

Metformin in the diabetic brain: friend or foe?

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Diabetes is fast becoming the epidemic of the 21st century. Individuals with type 2 diabetes (T2D) are at an increased risk for developing cognitive disorders, such as Alzheimer disease (AD). To avoid or slow the development of T2D-associated complications anti-diabetic agents should be capable of achieving the desired glycemic and metabolic control goal, which should be as close to normal as possible.

Metformin (1,1-dimethylbiguanide), an inexpensive, well-tolerated oral anti-diabetic agent is the most widely prescribed drug for treating T2D and is recommended, in conjunction with lifestyle modification (i.e., diet and physical activity), as a first-line oral therapy (1). Besides being highly effective in improving glycemic control, metformin has also a low risk of hypoglycemia. This anti-diabetic drug can be used at all stages of T2D progression, either as monotherapy or in combination with sulfonylureas and other secretagogues, thiazolidinediones, and insulin.

The mechanism of action of metformin depends on alterations in cellular energy metabolism (i.e., increased AMP/ATP ratio). Metformin exerts its glucose-lowering effect by inhibiting hepatic gluconeogenesis and opposing the action of glucagon. Metformin-mediated inhibition of mitochondrial complex I results in defective cAMP and protein kinase A signaling in response to glucagon. Although unnecessary for the glucose-lowering effect of metformin, the stimulation of AMP-activated protein kinase (AMPK) confers insulin sensitivity, mainly through the modulation of lipid metabolism (2).

Metformin can cross the blood-brain barrier and have specific effects on the central nervous system, although the exact mechanism and sites of its action remain uncertain. In addition, conflicting information exists about the beneficial versus adverse effects of metformin on the brain.

On the positive side, *in vitro* studies have recently

demonstrated that metformin prevented amyloid β (A β) generation and tau protein hyperphosphorylation, AD-like features, in a differentiated neuronal cell line submitted to chronic hyperinsulinemia (3). Using murine primary neurons from wild-type and human tau transgenic mice, Kickstein *et al.* (4) reported that the anti-diabetic drug metformin induced protein phosphatase 2A (PP2A) activity and reduced tau phosphorylation at PP2A-dependent epitopes. Several animal studies supported the positive effects associated with metformin. It was previously shown that metformin promoted neurogenesis and enhanced spatial memory in C57/129J mice (5), reduced oxidative stress in the brain of Goto-Kakizaki rats, a model of non-obese T2D (6) and avoided the reduction of cell proliferation and neuroblast differentiation in the subgranular zone of the hippocampal dentate gyrus in Zucker diabetic fatty rats (7). Also, acute metformin preconditioning induced neuroprotection against subsequent cerebral ischemia (8) and chronic metformin treatment mediated post-stroke recovery by enhancing angiogenesis (9); these effects being mediated by activated AMPK. It was also reported that AD-like features (e.g., increased levels of activated c-jun N-terminal kinase (JNK), a tau kinase, and phosphorylated tau protein and decreased synaptic integrity) observed in the brains of db/db mice, a model of T2D and obesity, are attenuated by metformin treatment. However, this anti-diabetic agent did not improve spatial learning and memory as well as long-term hyperglycemia in db/db mice. Similarly, McNeilly *et al.* (10) demonstrated that metformin did not alter high-fat diet-induced cognitive deficits in rats, although it attenuated insulin resistance and body weight gain. In the two last studies, the inability of metformin to counteract cognitive decline may be due to the treatment protocols (dose and/or duration) that were unable to restore

normoglycemia/insulin sensitivity.

