The Role of Insulin and Insulin-like Peptides in Ischemic Stroke and Cognitive Impairment

Avhandling

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SAHLGRENSKA AKADEMIN
INSTUTIONEN FÖR MEDICIN
The Role of Insulin and Insulin-like Peptides in Ischemic Stroke and Cognitive Impairment

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Abstract
Background and aims: Insulin, insulin-like growth factor-I (IGF-I), and the six high-affinity IGF-binding proteins (IGFBPs) play an important role in growth, metabolism and regeneration throughout the entire life span. In contrast, the role of IGF-II in adult life has been unclear. Animal studies have demonstrated that altered brain activity of the insulin/IGF-system is associated with reduced cognitive function and worse outcome after experimentally induced stroke and this is reversed by IGF-I-treatment. The overall aim of this thesis was to determine whether the insulin/IGF-I system is of importance for outcome of ischemic stroke (IS) also in humans and whether insulin and insulin-like peptides are dysregulated in patients with Alzheimer’s disease (AD).

Patients and methods: Two well-characterized clinical cohorts were studied. In SAHLSIS (Sahlgrenska Academy Study on Ischemic Stroke; originally 600 IS patients and 600 population-based controls), characterization of patients after IS included serum samples and stroke scales. Furthermore, serum and cerebrospinal fluid (CSF) levels of insulin, IGF-I, and IGF-II were determined in a cross-sectional study of patients (n=60) with AD and other forms of cognitive impairment, and healthy controls (n=20).

Results: In Paper I, high serum IGF-I concentrations were associated with better improvement of functional independence in SAHLSIS. In Paper II, analyses of single-nucleotide polymorphisms (SNPs) in the IGF1 gene showed that the major allele of rs7136446 was associated with favorable post-stroke outcome after 2 years. In Paper III, insulin resistance was associated with functional outcome, especially in patients with cryptogenic stroke. In Paper IV, serum but not CSF levels of IGF-I were increased in patients with AD whereas insulin levels were unchanged both in serum and CSF. In Paper V, CSF IGF-II level was increased in male but not in female patients with AD.

Conclusions: The IGF-I/insulin system is associated with functional outcome after ischemic stroke. Furthermore, levels of IGF-I and IGF-II are dysregulated in Alzheimer’s disease.

Keywords: Ischemic Stroke (IS), Alzheimer’s disease (AD), Cognitive Impairment, Dementia, Insulin-like Growth Factor I (IGF-I)