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Research Report

Effects of insulin-like growth factor 1 on voltage-gated ion channels in cultured rat hippocampal neurons

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ABSTRACT

Insulin-like growth factor 1 (IGF-1) has important functions in the brain, including metabolic, neurotrophic, neuromodulatory, and neuroendocrine actions, and it is also prevents amyloid β-induced death of hippocampal neurons. However, its functions on the voltage-gated ion channels in hippocampus remain uncertain. In the present study, we investigated the effects of IGF-1 on voltage-gated potassium, sodium, and calcium channels in the cultured rat hippocampal neurons using the whole-cell patch clamp recordings. Following incubation with different doses of IGF-1 for 24 h, a block of the peak transient A-type K^+ currents amplitude (IC_{50}: 4.425 ng/ml, Hill coefficient: 0.621) was observed. In addition, after the application of IGF-1, the amplitude of high-voltage activated Ca^{2+} currents significantly increased but activation kinetics did not significantly alter ($V_{1/2}$: −33.45 ± 1.32 mV, k = 6.16 ± 1.05) compared to control conditions ($V_{1/2}$: −33.19 ± 2.28 mV, k = 7.26 ± 1.71). However, the amplitude of Na^+, K^+, and low-voltage activated Ca^{2+} currents was not affected by the application of IGF-1. These data suggest that IGF-1 inhibits transient A-type K^+ currents and enhances high-voltage-activated Ca^{2+} currents, but has no effects on Na^+ and low-voltage-activated Ca^{2+} currents.

1. Introduction

IGF-1 is a pleiotropic factor with structural and functional homologies to IGF-2 and insulin. IGF-1 and its receptor are all present in rodent and human brain (Craft et al., 1998; Frolich et al., 1998; Schulingkamp et al., 2000), especially concentrated in the hippocampus. It is now known that IGF-1 is actively transported across the blood–brain barrier and possibly even produced locally in the brain (Schulingkamp et al., 2000). IGF-1 can promote the survival, proliferation, and maturation of cultured neurons (DiCicco-Bloom and Black, 1988), reduce neuronal loss in adult rat brain following hypoxic–ischemic injury (Guan et al., 1993), induce the differentiation of oligodendrocytes (McMorris et al., 1993), stimulate DNA synthesis (Lenoir and Honegger, 1983) and neurite outgrowth (Ruiz et al., 1992), direct the sprouting of spared afferents into a deafferented hippocampus (Guthrie et al., 1995), and modulate hippocampal acetylcholine release.

Recently, IGF-1 has gained increasing attention for the pathogenesis of age-related neurodegenerative diseases, such as Alzheimer's disease (AD) (Gasparini et al., 2002). AD patients show changes in insulin and IGF-1 levels and their response to insulin is defective. IGF-1 has been found to protect hippocampal neurons against the toxicity of amyloid β protein (Aβ)

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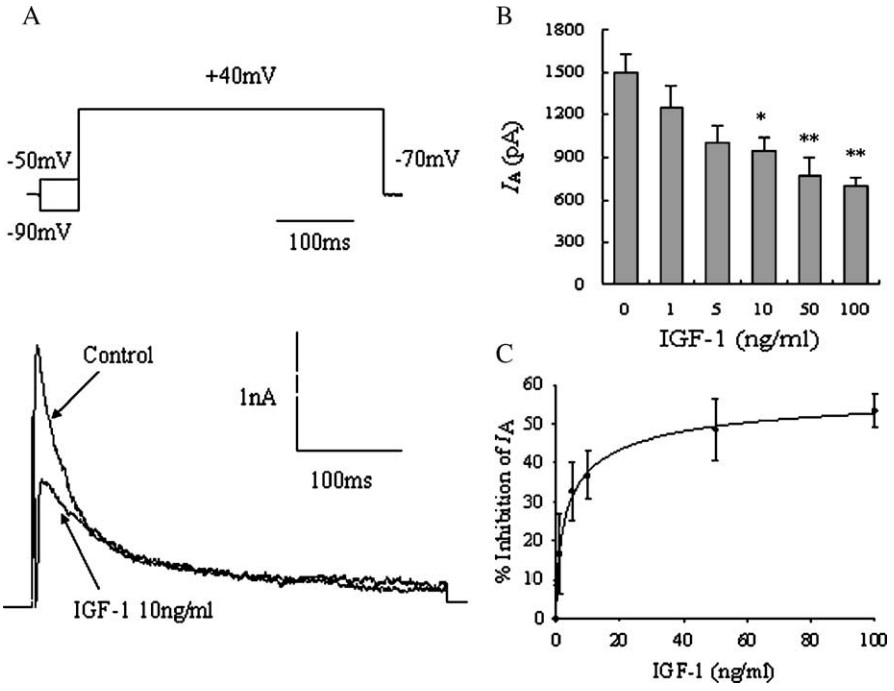

