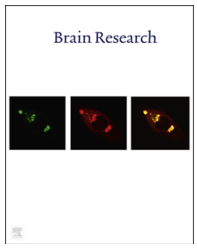
BRAIN RESEARCH 1564 (2014) 33–40

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research



Research Report

Effect of tolbutamide, glyburide and glipizide administered supraspinally on CA3 hippocampal neuronal cell death and hyperglycemia induced by kainic acid in mice

*Chea-Ha Kim, Soo-Hyun Park, Yun-Beom Sim, Sung-Su Kim, Su-Jin Kim, Su-Min Lim, Jun-Sub Jung, Hong-Won Suh**

Department of Pharmacology, Institute of Natural Medicine, College of Medicine Hallym University, 39 Hallymdaehak-gil, Chuncheon 200-702, Gangwon-do, Republic of Korea

ARTICLE INFO

Article history:
Accepted 30 March 2014
Available online 5 April 2014

Keywords:
Kainic acid
Neuronal cell death
Sulfonylureas
Blood glucose
Tolbutamide
Glyburide
Glipizide

ABSTRACT

Sulfonylureas are widely used oral drugs for the treatment of type II diabetes mellitus. In the present study, the effects of sulfonylureas administered supraspinally on kainic acid (KA)-induced hippocampal neuronal cell death and hyperglycemia were studied in ICR mice. Mice were pretreated intracerebroventricularly (i.c.v.) with 30 μg of tolbutamide, glyburide or glipizide for 10 min and then, mice were administered i.c.v. with KA (0.1 μg). The neuronal cell death in the CA3 region in the hippocampus was assessed 24 h after KA administration and the blood glucose level was measured 30, 60, and 120 min after KA administration. We found that i.c.v. pretreatment with tolbutamide, glyburide or glipizide attenuated the KA-induced neuronal cell death in CA3 region of the hippocampus and hyperglycemia. In addition, KA administered i.c.v. caused an elevation of plasma corticosterone level and a reduction of the plasma insulin level. The i.c.v. pretreatment with tolbutamide, glyburide or glipizide attenuated KA-induced increase of plasma corticosterone level. Furthermore, i.c.v. pretreatment with tolbutamide, glyburide or glipizide causes an elevation of plasma insulin level. Glipizide, but not tolbutamide or glyburide, pretreated i.c.v. caused a reversal of KA-induced hypoinsulinemic effect. Our results suggest that supraspinally administered tolbutamide, glyburide and glipizide exert a protective effect against KA-induced neuronal cells death in CA3 region of the hippocampus. The neuroprotective effect of tolbutamide, glyburide and glipizide appears to be mediated by lowering the blood glucose level induced by KA.

*Corresponding author. Fax: +82 33 248 2612.
E-mail address: hwsuh@hallym.ac.kr (H.-W. Suh).

http://dx.doi.org/10.1016/j.brainres.2014.03.046
0006-8993/

1. Introduction

Kainic acid (KA), an agonist for kainate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, causes depolarization of neurons followed by severe status epilepticus (SE), neurodegeneration, plasticity, memory loss and neuronal cell death (Izquierdo et al., 2000; Zagulska-Szymczak et al., 2001; Contractor et al., 2001). KA receptors are encoded by two gene families, GluR5-6 and KA1-2, both of which have significant structural homology to AMPA receptors (Glu1-4). Glu5-7 is all known to form homomeric, non-selective action channels, and heteromers containing KA-1 and KA-2 (Herb et al., 1992; Cui and Mayer, 1999). KA activates AMPA receptors; AMPA receptors containing GluR2 are relatively Ca^{2+} impermeable (Washburn et al., 1997; Perkinton et al., 1999) and down-regulation of this subunit may lead to formation of Ca^{2+}-permeable receptors and influx of toxic amounts of Ca^{2+} in response to endogenous glutamate. This calcium may cause neurotoxic properties of KA (Pollard et al., 1993; Friedman et al., 1994). It is known that seizures result in altered glucose metabolism, the reduction of intracellular energy metabolites such as ATP, ADP and phosphocreatine and the accumulation of metabolic intermediates, such as lactate and adenosine (Schauwecker, 2012). Also the modulation of the glycemic index through glucose rescue greatly aggravates the extent of seizure-induced cell death following KA administration. However, the direct effects of glycemic control on brain metabolism nor the effects of managing systemic glucose concentrations in epilepsy have not been well known.

