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Review

Neuropharmacological potentials of β-carboline alkaloids for neuropsychiatric disorders

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ABSTRACT

Neuropsychiatric disorders are diseases of the central nervous system (CNS) which are characterised by complex pathomechanisms that including homeostatic failure, malfunction, atrophy, pathology remodelling and reactivity anomaly of the neuronal system where treatment options remain challenging. β-Carboline (βC) alkaloids are scaffolds of structurally diverse tricyclic pyrido[3,4-b]indole alkaloid with vast occurrence in nature. Their unique structural features which favour interactions with enzymes and protein receptor targets account for their potent neuropharmacological properties. However, our current understanding of their biological mechanisms for these beneficial effects, especially for neuropsychiatric disorders is sparse. Therefore, we present a comprehensive review of the scientific progress in the last two decades on the prospective pharmacology and physiology of the βC alkaloids in the treatment of some neuropsychiatric conditions such as depression, anxiety, Alzheimer's disease, Parkinson's disease, brain tumour, essential tremor, epilepsy and seizure, licking behaviour, dystonia, agnosia, spasm, positive ingestive response as demonstrated in non-clinical models. The current evidence supports that βC alkaloids offer potential therapeutic agents against most of these disorders and amenable for further drug design.

1. Introduction

1.1. Neuropsychiatric disorders

The human Central Nervous System (CNS) consists of about 10^{13} neurons that make over thousands of synaptic connections regulating inhibitory and excitatory synaptic activities (Berezhnoy et al., 2007). The homeostatic failure, malfunction, atrophy, pathology remodelling and reactivity anomaly of the neuronal systems are inter-related pathomechanisms that hypothetically contribute to the development of various neuropsychiatric disorders. These disorders include epilepsy, seizure, Alzheimer's disease (AD), Parkinson's disease (PD), depression, anxiety, addiction, agnosia, dystonia, spasm and even neoplasms such as gliomas (Verkhratsky et al., 2015). In 2016, neurodegenerative diseases accounted for the second-highest causes of global mortality (16.5%) after cardiovascular diseases. Currently, neurodegenerative diseases are the most common causes of disability-adjusted life years (DALYs) (11.6%) and occupy the first position of the global burden of diseases (Feigin et al., 2019; WHO, 2018). Therefore, the discovery and development of effective therapeutic agents is urgently needed.

1.1.1. Pathways to neuropsychiatric disorders

Monoamine oxidases (MAO) A and B are flavoenzymes, located in the outer mitochondrial membrane which differ only in inhibitory and substrate specificity (Schieferstein et al., 2015). They are present in several parts of human organs and are involved predominantly in the oxidative degradation of the neurotransmitters and xenobiotic arylalkylamines (Bolasco et al., 2010). Selectively, inhibitors of MAO-A are clinically applied as antidepressants while those of MAO-B is involved in the treatment of PD, AD, and anxiety (Bolasco et al., 2010). The γ-aminobutyric acid (GABA) neurotransmitters, as well as their receptors, form approximately one-third of the neuronal synapses. Thus, their excitatory/inhibitory synaptic imbalances greatly affect the states of neuronal coordination (Berezhnoy et al., 2007; Jimenez-Gonzalez et al., 2011). Dual specificity tyrosine-phosphorylation-regulated kinase (DYRK1A), an eukaryotic kinase with gene location on human

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