Progress in Neurobiology 148 (2017) 40–56

Contents lists available at ScienceDirect

Progress in Neurobiology

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

Review article

Multiple beneficial effects of melanocortin MC_4 receptor agonists in experimental neurodegenerative disorders: Therapeutic perspectives

Daniela Giuliani[a], Alessandra Ottani[a], Laura Neri[a], Davide Zaffe[b], Paolo Grieco[c], Jerzy Jochem[d], Gian Maria Cavallini[e], Anna Catania[f], Salvatore Guarini[a,*]

[a] Department of Biomedical, Metabolic and Neural Sciences, Section of Pharmacology and Molecular Medicine, University of Modena and Reggio Emilia, Modena, Italy
[b] Department of Biomedical, Metabolic and Neural Sciences, Section of Human Morphology, University of Modena and Reggio Emilia, Modena, Italy
[c] Department of Pharmacy, University of Napoli "Federico II", Napoli, Italy
[d] Department of Basic Medical Sciences, School of Public Health in Bytom, Medical University of Silesia, Katowice, Poland
[e] Department of Ophthalmology, University of Modena and Reggio Emilia, Modena, Italy
[f] Center for Preclinical Surgical Research, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milano, Italy

ARTICLE INFO

Article history:
Received 20 May 2015
Received in revised form 22 November 2016
Accepted 28 November 2016
Available online 1 December 2016

Keywords:
Neurodegenerative diseases
Pathophysiological mechanisms
Melanocortin receptor agonists
Neuroprotection
Neurogenesis
Functional recovery

ABSTRACT

Melanocortin peptides induce neuroprotection in acute and chronic experimental neurodegenerative conditions. Melanocortins likewise counteract systemic responses to brain injuries. Furthermore, they promote neurogenesis by activating critical signaling pathways. Melanocortin-induced long-lasting improvement in synaptic activity and neurological performance, including learning and memory, sensory-motor orientation and coordinated limb use, has been consistently observed in experimental models of acute and chronic neurodegeneration. Evidence indicates that the neuroprotective and neurogenic effects of melanocortins, as well as the protection against systemic responses to a brain injury, are mediated by brain melanocortin 4 (MC_4) receptors, through an involvement of the vagus nerve. Here we discuss the targets and mechanisms underlying the multiple beneficial effects recently observed in animal models of neurodegeneration. We comment on the potential clinical usefulness of melanocortin MC_4 receptor agonists as neuroprotective and neuroregenerative agents in ischemic stroke, subarachnoid hemorrhage, traumatic brain injury, spinal cord injury, and Alzheimer's disease.

Contents

Abbreviations: Aβ, β-amyloid; ACTH, adrenocorticotropic hormone; AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; BrdU, 5-bromo-2′-deoxyuridine; CNS, central nervous system; DG, dentate gyrus; ERK, extracellular signal-regulated kinases; HMGB-1, high Mobility Group Box-1; JNK, c-jun N-terminal kinases; MSH, melanocyte-stimulating hormone; NDP-α-MSH, [Nle^4,D-Phe^7]α-melanocyte-stimulating hormone; SAH, subarachnoid hemorrhage; SCI, spinal cord injury; SGZ, subgranular zone; Shh, sonic hedgehog; IL, interleukin; SVZ, subventricular zone; TBI, traumatic brain injury; TNF-α, tumor necrosis factor-α.

* Corresponding author at: Department of Biomedical, Metabolic and Neural Sciences, Section of Pharmacology and Molecular Medicine, University of Modena and Reggio Emilia, Via G. Campi 287, 41125 Modena, Italy.
E-mail address: salvatore.guarini@unimore.it (S. Guarini).

http://dx.doi.org/10.1016/j.pneurobio.2016.11.004
0301-0082/

1. Introduction

Acute neurodegenerative conditions including stroke (ischemic or hemorrhagic), traumatic brain injury (TBI), spinal cord injury (SCI), and chronic neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis, and more, are responsible for high mortality and disability. Unfortunately, acute and chronic neurodegenerative disorders have no effective treatment options, as current therapies only relieve symptoms (with varying effectiveness, depending on the condition of individual patients), without counteracting the degenerative process progression (Adams et al., 2007; Antel et al., 2012; Banerjee et al., 2010; Bragge et al., 2012; Galimberti et al., 2013; Iqbal and Grundke-Iqbal, 2011; Laskowitz and Kolls, 2010; Lazarov et al., 2010; Loane and Faden, 2010; Tayeb et al., 2012; Van der Walt et al., 2010; Zhang and Chopp, 2009). Thus, these diseases bear a very high cost in both economic terms and life quality deterioration. A recent study by the European Brain Council estimated the total cost (direct and indirect) of brain disorders in Europe was about 800 billion euros in 2010, and neurodegenerative diseases account for a very large proportion (Gustavsson et al., 2011).