Sulfonylurea is widely used for the treatment of type II diabetes mellitus. Many studies have also reported that the major blood glucose-lowering activity of sulfonylureas appears to be primarily through enhance β-cell responsiveness. Also, increase intracellular cyclic AMP exerts insulinotropic effects by closing ATP-dependent potassium channels (Groop, 1992; Lebovitz and Feinglos, 1978). Its action on blood glucose suppresses glucagon secretion, increasing peripheral insulin sensitivity without affecting insulin binding (Groop et al., 1985). Skillman and Feldman reported that the sulfonylureas potentiate the biologic effect of the insulin, increasing the deficient numbers of insulin receptors and stimulating insulin secretion on skeletal muscle, fat and liver (Skillman and Feldman, 1981).

Several lines of evidence have demonstrated that seizure causes elevations of cerebral metabolic rates (Fernandes et al., 1999) and glycolysis (Fray et al., 1997). In addition, Uysal et al. (1996) have reported that insulin reduces KA-induced seizure activity. Furthermore, Koenig and Cho (2005) have shown that hypothalamic KA mRNA levels are increased in insulin-induced hypoglycemic rat, suggesting that KA receptors expression appears to be dynamically regulated depending on the level of the blood glucose. In a recent preliminary study, we found that KA administered supraspinally produces a hyperglycemic effect. In addition, we recently have reported that some of the sulfonylureas administered centrally exert the anti-diabetic effect in oral glucose tolerance test (Sim et al., 2012). However, the central pharmacological actions of sulfonylureas on KA-induced hippocampal neuronal cell death and hyperglycemia have not been studied yet. Thus, the present study was designed to examine the effects of sulfonylureas administered supraspinally on the neuronal cell death in CA3 region of the hippocampus and hyperglycemia induced by KA administered supraspinally.

2. Results

2.1. *Effects of sulfonylureas administered i.c.v. on hippocampal CA3 neuronal cell death induced by KA*

We have examined the CA3 neuronal cell death using the cresyl violet stain after i.c.v. administration with KA at the dose of 0.1 μg in the hippocampus. The morphological damage induced by KA in the hippocampus was markedly concentrated in the CA3 pyramidal neurons after 1 day (Figs. 1, 2 and 3). Mice were pretreated i.c.v. with 30 μg of tolbutamide, glyburide and glipizide for 10 min and mice were administered i.c.v. with KA (0.1 μg). Cresyl vilot staining was performed 24 h after i.c.v. KA administration. As revealed in Figs. 1A, 2A, and 3A, KA-induced hippocampal CA3 neuronal death was attenuated by i.c.v. pretreatment with tolbutamide, glyburide or glipizide.

2.2. *Effects of sulfonylureas administered i.c.v. on the blood glucose level induced by KA*

After mice were pretreated i.c.v. with 30 μg of tolbutamide, glyburide or glipizide for 10 min, mice were administered i.c.v. with KA (0.1 μg). The blood glucose level was measured at 30, 60 and 120 min after KA administration. As shown in Figs. 1B, 2B, and 3B, KA produced a hyperglycemia effect. The blood glucose level began to increase at 30 min and a KA-induced hyperglycemic effect was maintained up to 2 h after i.c.v. treatment with KA. Tolbutamide, glyburide or glipizide pretreated i.c.v. attenuated the elevation of the blood glucose level induced by KA (Figs. 1B, 2B, and 3B).

2.3. *Effects of sulfonylureas administered i.c.v. on plasma corticosterone and insulin levels induced by KA*

To examine if the glucocorticoid and insulin systems are involved in a sulfonylureas-induced lowering effect against KA-induced hyperglycemia, effects of sulfonylureas administered i.c.v. on plasma corticosterone and insulin levels are investigated. As shown in Figs. 1C and D, 2C and D, 3C and D, i.c.v. administration with KA caused an elevation of blood corticosterone level, whereas plasma insulin level was decreased by i.c.v. KA administration. The i.c.v. pretreatment with tolbutamide, glyburide or glipizide attenuated KA-induced up-regulation of plasma corticosterone level. Furthermore, i.c.v. administration with tolbutamide, glyburide or glipizide caused an up-regulation of plasma insulin level (Figs. 1D, 2D, and 3D). However, the down-regulation of insulin level induced by KA was significantly reversed by glipizide, but not by tolbutamide or glyburide (Figs. 1D, 2D, and 3D).