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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Title: Novel Analgesic Potential of ß2-Agonists for Neuropathic Pain via ß2-Agonist Action

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Abstract

Purpose of Review Multimodal therapies are often employed to treat chronic pain, and ß2-agonists are a potential drug class that shows promise. The primary aim of this paper is to discuss the role of ß2-agonists as an adjunctive therapy for chronic pain based on the current literature.

Recent Findings Recent studies in mouse models have shown that the ß2-adrenergic system plays an essential role in the analgesic properties of antidepressant drugs used to treat neuropathic pain and that the adrenergic relies on an intact endogenous opioid system to be effective. Studies also show that ß2-agonism alone is adequate to exert anti-allodynic effects in a mouse model.

Summary This paper summarized the basic physiology and pharmacology of the sympathetic nervous system and specifically the ß2-adrenergic system and summarized current literature in its involvement in the treatment of chronic neuropathic pain.

Keywords ß2-Agonist Analgesia · Chronic Pain · Neuropathic Pain

Introduction

Pain is a major healthcare concern. In 2020, the International Association for the Study of Pain (IASP) redefined pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [1]." *Acute* pain is initiated by tissue damage activating nociceptive receptors to elicit a physiologic response. In contrast, c*hronic* pain includes factors which are remote from the inciting cause, extend for a prolonged duration of time, and may have underlying pathology that does not fully explain the extent of the painful response [2]. Because of its prolonged duration, chronic pain causes many patients to seek medical care. In fact, studies in both the USA and abroad have shown that pain is one of the most common symptoms for patients to seek medical care [3, 4].

According to 2016 data from the Centers for Disease Control and Prevention (CDC), an estimated 50 million (20.4%) of the US adults had chronic pain [5•]. Given the high prevalence of chronic pain and increasing prevalence associated with advancing age, many treatment modalities have been developed to treat pain. These include cognitive behavioral therapy, holistic noninvasive approaches, pharmaceuticals, interventional procedures, and invasive surgeries [6–8].

Within the pharmaceutical class of therapies, a myriad of drug classes have been developed over the decades to relieve pain including non-steroidal anti-inflammatory drugs, opioid agonists, serotonin–norepinephrine reuptake inhibitors, and anticonvulsant drugs. Each class of drug has its own side effect profile. With more recognition of the opioid epidemic and the physical, psychological, and social harm associated with chronic opioid use and misuse, physicians who treat pain are turning toward other drug classes as adjunctive medications for the treatment of pain.

One class of drug that is starting to show promise for the treatment of pain, specifically neuropathic pain, is β2-agonists. Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory

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system [9]." Neuropathic pain may be characterized by paresthesias, allodynia, or thermal hypersensitivity, and treatment is often difficult [10]. The primary aim of this paper is to discuss the role of β2-agonists as an adjunctive therapy for pain. This paper will review the basic physiology of the sympathetic nervous system interactions with pain pathways and how β2-agonists interact with these pathways to modulate painful responses. Finally, this review will discuss the analgesic considerations when using these drugs for chronic pain as well as future considerations for research.

Physiology

The human nervous system is divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The PNS conducts information back to the CNS, which processes all types of stimulation and regulates mechanisms that produce painful responses. Organization of the PNS is further divided into the somatic and autonomic nervous system, and the autonomic nervous system (ANS) is itself divided into the parasympathetic (PSNS) and sympathetic (SNS) divisions. The ANS has been linked to many painful states, and the SNS has been shown to interact with many components of the pain pathway [11•]. Most preganglionic neurons in the ANS are cholinergic, meaning they release acetylcholine (Ach) as their neurotransmitter. Ach then binds to the nicotinic receptors of the postganglionic neurons. Postganglionic parasympathetic neurons release Ach which binds to muscarinic receptors in organs to exert a parasympathetic response. In contrast, norepinephrine (NE) is the neurotransmitter in the majority of sympathetic postganglionic nerves. The response to norepinephrine is mediated by either the α- or β-adrenergic receptors, and the response to norepinephrine depends on which effector organ is being stimulated. For example, norepinephrine binding to β-adrenergic receptors in myocardium will result in increased heart rate.

