify the physiological response in order to achieve a clinico-therapeutic effect.

Both alpha-receptor subtypes are G-protein linked, although alpha-1 causes an effect via Gq-protein, while alpha-2 performs his inhibitory effect via Gi-protein. Both mechanisms of action can be observed in the pre- and postsynaptic functioning of the receptors [3].

ADRENERG A1- AND A2-RECEPTOR AGONISTS

Many catecholamines, including epinephrine and norepinephrine, bind to alpha-1 receptors. Hypoperfusion which associates decreased cardiac output or decreased vascular resistance will stimulate alpha-1receptors, making them point of attack for many different drugs in the therapy of shock, cardiopulmonary resuscitation and acute heart failure [14-16].

Approved mechanisms of action of the alpha1-adrenergic receptors

Among the FDA-approved indications for alpha-1 agonists there are a wide variety of uses, such as midodrine, an oral agent used to treat symptomatic orthostatic hypotension. naphazoline / naphazoline-pheniramine, which is applied topically, causes vasoconstriction of the eye and relieves eye redness or itching when combined with pheniramine [7].

The presynaptic effects of alpha-1 receptors can be observed in the CNS, where they participate in the neuromodulation. Norepinephrine, the main ligand of these receptors, is involved in stress, arousal and attention control. It's dysfunction is contributing therefore to the pathomechanism of depression, ADHD, schizophrenia and also addictive syndromes. Approved medications with action on alpha-1 receptors have an effect on these presynaptically localized receptors: for example the antihypertensive prazosin is modulating DA release and behavioral responses to drugs of abuse [8].

Approved mechanisms of action of the alpha2-adrenergic receptors

Contrary to the mainly postsynaptic positioned alfa1 receptors, the alfa2 are presynapticly situated. Their stimulators, clonidine and guanfacine are recommended for the treatment of attention deficit - hyperactivity disorder (ADHD) as monotherapy or combinations[8]. They are also effective for neuropathic pain and less effective (or possibly ineffective) for somatic or visceral pain [9] [10]. Methyldopa is also implicated in the treatment of hypertension (also not as a first-line drug), but it is of particular importance in pregnancy, if used with care, as it can cause a positive Coombs test [10].

Other substances approved to be used and acting on the alpha-2 presynaptic receptors are as example: brimonidine with indication as a topical treatment for persistent erythema rosacea in adults; lofexidine used for the treatment of opioid withdrawal syndrome, mitigating symptoms and facilitating abrupt discontinuation of opioids in adults [11] and tizanidine used in the treatment of spasticity with a short half-life, so its use should be reserved for daily activities and times when spasticity relief is essential [12].

Novel drug dexmedetomidine is already approved for clinical use but it is also a subject for several clinical trials. Provides sedation of initially intubated and mechanically ventilated patients during treatment in intensive care units [13].

The Annals of Internal Medicine (ISSN 3064-6650)

Alpha-adrenergic agonist mechanisms of action under current research

Although autonomous nervous system is widely studied and provided already a vast amount of pharmacological possibilities that does not mean that there are no further options for research and discovery of new points of attack. The alfa1 agonist midodrine is an already approved substance for medical use, and it is currently under research because it is showing beneficial effects in different types of volemic disturbances, such non-azotemic hepatic cirrhosis and prevention of hypotension which can occur during spinal anesthesia [14].

Alpha-2 adrenergic presynaptic receptors represents an interest for current research since we have several ongoing trials regarding it [15]. The already mentioned dexmedetomidine is a lipophilic α2 receptor agonist with alfa2 selectivity is 8 times higher thant of clonidine [15], having sedative and analgesic properties. In previous reports, this drug improved smoothness of postoperative recovery and reduces intraoperatory inflammatory responses. There are trials regarding the effect of this substance for use in different types of surgical interventions, mechanical ventilation, alcohol abuser withdrawal syndrome and also postpartum sedation[16].

ADRENERGIC A1- AND A2-RECEPTOR ANTAGONISTS

Alpha antagonists (known colloquially as alpha blockers) already have many clinical indications. They act on the peripheral vasculature causing vasodilation and lowering of blood pressure. Some of them are used primarily in the treatment of resistant hypertension and urinary retention [17]. Alpha blockers are also important in the preoperative care of pheochromocytoma. They are also used off-label for the treatment of post-traumatic stress disorder (PTSD) [18-21].

Approved mechanisms of action of the alpha1-adrenergic receptor antagonists

The alfa1 selective alfuzosin, tamsulosin, doxazosin, terazosin and silodosin are oral agents indicated in the treatment for signs and symptoms of benign prostatic hyperplasia (BPH) and in the expulsion therapy for distal ureteral calculi [22].

Approved mechanisms of action of the alpha2-adrenergic receptor antagonists

Due to their different synaptic localization and function, alfa2 antagonists are quite different as compared to alfa1 blockers. Mianserin and mirtazapine belong to the class of NaSSA antidepressants and are used especially in the treatment of mood disorders: bipolar affective disorder and schizoaffective disorders. Mirtazapine shows α2-blocking, antiserotonergic, and antihistaminergic activity. It is a potent antagonist or inverse agonist of α2A, α2B and α2C adrenergic receptors, 5-HT2A, 5-HT2C and 5-HT3 serotonin receptors, and histamine H1 receptors. Both mianserin and mirtazapine have a strong antidepressant effect and beside that they present efficacy in anxiety syndromes, appetite-stimulating effect and can be used in the therapy of nausea, vomiting and itching syndromes [23].

Alpha-adrenergic antagonist mechanisms of action under current research

the therapy of type-1 diabetes the neuronal and hormonal sympathetic output can lead to insulin-induced hypoglycaemia. This effect is related to epinephrine. The counterregulatory glucose responses induced by the administration of the α-adrenergic blocker phentolamine to the response of transplanted islet cells to hypoglycemia are critical to understanding the mechanism of protection against hypoglycemia provided by intrahepatic transplants. This hypothesis is based on the neuronal alpha-1 adrenergic blockade is abolishing [24].

SUMMARY

In the brain, alfa-1 receptors can be situated both presynaptic or postsynaptic. The already existing drugs, which have stimulator or inhibitor effect on this receptors are widely used, The presynaptic alfa-2 agonist are also widespread, with a broad range of usefulness (from serious hypertension to heroin addiction), and we can see also a lot of ongoing trials which target this presynaptic structure.

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The Annals of Internal Medicine (ISSN 3064-6650)

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The Annals of Internal Medicine (ISSN 3064-6650)

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