Ng *et al.* (11) used data of 365 older persons with diabetes from the population-based Singapore Longitudinal Aging Study to investigate the effect of metformin usage on the risk of cognitive impairment and its possible modulation by apolipoprotein E (APOE) $\epsilon 4$ gene polymorphism. The authors found no significant interactive effects of metformin use with APOE $\epsilon 4$, depression, or fasting glucose level. It was also observed that among individuals with diabetes, long-term treatment (>6 years) with metformin may reduce the risk of cognitive decline. But this study presents some limitations: (I) fasting blood glucose levels were used to account for differences in glycemic control instead of glycated hemoglobin (HbA_{1c}) levels; (II) metformin treatment duration was determined by participants' self-reports instead of medical records; and (III) only the Mini-Mental State Examination (MMSE) was done in the study's participants. However, the beneficial effects of metformin on cognitive function were also highlighted by a prospective cohort study (12) that showed that metformin as well as sulfonylureas decreased the risk of dementia. It was also reported that the combination of sulfonylureas and metformin decreased the risk of dementia in diabetic individuals by 35% over 8 years (12). The study involved T2D subjects that had not taken any anti-diabetic medication (n=10,519), T2D subjects who used sulfonylureas only (n=3,753), T2D subjects who used metformin only (n=1,864), and those who used both sulfonylureas and metformin (n=9,257). However, this study lacks detailed clinical observations and laboratory data. Therefore, the diagnosis of pre-diabetes and/or dementia were not verified by recognized clinical criteria. Other possible confounders (e.g., body weight and composition, socio-economic status, education and APOE polymorphisms) were not available, which may bias the interpretation of the results.

The apparently promising effects of metformin against cognitive impairment and AD are challenged by conflicting observations. Chen *et al.* (13) reported that metformin, at doses that lead to activation of the AMPK, significantly increased the generation of both intracellular and extracellular A β species in mouse primary cortical cultures and N2a neuroblastoma cells stably expressing human amyloid precursor protein (APP). The authors also demonstrated that the effect of metformin on A β generation was mediated by transcriptional up-regulation of β -secretase (BACE1), which results in an elevated protein level and increased enzymatic activity (13).

A recent study performed by Moore *et al.* (14) reported that individuals with T2D or impaired glucose tolerance (n=126) had overall worse cognitive performance and, among the participants with T2D, those treated with metformin performed less well on the cognitive tests than those managing diabetes with other approaches. The participants of the study were recruited from two prospective studies: the Primary Research in Memory (PRIME) clinics study and the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, and included individuals with AD, mild cognitive impairment (MCI) and cognitively intact. However, the study lacks sufficient information on the duration and severity/control of diabetes, metformin treatment duration, and the potential use of other medications that could be major confounding factors. It was suggested that the adverse effects of metformin can be due, at least in part, by a decrease in serum vitamin B12 levels, an effect that can be reversed by calcium supplements. In fact, Moore *et al.* (14) also reported that diabetics who used calcium supplements displayed better cognitive performance on average than those who did not, although calcium supplements have been reported to be associated with an increased risk for myocardial infarction in postmenopausal women and in individuals with chronic kidney disease. Nevertheless, a previous case-control study of more than 14,000 patients show that metformin long-term use may be associated with a slightly increased risk of AD in those aged 65 or older (15). A limitation of this study is that the diagnosis of AD and of other dementia types is not straightforward and it was not possible to adjust for certain potential confounders such as APOE $\epsilon 4$ status, level of education, and lifestyle habits.

At this moment we cannot draw definitive conclusions about the effects of metformin on cognitive function as well as about the cellular and molecular basis of its actions. In fact, basic research and epidemiological studies have yielded conflicting evidence regarding the beneficial versus harmful effects of metformin. Although the *in vitro* studies are essential to dissect and identify cellular and molecular mechanisms, cells are manipulated outside their normal environment and the *in vivo* exposures may be difficult to mimic, which may account for the differences observed in the above-mentioned *in vitro* studies. The disparities (positive versus lack of effect of metformin on cognitive function) found in animal studies, which are instrumental in studying disease mechanisms and testing therapeutic strategies, may be due to differences in the metformin treatment protocols (i.e., dose and duration). Population-

based studies suggest that the cognitive effect of metformin possibly depends on doses and duration of treatment, and target population as defined by the subtype, stage, and severity of cognitive impairment and dementia as well as APOE gene polymorphism. More studies, particularly large-scale epidemiological studies, must be done to evaluate the effect of dose and duration of metformin therapy (monotherapy or in combination with other anti-diabetic agents) using a battery of cognitive tests and the participants must be followed over a number of years. Future studies should also take into consideration the individual biological variation that results from a complex interplay between environmental, genetic and epigenetic factors. In fact, a recent genome-wide complex trait analysis revealed that glycemic response to metformin is heritable (16) suggesting that metformin's action depends, at least in part, on the individual biological variation.

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