Pain that is dependent on sympathetic efferent activity is termed sympathetically maintained pain (SMP). By definition, SMP is relieved by sympathetic blockade or sympathectomy. The mechanisms by which sympathectomy leads to pain relief are through interruption of flow of nociceptive signaling to the CNS, improving ischemia by producing vasodilation, and by eliminating norepinephrine-mediated activation of nociceptors [2].

Pharmacology

There exists a host of pharmacologic agents that agonize or antagonize the adrenergic receptors that comprise the SNS. This paper focuses on ß-adrenergic receptors, specifically β2-adrenergic receptors. β-adrenergic receptors are G protein-coupled receptors, and are divided into β1, β2, and β3 subclasses. These receptors are coupled with adenylyl cyclase and G_s proteins, which create and use cyclic adenosine monophosphate as a second messenger after receptor activation. Epinephrine and NE activate these ß-adrenergic receptors to cause widespread effects across the entire body including increased heart rate, vasoconstriction, bronchial dilation, and more [12].

β-adrenergic antagonists such as propranolol have been used extensively as pharmacologic agents to treat or prevent painful conditions such as migraines or erythromelalgia [13, 14]. However, β-agonists have not traditionally been used as sole therapeutic options for pain conditions.

Analgesic Considerations

Rising rates of chronic pain in combination with the opioid epidemic has led to an increased need for opioid-sparing pain therapies [15, 16]. Multimodal analgesia with medications working via different but unopposed mechanisms is often necessary to treat chronic pain, as a single-agent regimen alone often is not sufficient [17]. As such, it is important to be aware of new adjunctive agents that may be helpful in alleviating pain.

Some existing pain medications utilize β-adrenergic agonism. Tramadol is an opioid analgesic which inhibits neuronal reuptake of serotonin and norepinephrine [18]. This part of Tramadol's mechanism of action resembles that of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), highlighting the role of the β-adrenergic system in pain pathways. Furthermore, Tramadol has structural similarities to Venlafaxine, another SNRI antidepressant [19].

Antidepressants are some of the best available treatments for neuropathic pain, and their mechanisms remain poorly understood [20, 21]. Studies in mice have shown that β2-adrenergic receptors are essential for the role of analgesia for Venlafaxine as well as Desipramine and Nortriptyline, both tricyclic antidepressants [22]. Chronic antidepressant treatment suppressed allodynia in wild-type mice but not mice that were β2-adrenergic receptor-deficient. In addition, the anti-allodynic response was blocked by injection of β2-antagonists, further suggesting a role for β2-agonism for analgesia [23]. Yalcin, *et. al*. found that chronic stimulation of β2-receptors in a mouse model with agonists such as clenbuterol, formoterol, metaproterenol, and procaterol suppressed neuropathic allodynia [24]. This effect was specific for β2-adrenergic receptors and not β1- nor β3-receptors. The study demonstrated not only that ß2-adrenergic receptors are essential for relieving neuropathic pain, but moreover that ß2-adrenergic stimulation alone was adequate for neuropathic pain relief [24].

Additional studies investigated whether opioid receptors were necessary for the anti-allodynic actions of β2-agonists. These studies found that chronic treatment with terbutaline or formoterol alleviated hypersensitivity which remained effective in μ- and κ-opioid receptor-deficient mice but not in δ-opioid receptor-deficient mice, suggesting that the analgesic effect of chronic β2-agonism is dependent on an endogenous opioid system, specifically the δ-opioid receptor [25••, 26].

