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LETTER TO THE EDITOR

Increased risk for cerebral ischemic stroke in diabetes: genetically polymorphic CYP mediated production of neuroprotective EETs and sulfonylurea metabolism in relation with K_{ATP} channels

Umit Yasar[1] and Melih O. Babaoglu[1]

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Dear Editor,

Szeto et al. thoroughly reviewed the role of ATP sensitive potassium (K_{ATP}) channels in cerebral ischemic stroke and diabetes in a recent article [1]. K_{ATP} channels are expressed in many organs, such as brain, heart, and pancreas. Recent studies demonstrated the protective role of these channels in cardiac pathologies and ischemia of brain [1]. Diabetic patients are often prescribed with sulfonylurea oral antidiabetics, for which the mechanism of action is inhibition of K_{ATP} channels and thereby, increased excretion of insulin by pancreatic islet cells. Tolbutamide, glyburide, glibenclamide, glipizide, gliclazide, and glimepiride are among sulfonylureas that are mainly metabolized by cytochrome P450 (CYP) 2C9 [2, 3]. Meglitinides are another group of frequently used oral antidiabetics. Nateglinide and repaglinide are members of this newer group. They stimulate insulin release by partly acting on K_{ATP} channels and this group of drugs are also partly metabolized by CYP2C9 and 2C8 [3].

CYP2C8 and 2C9 are genetically polymorphic enzymes and more than 14 and 60 allelic variants have been identified, respectively, as listed in the official CYP allele nomenclature website (www.pharmvar.org/genes). Among those variants, **2* and **3* of *CYP2C9* are the most widely investigated polymorphisms regarding their effects on drug metabolism [2]. Several reports demonstrated that decreased activities of these variants were associated with slower biotransformation of oral antidiabetics [2, 3]. Hypoglycemia due to the decreased metabolism of sulfonylureas has been previously reported in diabetic patients [2, 3].

Beside their main action on drug metabolism, CYP2C8 and 2C9 are partly responsible for production of endogenous biologically active substances [4]. CYP 2J2, 2C8, and 2C9 synthesize epoxyeicosatrienoic acid (EET) derivatives endogenously [4]. Similar to CYP2C8 and 2C9, CYP2J2 is another genetically polymorphic enzyme. Genetic polymorphisms and expression levels of these three enzymes have been associated with various pathologic conditions, such as acute myocardial infarction, ulcerative colitis, and Behcet's disease [5–7].

Cytoprotective role of K_{ATP} channels in brain and heart have been reported previously as mentioned by Szeto et al. [1]. EETs produced by the CYP 2J2, 2C8, and 2C9 have been reported to have protective effects [8]. Neuroprotective function of EETs on cerebral ischemia-reperfusion injury have been associated with K_{ATP} channels [8].

Considering the findings in the literature above, it is likely that cerebral ischemic stroke risk would be increased in diabetic patients carrying *CYP2C8* and/or *2C9* genetic polymorphisms who are treated with oral antidiabetic drugs. A plausible double effect, as described in Fig. 1, may cause increased risk for ischemic brain injury in diabetic patients with functionally important variant alleles of the CYPs that are responsible for the production of EETs. Genetic variations of CYP2C8 and CYP2C9, which are contributing enzymes in EET production may be of interest since a genetic linkage between *CYP2C8*3* and *CYP2C9*2* variants was previously reported by Yasar et al. [9]. In that study, about 85% of the subjects concurrently carried both polymorphisms [9]. These patients would likely produce less EETs and metabolize oral antidiabetics more slowly, resulting in less K_{ATP} channel functioning. This double effect may likely to cause less neuroprotection and result in increased risk for ischemic brain injury (Fig. 1).

As a conclusion [1], comprehensively reviewed the literature related with the role of K_{ATP} channels in cerebral ischemic stroke and diabetes. In this correspondence we would like to draw a special attention to role of genetic polymorphisms of CYPs in relation with metabolism of oral antidiabetics and production of EETs that are both associated with K_{ATP} channel functioning. Further studies should focus on the risk of ischemic heart and brain diseases to demonstrate the role of genetic polymorphisms of *CYP2C8, 2C9*, and *2J2* in diabetic patients treated with oral antidiabetic medications.

[1]Department of Medical Pharmacology, Hacettepe University, Faculty of Medicine, Ankara, Turkey
Correspondence: Umit Yasar (uyasar@hacettepe.edu.tr)

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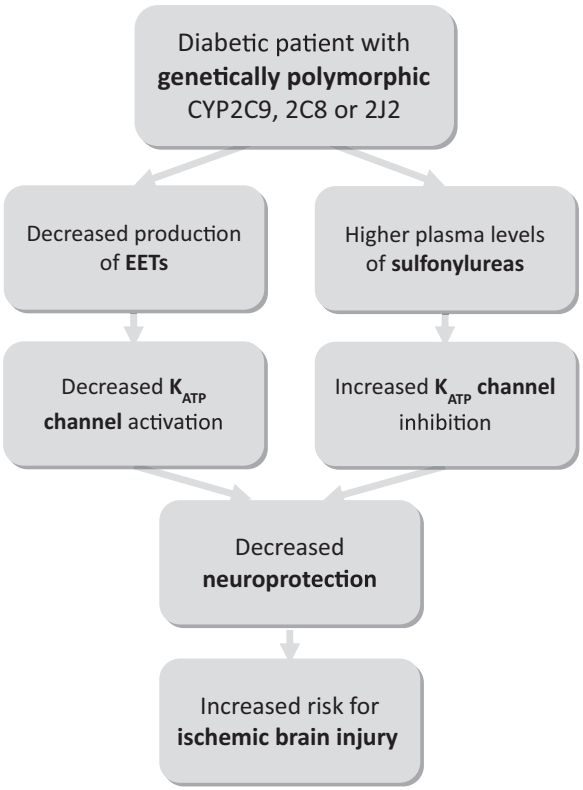

Fig. 1 A plausible double effect for increased risk for ischemic brain injury in diabetic patients carrying genetically polymorphic CYP variants

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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