Preclinical investigations aimed at developing novel therapeutics for neurodegenerative disorders indicate that melanocortins could be promising drug candidates. The melanocortin family encompasses adrenocorticotropic hormone (ACTH), α-, β- and γ-melanocyte-stimulating hormones (α-, β- and γ-MSH) and shorter fragments: all are products of the pro-opiomelanocortin gene, and all melanocortins share a core sequence of four amino acids, His-Phe-Arg-Trp, which are the residues (6–9) in ACTH and α-MSH (Brzoska et al., 2008; Caruso et al., 2014; Catania et al., 2004; Getting, 2006; Giuliani et al., 2012; Schiöth, 2001; Versteeg et al., 1998; Wikberg and Mutulis, 2008). Intensive preclinical research by several independent groups started in the fifties of the last century, as well as more recent clinical investigations, showed many extra-hormonal effects of melanocortins: in this research field, the studies by the pharmacological schools of Modena (Italy) and Utrecht (The Netherlands) have given an important propulsion. Indeed, a growing body of evidence indicates that melanocortin peptides and synthetic analogs affect many central and peripheral body functions, such as food intake, sexual behavior, pain sensitivity, fever control, pigmentation, learning and memory (Bertolini et al., 1969, 1986; Brzoska et al., 2008; Catania et al., 2004; de Wied, 1969; de Wied and Bohus, 1966; Diano, 2011; Ferrari, 1958; Ferrari et al., 1963; Getting, 2006; Gispen et al., 1970; O'Donohue and Dorsa, 1982; Schiöth, 2001; Tatro and Sinha, 2003; Vergoni and Bertolini, 2000; Wikberg and Mutulis, 2008). Of note, melanocortins also play a protective and life-saving role in experimental hypoxic and degenerative conditions (Altavilla et al., 1998; Bazzani et al., 2001, 2002; Bertolini, 1995; Bertolini et al., 1989; Giuliani et al., 2007a, 2010, 2012; Guarini et al., 1990, 1996, 1997, 2004; Jochem, 2004; Lonati et al., 2012; Minutoli et al., 2011a, 2011b; Mioni et al., 2003; Ottani et al., 2013, 2014; Versteeg et al., 1998), including acute and chronic neurodegenerative disorders (Catania, 2008; Corander et al., 2009; Gatti et al., 2012; Giuliani et al., 2006a, 2006b, 2007b, 2009, 2011, 2012, 2014a, 2014b, 2015; Holloway et al., 2011; Lasaga et al., 2008).

In the present paper we review the protective actions of melanocortins in the experimental neurodegenerative conditions thus far investigated, including mechanisms of action, and discuss the possibility to extend the use of melanocortin agonists for treatment of other neurodegenerative disorders.

2. Neurodegeneration, endogenous compensation and brain repair

Impairment in cognitive, behavioral, motor and basic vital functions are common in patients with neurodegenerative disease. The broad variety of neurodegenerative phenotypes is consistent with differences in the initial disease triggers and pathological hallmark biomarkers of the disease. However, despite differences in origins, many disease-related pathways that cause neuronal damage and death are common to most acute and chronic neurodegenerative disorders (Antel et al., 2012; Banerjee et al., 2010; Blennow, 2010; Bragge et al., 2012; Drouin-Ouellet and Cicchetti, 2012; Dumont et al., 2001; Friedlander, 2003; Gao et al., 2012; Glass et al., 2010; Haass, 2010; Heneka et al., 2015; Iqbal and Grundke-Iqbal, 2011; Karbowski and Neutzner, 2012; Kumar and Loane, 2012; Leker and Shohami, 2002; Leuner et al., 2012; Lo, 2010; Loane and Faden, 2010; Mehta et al., 2013; Moskowitz et al., 2010; Walsh et al., 2014; Yuan and Yankner, 2000; Zipp and Aktas, 2006). It has been hypothesized that the spread of neurodegeneration occurs not only by proximity, but also transneuronally through propagation of toxic molecules along network connections (Guo and Lee, 2014; Raj et al., 2012; Zhou et al., 2012). Therefore, over the last decades, significant progress has been made in the understanding of pathophysiological mechanisms of neurodegeneration. In particular, the discovery of the important role played by excitotoxicity, oxidative stress, mitochondrial dysfunction, inflammatory response, defective autophagy and apoptosis provided potential targets for novel neuroprotective drugs. There is evidence that also astrocyte dysfunction can play a pivotal role in neurological disorders (Sofroniew, 2015). Epigenetic mechanisms — that is, various types of reversible DNA aberrant methylation and histone modifications — have been recently considered to be involved in neurodegeneration. Consistently, methyl donors and histone deacetylase inhibitors are under investigation in treatment of neurodegenerative disorders (Adwan and Zawia, 2013; Jakovcevski and Akbarian, 2012; Lardenoije et al., 2015).

Notably, neurodegenerative stimuli also induce endogenous compensation and brain repair, through mechanisms that could likewise be implemented as novel drugs. Such endogenous mechanisms include triggering of neuroprotective pathways,