There have been studies looking at the genetics of how polymorphisms or haplotypes of different β2-receptors can influence the risk of developing chronic pain in patients with painful diseases. Sickle cell disease is a severe disease associated with chronic pain, and the treatment of pain crises in patients with this disease is difficult. Research has shown that there are β2-adrenergic receptor polymorphisms associated with chronic pain in sickle cell disease and that β2-adrenergic receptors may be a target for potential pharmacologic therapies for relieving chronic pain in sickle cell patients [27]. Polymorphisms in other β2-receptors such as the ADRB2 adrenergic receptor have been shown to increase the risk of development of temporomandibular joint disorder, another chronic pain condition [28].

Future Considerations

Research on ß2-adrenergic agonists and pain relief has so far been limited to animal models. Human trials must be performed prior to any clinical application and further study is required to understand how this novel use of ß2-adrenergic agonists would best relieve pain. One area of potential research is to evaluate benefit from β2-adrenergic agonists in patients already taking a SNRI or TCA. Perhaps the β2-adrenergic system is already activated and further agonist activity may not provide any additional pain relief, but at this time, such studies have not been performed.

The safety of β2-adrenergic agonist use needs to be further studied in reference to pain. Classically, β2-agonists are used for the treatment of asthma and chronic obstructive pulmonary diseases but long-term therapy has been problematic. In patients with mild asthma, long-term treatment with salmeterol leads to tolerance just as opioids do [29, 30]. The Salmeterol Multicenter Research Trial (SMART) found a statistically significant increase in the number of respiratory- and asthma-related deaths in patients who had the addition of salmeterol to their medication regimen [31]. This study emphasizes the importance of studying the long-term effects of β2-agonists before physicians consider their use for chronic pain.

After establishing safety, the clinical feasibility of β2-adrenergic agonists must be determined. One study looked at the pharmacokinetics in healthy volunteers of formoterol, a highly potent β2-adrenergic receptor agonist and the same drug used in the mouse studies previously cited [32]. Formoterol had high plasma concentrations after inhalation with slow elimination, with a terminal half-life of about ten hours [32]. This predicted a sustained plasma concentration after twice daily dosing, with a high safety margin without any clinically significant consequences seen with β-receptor agonism such as tachycardia, hyperkalemia, or QTc interval prolongation [32].

Conclusions

Chronic pain, regardless of etiology, is widespread and is of significant medical and public health concern. The economic costs of chronic pain in the USA alone is estimated to be between $560 and $635 billion [33, 34]. Because of the high impact to the population, much research has gone into developing therapies for the treatment of pain. While opioids are efficacious in the treatment of pain, their overuse and misuses has led to high levels of morbidity and mortality [15, 16]. Because of this, there is a necessity to find different pharmacologic agents to augment, reduce, or replace opioid medications in the treatment of chronic pain. Multimodal analgesia is crucial, and novel pain medications will be welcome.

Many non-opioid drug classes currently exist for the treatment of chronic pain. Nonsteroidal anti-inflammatory medications, acetaminophen, various topical patches and creams, and supplements are available over the counter. Medications initially developed for other fields of medicine have been co-opted for pain control, and today, SNRIs, TCAs, gabapentinoids, and anticonvulsant medications are all commonly seen in chronic pain regimens. These medications are reinforced with various other therapies, ranging from mindfulness to invasive surgical techniques [35–37]. However, despite the wide array of available medications and therapies, chronic pain remains difficult to treat, and research into novel pain medications is necessary.

One such target is the sympathetic nervous system and, specifically, the β2-adrenergic receptor. The β2-adrenergic agonist class of medications has previously been used extensively to treat asthma and chronic obstructive pulmonary diseases [38], but their potential use for pain relief is only now being investigated. The current studies have shown that β2-adrenergic receptors are essential for the analgesic effect of SNRIs and that analgesia from β2-adrenergic agonism is mediated by the δ-opioid receptor [21, 25••, 26]. These studies show that β2-adrenergic receptor agonists may be potential targets for future drug therapies to treat chronic pain. However, questions remain regarding safety, clinical feasibility, and how this novel drug class would best be integrated into existing pain treatment regimens.

Declarations

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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