Brain Insulin Dysregulation: Implication for Neurological and Neuropsychiatric Disorders

Rasoul Ghasemi · Leila Dargahi · Ali Haeri · Maryam Moosavi · Zahurin Mohamed · Abolhassan Ahmadiani

Received: 9 December 2012 / Accepted: 3 January 2013 © Springer Science+Business Media New York 2013

Abstract Arduous efforts have been made in the last three decades to elucidate the role of insulin in the brain. A growing number of evidences show that insulin is involved in several physiological function of the brain such as food intake and weight control, reproduction, learning and memory, neuromodulation and neuroprotection. In addition, it is now clear that insulin and insulin disturbances particularly diabetes mellitus may contribute or in some cases play the main role in development and progression of neurodegenerative and neuropsychiatric disorders. Focusing on the molecular mechanisms, this review summarizes the recent findings on the involvement of insulin dysfunction in neurological disorders like Alzheimer’s disease, Parkinson’s disease and Huntington’s disease and also mental disorders like depression and psychosis sharing features of neuroinflammation and neurodegeneration.

Keywords Insulin · Diabetes mellitus · Alzheimer’s disease · Parkinson’s disease · Huntington’s disease · Depression · Schizophrenia

Introduction

Over the past decades, substantial progress has been achieved with respect to the link between insulin and brain and it is now obvious that insulin possesses physiologic roles in central nervous system (CNS), though the brain insulin uptake occurs independently of insulin. In a historical overview, the relation between insulin and CNS was initially reported in 1960s, as it was shown that intracisternal injection of insulin in dogs reduces glucose level both in cerebrospinal fluid (CSF) and blood through direct effects on the parasympathetic area of the brain stem [1, 2]. This primary evidence was then verified in late 1970s by Havrankova et al. [3] who showed insulin is present in the rat brain in high concentrations, and independent of peripheral insulin levels [4]. Since then, further efforts have been made to confirm the presence of insulin in CNS, and to elucidate the origin of central insulin and its physiologic roles. Some studies show that pancreatic derived insulin may pass the blood–brain barrier (BBB) and reach the brain and CSF through a saturable transporter system [5, 6] which its function causes regional differences in BBB insulin permeability (highest in pons medulla and hypothalamus and lowest in occipital cortex and thalamus) [7], and can be regulated by a variety of factors and situations such as glucocorticoids [8], fasting [9], hibernation [10], and obesity [11].

Some other studies also argue the probability of the local production of insulin in CNS based on the detection of c-peptide in the same neurons that contain insulin [12], detection of pro-insulin in brain cell cultures [13], lack of any report showing that c-peptide can cross the BBB [14], and detection of insulin mRNA in some brain regions [15, 16] and neuronal cell culture [17].

Widely distributed insulin receptors (IRs) in CNS firstly shown by Havrankova et al. [18] in rat brain and thereafter