Neurobiology of Disease 85 (2016) 11–24

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

β_2-Adrenoceptor agonists as novel, safe and potentially effective therapies for Amyotrophic lateral sclerosis (ALS)

Raymond T. Bartus [a,*], Alexandre Bétourné [b], Anthony Basile [c], Bethany L. Peterson [b], Jonathan Glass [d], Nicholas M. Boulis [e]

[a] RTBioconsultants, Inc., San Diego, CA 92130, United States
[b] Above and Beyond, LLC, Atlanta, GA, United States
[c] Independent Consultant, Carlsbad, CA, United States
[d] Dept Neurology and Emory ALS Center, Emory University School of Medicine, Atlanta, GA, United States
[e] Dept Neurosurgery, Emory University School of Medicine, Atlanta, GA, United States

ARTICLE INFO

Article history:
Received 7 July 2015
Revised 25 September 2015
Accepted 8 October 2015
Available online xxxx

Keywords:
β_2-Adrenoceptor agonists
Repurposing drugs
ALS
Neuroprotection
Neurorestoration
Anabolic muscle effects
Neuromuscular junction
Motor neuron degeneration
Neuromuscular disease

ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a chronic and progressive neuromuscular disease for which no cure exists and better treatment options are desperately needed. We hypothesize that currently approved β_2-adrenoceptor agonists may effectively treat the symptoms and possibly slow the progression of ALS. Although β_2-agonists are primarily used to treat asthma, pharmacologic data from animal models of neuromuscular diseases suggest that these agents may have pharmacologic effects of benefit in treating ALS. These include inhibiting protein degradation, stimulating protein synthesis, inducing neurotrophic factor synthesis and release, positively modulating microglial and systemic immune function, maintaining the structural and functional integrity of motor endplates, and improving energy metabolism. Moreover, stimulation of β_2-adrenoceptors can activate a range of downstream signaling events in many different cell types that could account for the diverse array of effects of these agents. The evidence supporting the possible therapeutic benefits of β_2-agonists is briefly reviewed, followed by a more detailed review of clinical trials testing the efficacy of β-agonists in a variety of human neuromuscular maladies. The weight of evidence of the potential benefits from treating these diseases supports the hypothesis that β_2-agonists may be efficacious in ALS. Finally, ways to monitor and manage the side effects that may arise with chronic administration of β2-agonists are evaluated. In sum, effective, safe and orally-active β_2-agonists may provide a novel and convenient means to reduce the symptoms of ALS and possibly delay disease progression, affording a unique opportunity to repurpose these approved drugs for treating ALS, and rapidly transforming the management of this serious, unmet medical need.

Contents

* Corresponding author at: RTBioconsultants, Inc., 5442 Shannon Ridge Lane, San Diego, CA 92130, United States.
E-mail address: bartus@RTBioconsultants.com (R.T. Bartus).
Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2015.10.006

1. Introduction

Amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease) is a chronic, progressive neuromuscular disease that primarily involves a gradual loss of function and eventual death of motor neurons in the spinal cord and brain, as well as significant atrophy of the muscles they innervate. Clinically, ALS is characterized by stiff and/or twitching muscles and significant muscle weakness due to gradual muscle wasting, resulting in difficulty ambulating, speaking, swallowing, and eventually breathing. The average survival from diagnosis to death is three to four years, though about 10% of ALS patients may survive 10 years or more. There is no cure, with few treatment options currently available. Riluzole reportedly can extend life expectancy about two to three months and non-invasive ventilation may temporarily improve quality and length of life. For all these reasons, efforts continue to try to identify and develop more effective treatment options.

β-Adrenergic agonists share structural and pharmacological similarities with epinephrine. While these agents have been developed and approved primarily for the treatment of bronchial ailments such as asthma and COPD (chronic obstructive pulmonary disease), accumulating evidence demonstrates that their effects extend beyond smooth muscle relaxation and bronchodilation. Among the varied pharmacologic effects of β-agonists, they may enhance skeletal muscle structure and function, significantly increasing muscle repair, bulk and strength by stimulating protein synthesis and inhibiting protein degradation while significantly reducing body fat via the well-established 'repartitioning effect' (Lynch and Ryall, 2008). While these effects were initially exploited by the livestock industry, this use quickly expanded to include human body builders and strength-training athletes. In more recent years, experimental interest has further expanded to include clinical tests of β-agonists in the treatment of a wide range of muscle-wasting and neuromuscular diseases. These novel pharmacological effects, if induced safely and reliably in humans, might significantly improve the status of ALS patients by reducing the magnitude of symptoms and possibly slowing disease progression.

This paper reviews data collected from various animal models of muscle and neural degeneration that supports the use of β-agonists in treating these pathologies, and examines the signaling pathways induced by β_2-agonists that may be responsible for these effects. However, the major focus is a detailed review of nearly three dozen clinical publications reporting on the efficacy of β-agonists in a number of human neuromuscular disorders, including ALS. Collectively, these papers offer intriguing evidence supporting the hypothesis that β_2-agonists may be therapeutically valuable for treating ALS, as each of the diseases share one or more important pathologies with ALS. The review concludes with suggestions for monitoring and mitigating the potential side effects that may occur following chronic β_2-agonist administration, to help assure that the hypothetical risks might be acceptable relative to the anticipated benefits.

2. β_2-Adrenoceptors: multiple signaling pathways produce diverse pharmacologic benefits

There are two groups of adrenergic receptors, α and β, each composed of several subtypes ($\alpha_{1A,B,D}$, $\alpha_{2A,B,C}$; β_1, β_2 and β_3). Within skeletal muscles, α_1-adrenoceptors are primarily located on the vascular smooth muscle of arterioles, where they control blood flow through the skeletal muscle (Lynch and Ryall, 2008), but otherwise do not affect skeletal muscle function. In rodent skeletal muscles, β_2 adrenoceptors are the dominant subtype, accounting for 80–90% of the total adrenoceptor content. The other isoform found in this tissue is the β_1-subtype, accounting for the remaining 10–20% of total adrenoceptor content (Jensen et al., 1995; Kim et al., 1991). The β adrenoceptor population in human skeletal muscles is almost exclusively comprised of the β_2-subtype (Liggett et al., 1988), although the presence of low densities of β_3-adrenoceptors has been suggested (Chamberlain et al., 1999).

β_2-Adrenoceptors are widely expressed on neurons throughout the human central nervous system, particularly in the hippocampus, and the prefrontal, parietal, temporal and motor cortices (Joyce et al.,