Chapter 7
Role of Cannabinoids in the Regulation of Amyotrophic Lateral Sclerosis (ALS)

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a degenerative disease that manifests in older adults as a result of death of motor neurons. Incidence is 60-80% sporadic and 10-20% familial. The most common mutations are SOD-1, TARDBP, and FUS. Abnormal protein aggregation, inflammation, and dysfunction of RNA are seen. Tremors, dyslexia, and inability to walk progress to death. No cure is available to date. Medical cannabis may delay ALS progression by its neuroprotective, antioxidant, and anti-inflammatory properties. This chapter examines the effects of cannabinoids in ALS and discusses their mechanisms of action. Several psychoactive compounds like THC delay the progression and increase survival rates in a few animal models including the G93A mouse model. The binding of THC to CB receptors, CB1 and CB2, can reduce glutamate secretion thereby reducing excitotoxicity. Targetting CB1 and CB2 receptors with THC agonists could inhibit inflammatory responses, prevent oxidative damage, and reduce microglial activation. This study reviews the evidence for therapeutic effects of cannabinoids in ALS.

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INTRODUCTION

Amyotrophic refers to a disease in the lower motor neurons that causes muscle twitch and thinning, of muscle leading to weakness in the muscle. Lateral sclerosis denotes the stiff feeling in the spinal cord's lateral part due to glial cell damage and cell damage in the corticospinal area (Wijesekera & Nigel Leigh, 2009; Oskarsson et al., 2018). On a microscopic basis, axons and neurons are lost in the lateral and anterior parts of the spinal cord (Saberi et al., 2015; Owens, 2017). It is the third most common degenerative disorder (Hulisz, 2018; Gentile et al., 2021). ALS is a neural disorder due to the degeneration of the motor neurons in the lower and upper regions, followed by damage to glial cells. Typical areas of cell damage are in the spinal cord, brain stem, and motor cortex. The reason behind their progression was not known for decades (Hardiman, Al-Chalabi, Chio, et al., 2017; Rowland & Shneider, 2001). Researchers have come up with many speculations regarding neuropathological conditions, but they are still unclear.

In 1824, Charles Bells reported the first case of ALS, and there were many debates regarding this throughout the era. The clinical reason behind the muscle twitch, weakness, lateral sclerosis, and loss of horn cells was reported by Charcot in 1860. Patients associated with ALS start losing their voluntary movements and feel weak and unable to speak and walk; these symptoms worsen in the future stage. Limbic and bulbar onset are common symptoms in patients in the earlier stage. ALS is a progressive disease; the survival range after the symptoms is 3-5 years to the maximum (Kiernan et al., 2011; Kaur et al., 2016). Sporadic cases were 5.2 per 100000 in western countries while 1.5-2.7 per 100000 in Europe and America (Wijesekera & Nigel Leigh, 2009).

BACKGROUND

Overview of Amyotrophic Lateral Sclerosis

ALS can be of two types, namely familial or sporadic. The sporadic type is the most prevalent form found in patients. Spinal muscular atrophy progression was found in the lower motor neurons, while primary lateral sclerosis was identified in the upper motor neurons; they are considered a potent variant. The confirmation was made when the ALS patients underwent an autopsy, and it was found that there were so many abnormalities in the motor neurons, altogether they account for nearly 10% of the disease (Rowland & Shneider, 2001). Only 10% of the cases worldwide are familial due to family history, mutation in specific genes, and some non-functional genes. The common mutations causing ALS are Superoxide dismutase *(SOD)-1*, TDP Binding protein *TARDBP*, and Fused Sarcoma (*FUS)*.

On the other hand, sporadic ALS (sALS) is due to environmental effects and random risk factors. The family members of the sporadic case are at low risk compared to people with familial history. An animal model with mutation G59S human dynactin $p150^{glued}$ transgenic model showed slow progression autosomal dominant disease. The mice cause damage to the dynactin complex, leading to motor neuron disorder. It shows the same behavior in humans, and any mutation in this gene is said to induce the exact pathology of ALS (Brown and Al-Chalabi, 2017; Heiman-Patterson et al., 2015). Several plant compounds like β-asarone and Gingko Biloba extract are used to treat various neurological disorders (Singh et al., 2019; Yang et al., 2017). Several phytochemicals like alkaloids and flavonoids were reported for their use in clinical treatment (Silva et al., 2020).