Pharmacological Reports
2011, 63, 1442–1449
ISSN 1734-1140

Novel I_1-imidazoline S43126 enhance insulin action in PC12 cells

Jerusalem Tesfai[1], Louis Crane[2], Genevieve Baziard-Mouysset[2], Wentsworth Kennedy[3], Lincoln P. Edwards[3]

[1]Department of Biochemistry, Loma Linda University School of Medicine, Loma Linda, CA 92350, USA

[2]Laboratoire de Chimie Pharmaceutique, Universite Paul Sabatier, Faculté de Pharmacie, F-31062 Toulouse Cedex 9, France

[3]Schools of Dentistry/Medicine, Loma Linda University, Loma Linda, CA 92350, USA

Correspondence: Lincoln P. Edwards, e-mail: lpedwards@llu.edu

Abstract:
The I_1-imidazoline receptor is a novel target for drug development for hypertension and insulin resistance, major disorders associated with type 2 diabetes. In the present study, we examined the effects of a novel imidazoline agonist S43126, on phosphorylation of protein kinase B (PKB/Akt) and extracellular signal-regulated kinase (ERK1/2) in PC12 cells. We further examined the effects of S43126 on insulin stimulated PKB and ERK phosphorylation. PC12 cells were treated with varying doses of S43126 (10^{-10} to 10^{-6} M) or insulin (10^{-10} to 10^{-6} M) or combination treatment with insulin (10^{-6} M) and varying doses of S43126 (10^{-6} – 10^{-11} M) for 10 min. Western blot analysis of treated samples showed that S43126 increased both ERK1/2 and PKB phosphorylation by 5 fold. Combination treatment with insulin (10^{-6} M) and varying doses of S43126 (10^{-6} – 10^{-11} M) enhanced phosphorylation of PKB and ERK1/2 above the level of insulin alone, in a dose and time dependent manner. Treatment with siRNA against Nischarin (mouse homologue of I_1-imidazoline receptor) reduced the phosphorylation of both ERK and PKB following combination treatments. These results indicate that S43126 has the potential to augment insulin action and should be further studied as a possible candidate drug for the treatment of insulin resistance states.

Key words:
I_1-imidazoline receptor, protein kinase B, extracellular signal-regulated kinase, insulin, nischarin, type 2 diabetes, insulin resistance