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A short-term diabetes induced changes of catecholamines and p38-MAPK in discrete areas of rat brain

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Abstract

Chronic diabetes is associated with the alteration of second messengers and CNS disorders. We have recently identified that protein kinases (CaMKII and PKC-α) and brain neurotransmitters are altered during diabetes as well as in hyperglycemic and acidotic conditions. In this study, we investigated the effects of acute diabetes on the levels of dopamine (DA), norepinephrine (NE), epinephrine (E) and p38-Mitogen-Activated Protein Kinase (p38-MAPK) in striatum (ST), hippocampus (HC), hypothalamus (HT), midbrain (MB), pons medulla (PM), cerebellum (CB) and cerebral cortex (CCX). Alloxan (45mg/kg) diabetic untreated rats that showed hyperglycemia (>260mg%), revealed significant increases of DA level in ST (1.5 fold), HC (2.2 fold) and PM (2.0 fold) and the E level also found to be increased significantly in HT (2.4 fold), whereas the NE level was decreased in CB (0.5 fold), after 7 days of diabetes. Immunoblotting study of p38-MAPK expression under identical conditions showed significant alterations in ST, HC, HT and PM ($p < 0.05$) correlated with the changes of catecholamines (DA and E). On the other hand, the above changes were reversed in insulin-treated diabetic rats maintained under normal glucose level (80 –110mg %). These results suggest that p38-MAPK may regulate the

Abbreviations: DA, dopamine; NE, norepinephrine; E, Epinephrine; ST, Striatum; HC, Hippocampus; HT, Hypothalamus; MB, Mid brain; PM, Pons medulla; CB, Cerebellum; CCX, Cerebral cortex.

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rate of either the synthesis or release of DA and E in corresponding brain areas, but not NE, under these conditions.

Keywords: Alloxan; Rat brain; Catecholamines; p38-MAPK

Introduction

The most and well known effects of diabetes mellitus on central nervous system (CNS) is dysfunction of neurotransmitters, which is secondary to the metabolic disorders such as hyperglycemia and acidosis (Djursing et al., 1984; Saller, 1984; Lackovic et al., 1985; Bitar et al., 1986; Trulson et al., 1985; Kwok et al., 1985; Chen and Yang, 1991; Tasaka et al., 1992; Ramakrishnan and Namasivayam, 1995; Ramakrishnan et al., 1996, 2003, 2004, 2005). Diabetes mellitus have also been reported to be accompanied by a number of behavioral and hormonal abnormalities, including hyperphagia, reduced motor activity (Marchall et al., 1976; Marchall, 1978) and decreased serum levels of growth hormone (Tannendaum, 1981), luteinizing hormone (Katayama et al., 1984) and thyroid stimulating hormone (Serif and Sihotang, 1962). CNS abnormalities including neuronal atrophy and axonal degenerations (Rossi and Bestetti, 1981; Reske-Nielsen and Lunbeak, 1963) are also associated with diabetes. The altered levels of neurotransmitter in specific brain areas in patients with diabetes mellitus (Lackovic et al., 1985) and in animals with experimental diabetes (Bitar et al., 1986; Saller, 1984; Trulson et al., 1985; Kwok et al., 1985; Chen and Yang, 1991; Tasaka et al., 1992) have been documented and implicated in the CNS disorders.

Our previous study has shown that neurotransmitters, in alloxan-diabetic (Ramakrishnan and Namasivayam, 1995; Ramakrishnan et al., 1996, 2004, 2005) as well as in glucose-induced hyperglycemic and NH_4Cl-induced acidotic (Ramakrishnan et al., 2003) rats were altered in specific areas of brain. These changes were reversed after insulin administration. Recently, we have shown that during diabetic, hyperglycemic or acidotic conditions, the Ca^{2+}-dependent, phorbol esters sensitive and a family of serine/threonine protein kinases, PKC-α (Ramakrishnan et al., 2004) and CaMKII (Ramakrishnan et al., 2005) were altered correlating with the changes of neurotransmitters in various brain regions. We have also shown altered MAPK in human breast tumor-derived GI-101A cell line by phorbol 12, 13-dibutyrate (PDB) treatments (Zell et al., 2002).

It has been reported that protein kinases play a crucial role in cellular and molecular functions and have a wide tissue and sub-cellular distribution (Kelly et al., 1984). MAPK, yet another type of Ca^{2+}-dependent, phorbol esters sensitive and a family of serine/threonine protein kinase, activates/mediates many of the cellular and molecular functions in response to Ca^{2+}-based or phorbol esters-induced signals, including neurotransmitters synthesis and release (Chen, 2004; Yu et al., 1996; Wu et al., 1998; Martin-Pere and Thomas, 1983; Thomas, 1992; Davis, 1993; Zell et al., 2002). Since our previous results on PKC-α and CaMKII expressions showed correlated alterations with corresponding changes of neurotransmitters under diabetic conditions, the current study was undertaken to find out the status of p38-MAPK expression and neurotransmitters level, and to elucidate the role of a family of Ca^{2+}-dependent, phorbol esters sensitive and serine/threonine protein kinases in diabetic animals.