Fig. 1 – IGF-1 inhibits A-type potassium currents in hippocampal neurons in a dose-dependent manner. (A) I_A was obtained by subtracting the currents induced by the two voltage protocols shown on top. Bottom, representative recording of I_A under control condition and 10 ng/ml IGF-1 application. (B) Concentration–amplitude relationship. Compared to the control group, $^*P < 0.05$, $^{**}P < 0.01$. (C) Dose–response curve. IC_{50} = 4.425 ng/ml, Hill coefficient was 0.621.

(Dore et al., 1997). Evidence indicates that insulin and IGF-1 have a direct effect of on the metabolism and clearance of Aβ and IGF-1 may be a key factor in regulating the clearance of Aβ from the brain through carrier-mediated transport (Carro et al., 2002). Therefore, IGF-1 is considered as a potential therapeutic agent for AD.

Although the presence and regulation of IGF-1 and its receptor were widely reported in hippocampal neurons, little

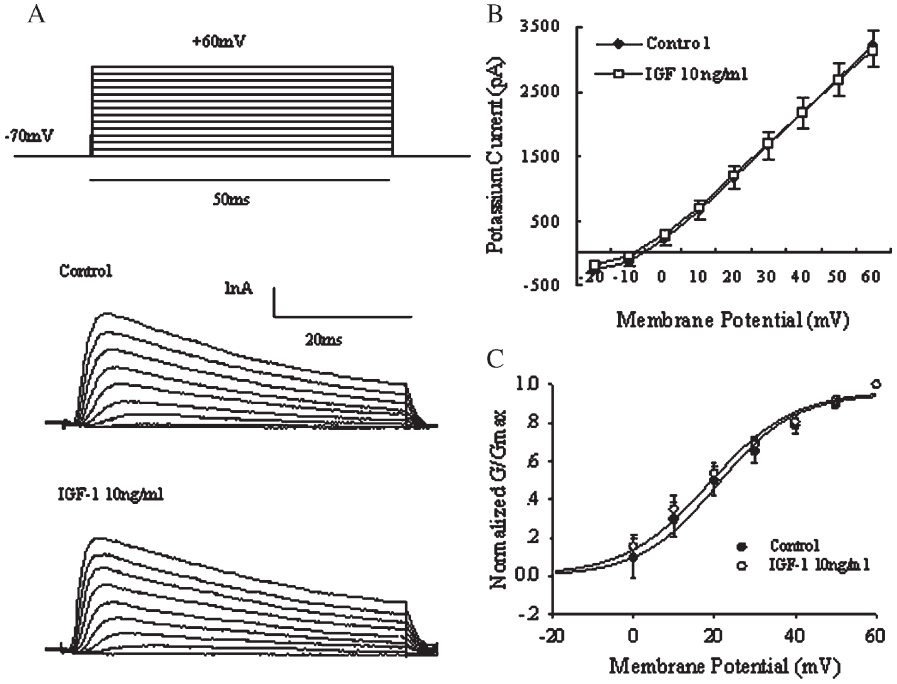

Fig. 2 – IGF-1 has no effect on potassium currents. (A) Representative recordings of I_K, induced by a series of depolarizing steps shown on top, without and with 10 ng/ml IGF-1 application. (B) *I–V* curve for I_K showing the peak K^+ currents not changed after IGF-1 application. (C) Activation curve of I_K under control conditions and during application of 10 ng/ml IGF-1.