

Editorial

# Is Cellular Prion Protein (Prp<sup>c</sup>) an important missing link in Diabetic Stroke?

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**Received:** Aug 02, 2014; **Accepted:** Aug 05, 2014;

**Published:** Aug 08, 2014

More than 347 million people worldwide have diabetes and the number grows considering many more are living with pre-diabetes/insulin resistance [1]. In Canada, more than 9 million Canadians live with diabetes or pre-diabetes with an estimated cost to the Canadian healthcare system of \$16.9 billion a year by the year 2020 (<http://www.diabetes.ca/diabetes-and-you/what/prevalence/>). The overall risk of death among people with diabetes is at least double the risk of those without diabetes [2]. Diabetes contributes to the deaths of 41,500 Canadians each year and most of these (80%) will succumb to heart disease or stroke. Stroke, particularly ischemic stroke, is the leading cause of disability and the second most frequent cause of death in Canada and worldwide. The risk of stroke is increased 1.5 to 3-times in diabetic patients. Moreover, pre-diabetes is now also recognized as a stroke risk factor [3,4]. The widespread obesity and insulin resistance will most likely increase the incidence of stroke. The situation is further exacerbated given that diabetes and hyperglycemia also drastically hinder and worsen post-stroke clinical recovery outcomes [5-7]. A strong body of evidence suggests that diabetes and insulin resistance is no longer affecting peripheral tissues, and also has far reaching pathological consequences on the central nervous system (CNS).

Insulin and its signaling pathway play a pivotal role in brain physiology and pathophysiology (recently Reviewed in [8,9]). However, the direct effect of diabetes, as it pertains to stroke, on the CNS has not been well understood.

Pre-diabetes and diabetes, particularly diet-induced type 2 diabetes, has reached epidemic levels in all age groups. These conditions have been found to impair peripheral insulin functions and also compromises brain insulin signaling pathway [10,11]. The age-related decrease in neuronal insulin receptor (IR) expression [12], may contribute to the accelerated cognitive decline and pathogenesis of Alzheimer's disease (AD) [13,14], as well as more susceptibility to ischemic stroke due to brain insulin resistance. We have recently found that in a rat model of diet-induced brain insulin resistance, the expression of cellular prion protein (PrP<sup>c</sup>) was significantly suppressed compared with normal control rats [11]. The PrP<sup>c</sup>, in contrast to its misfolded scrapie isoform (PrP<sup>sc</sup>), has several important physiological functions including neuro protective activity (reviewed in [15]). It is thus plausible to suggest that the drastic suppression in the insulin resistant brain may partly be involved in higher

susceptibility and vulnerability of pre-diabetic/diabetic individuals to ischemic stroke or even neurodegenerative disease. Insulin and other growth factors may have a regulatory role on PrP<sup>c</sup> gene expression. Both insulin and nerve growth factor can enhance PrP<sup>c</sup> expression levels in a PI-3kinase-independent manner [16]. Human growth hormone and dexamethasone also increase PrP<sup>c</sup> gene expression [17]. Furthermore, insulin receptor functional impairment and glucose-intolerance have been reported in PrP<sup>c</sup> knockout mice [18], as well as scrapie- infected animals and cells [19,20]. It is also noteworthy that in the prion knockout fibroblasts, IGF1 levels increase (most likely to compensate IR signaling impairment) [21], but it was functionally impaired [19,20].

Although studies in animal models of diabetes suggest co-existence of peripheral and central diabetes/insulin resistance [10,11,22], there is still a need for finding specific biomarkers for identifying pre-diabetic brains in individuals with no apparent symptoms but in a higher risk of having ischemic stroke. Moreover, it appears that those therapeutic agents with positive impacts on PrP<sup>c</sup> expression may also be beneficial against ischemic diabetic stroke or reduce its risk. However, more studies are needed to prove the neuro protective role of PrP<sup>c</sup> in diabetic stroke.

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