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Critical review

Role of sigma-1 receptors in neurodegenerative diseases

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ABSTRACT

Neurodegenerative diseases with distinct genetic etiologies and pathological phenotypes appear to share common mechanisms of neuronal cellular dysfunction, including excitotoxicity, calcium dysregulation, oxidative damage, ER stress and mitochondrial dysfunction. Glial cells, including microglia and astrocytes, play an increasingly recognized role in both the promotion and prevention of neurodegeneration. Sigma receptors, particularly the sigma-1 receptor subtype, which are expressed in both neurons and glia of multiple regions within the central nervous system, are a unique class of intracellular proteins that can modulate many biological mechanisms associated with neurodegeneration. These receptors therefore represent compelling putative targets for pharmacologically treating neurodegenerative disorders. In this review, we provide an overview of the biological mechanisms frequently associated with neurodegeneration, and discuss how sigma-1 receptors may alter these mechanisms to preserve or restore neuronal function. In addition, we speculate on their therapeutic potential in the treatment of various neurodegenerative disorders.

1. Introduction

Neurodegeneration is characterized by the progressive loss of neuronal integrity, in both structure and function. Alzheimer's disease and Parkinson's disease are the most common neurodegenerative disorders worldwide, affecting approximately 10% of individuals over the age of 60. Current therapies for these and other neurodegenerative conditions focus on symptomatic treatment, and there remains an urgent need to identify and develop effective therapeutics to protect and restore neuronal integrity. To achieve this goal, a better understanding of cellular targets and processes involved in neurodegeneration and regeneration is needed.

Among the putative therapeutic targets being studied, sigma receptors have gained attention for their involvement in modulating cell survival and function. Originally misclassified as a subtype of opioid receptor in the 1970s, sigma receptors are now recognized as a unique class of intracellular proteins, distinct from G protein-coupled and ionotropic receptors (1). They are capable of modulating a variety of cellular processes relevant to neurodegeneration (1,2). The two established subtypes, sigma-1 and sigma-2, are both highly expressed in the central nervous system (CNS), and can be distinguished by their distinct pharmacological profiles and molecular characteristics (1).

Over the past decade, significant advances have been made in our understanding of the sigma-1 receptor subtype in both pathological and physiological processes. The contribution of the sigma-2 subtype, however, remains less well understood due to the paucity of available experimental tools to study its functions. This review focuses on the role of sigma-1 receptors in neurodegeneration,

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beginning with a brief overview of sigma-1 receptor biology, followed by a summary of the common mechanisms of neurodegeneration and how sigma-1 receptor ligands may modulate these mechanisms to elicit neuroprotective and/or restorative effects. Finally, we discuss the potential application of sigma-1 receptor modulation to specific therapeutic interventions.

2. Sigma-1 receptor structure and functions

The sigma-1 receptor is a small (28 kDa), highly conserved, transmembrane protein located in the endoplasmic reticulum (ER) membrane. It is specifically enriched in the ER subregion contacting mitochondria, called the mitochondrial-associated membrane (MAM). Localization studies also report the sigma-1 receptor at or in i) neuronal nuclear, mitochondrial, and plasma membranes, ii) multiple other CNS cell types (astrocytes, microglia and oligodendrocytes), and iii) CNS-associated immune and endocrine tissues (1). The varied sites at which sigma-1 receptors are present suggest multiple pathways by which these receptors may influence physiological and pathological processes.

The sigma-1 receptor can migrate between different organellar membranes in response to ligand binding (3,4). As chaperone proteins, sigma-1 receptors do not have their own intrinsic signaling machinery. Instead, upon ligand activation, they appear to operate primarily via translocation and protein-protein interactions to modulate the activity of various ion channels and signaling molecules, including inositol phosphates, protein kinases, and calcium channels (3). The characteristics of sigma-1 interactions in each pathway are still being determined.

Because sigma-1 receptors exhibit no homology to other mammalian proteins, genetic manipulation has been instrumental in investigating their functions in experimental systems. These studies allow the results of pharmacological manipulation, which is more amenable for potential therapeutic intervention, to be interpreted as either agonistic or antagonistic. By convention, “antagonists” are those compounds that recapitulate the gene knockdown phenotype; they generally have no effects on their own, but attenuate the effects of sigma-1 stimulation. Sigma-1 receptor antagonists that are commonly cited in the literature, including this review, include: BD1047 (N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino) ethylamine), BD1063 (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine), and NE-100 (4-methoxy-3-(2-phenylethoxy)-N,N-dipropylbenzeneethanamine). In contrast, sigma-1 “agonists” are those compounds that recapitulate the phenotypes of receptor overexpression, either autonomously or additive to the effects of other compounds. Common selective sigma-1 receptor agonists include: (+)-pentazocine, (+)-SKF10,047, PRE084 (2-morpholin-4-ylethyl 1-phenylcyclohexane-1-carboxylate), and SA4503 (1-[2-(3,4-dimethoxyphenyl)ethyl]-4-(3-phenylpropyl)piperazine). Many currently marketed drugs (e.g., haloperidol, donepezil, and fluvoxamine) interact with sigma-1 receptors, but are not selective for them. The involvement of the sigma-1 subtype in a given system therefore requires careful analysis and verification using selective genetic and pharmacological tools.

3. Common mechanisms of neurodegeneration

3.1. Excitotoxicity and calcium overload

Glutamate is the major excitatory neurotransmitter in the CNS, and its interaction with specific membrane receptors is responsible for many neurologic functions, including learning and memory. Sustained release of glutamate, however, causes persistent (and only partially desensitizable) activation of N-methyl-D-aspartate (NMDA) receptors, leading to neuronal excitotoxicity. In addition to transporting sodium, NMDA receptors also transport calcium. Persistent activation therefore increases intracellular calcium levels, followed by stochastic failure of calcium homeostasis and necrotic cell death (5). This toxicity does not result from superoxide free radical production, as initially proposed (6), but rather from activation of the mitochondrial permeability transition pore opening triggered by membrane potential-dependent uptake of calcium into the mitochondrial matrix (7,8). The identity of the pore itself has recently been proposed to be the Fo portion of the FoF1 adenosine triphosphate (ATP) synthase (9). Excitotoxicity and excess intracellular calcium contribute to neurodegeneration in many acute CNS diseases, including stroke and traumatic brain injury, and are also implicated in chronic diseases, including amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and Parkinson's disease (5,10,11).

3.2. Oxidative and nitrosative stress

Oxygen (O_2) is critical to meet the energetic demands of biological tissues through the production of ATP by oxidative phosphorylation. However, aberrant O_2 reduction produces radical species that can cause extensive damage to cellular components, cells, and tissues. This phenomenon of “oxidative stress” is defined by a broad range of phenotypes, including the accumulation of oxidized molecules and the disruption of normal cellular processes and viability. Oxidative stress is typically considered to be the state in which these phenotypes are measurable at higher levels than in a “normal” state. Neurons may be particularly vulnerable to oxidative stress due to their terminally differentiated state, complex morphology, and dependence on surrounding glia for metabolic substrates and glutathione (12). Reactive oxygen species (ROS) are generated by multiple conditions and sources, including sustained neurotransmission (e.g., of glutamate, dopamine, or serotonin), mitochondrial dysfunction, and production by glial cells. Depending on the species and location of the ROS, oxidative damage can affect nucleic acids, proteins and lipids. The best evidence that ROS may be an underlying cause of neurodegeneration is the strong association between the detection of increased ROS production and the increased oxidative damage observed in CNS disorders such as Parkinson's disease, Alzheimer's disease and ALS (12,13). Oxidative stress can also impair mitochondrial function, leading to a depletion of ATP and decreased antioxidant capacity (13). Along with ROS, reactive nitrogen species (RNS) can also be generated under pathological conditions in the CNS.

3.3. Endoplasmic reticulum (ER) stress

The ER plays an important role in protein synthesis and folding as well as cellular homeostasis. Different perturbations, such as calcium dysregulation and oxidative stress, can alter ER function and lead to the accumulation of unfolded or misfolded proteins within the ER lumen. This triggers a stress response by the ER known as the unfolded protein response (UPR) to restore protein folding homeostasis (Fig. 1). Three major signaling pathways mediate the UPR: protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 alpha (IRE1α), and activating transcription factor 6 (ATF6).

The downstream activities of all three pathways have been implicated in protective or adaptive responses to the protein accumulation as well as in the promotion of apoptosis. Adaptive responses include a reduction in global protein translation by PERK to decrease the protein load to the ER, and an upregulation of proteins involved in the UPR by IRE1α and ATF6 to increase ER folding capacity and ER-associated protein degradation (ERAD). Conversely, PERK activation can also lead to apoptosis. Some