

## Editorial

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# Adipocytokines: A Potential Link Between Obesity and CNS Disorders

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The interrelationships between obesity and high fat mass with different chronic pathophysiological conditions have been taken into consideration in recent decades along with the growing prevalence of obesity. Epidemiological evidence supports the increased risk of the onset and progression of cardiovascular disease (CVD), hypertension, dyslipidemia, type 2 diabetes and some types of cancers with obesity.<sup>1</sup> Studies in neurological disorders have also suggested the potential contribution of obesity in developing structural pathologies in the brain in different life stages.<sup>2</sup>

Obesity can induce atrophic changes in vulnerable areas of the brain including hippocampus, cingulate gyrus and frontal lobes, which in turn could be a risk factor for Alzheimer's disease (AD).<sup>3,4</sup> Age-related deficits such as decline in immediate memory function have also been exacerbated with higher body mass index (BMI) and abdominal obesity especially in people with AD.<sup>5</sup> Furthermore, the risk of dementia is 2.34 to 3.60 fold higher in obese people with a waist circumference above recommended cut offs.<sup>6</sup> Although, the exact mechanisms by which obesity could influence the CNS are not fully understood, they may involve many mediators including systemic and brain peptides and cytokines.<sup>7</sup> In 2009, it has been confirmed that circulating inflammatory cytokines might mediate the effect of midlife obesity on brain gray matter reduction in pre- and post-menopausal women.<sup>8</sup>

Adipocytes can produce and release some water soluble peptides, adipocytokines, such as leptin, resistin, adiponectin, visfatin,<sup>9</sup> inflammatory cytokines including tumor necrosis factor alpha, transforming growth factor beta, and interleukins (e.g., IL-1, IL-6, IL-10 and IL-8), and some components of the complement system.<sup>10</sup> White adipose tissue deposition may lead to systemic inflammatory state due the imbalance between pro- and anti-inflammatory adipocytokines.<sup>11</sup> Obesity associated inflammation could be deleterious for blood brain barrier (BBB) integrity and predispose of penetration of inflammatory molecules. Abnormal increased concentration of inflammatory cytokines in the local micro-environment of brain parenchyma would be a major contributor of neurological disorders.<sup>12,13</sup>

Adiponectin almost exclusively synthesized by adipocytes. It is well described as an insulin-sensitizing, anti-atherogenic, and anti-inflammatory agent.<sup>14</sup> Serum concentrations of adiponectin may reflect its cerebrospinal fluid (CSF) levels.<sup>15</sup> Brain expression of adiponectin receptors, AdipoR1 and AdipoR2, suggests that adiponectin signaling could participate in neurological pathways<sup>16</sup>; however, the precise role of this adipokine in CNS disorders is not clear. While various studies suggest that decrease in serum levels of adiponectin is associated with cognitive dysfunction, others did not find any clear relationship between adiponectin levels and AD progression.<sup>17</sup> In addition, it has been reported that low serum levels of adiponectin may increase the risk of multiple sclerosis (MS).<sup>17</sup> Although, adiponectin levels remained unchanged in some investigations in Parkinson's disease (PD),<sup>18,19</sup> other studies supported a protective effect of treatment with recombinant adiponectin against neurodegeneration.<sup>20</sup> It seems that understanding the relationship between adiponectin with neurodegenerative and CVD is complex and requires more studies.

Visfatin is another major adipocytokine, which is strongly correlated with visceral fat

mass and higher BMI.<sup>21</sup> The pro-inflammatory properties of visfatin could stimulate other inflammatory cytokines, which in turn might induce some inflammatory disorders.<sup>22,23</sup> Serum level of visfatin is associated with ischemic stroke<sup>24</sup> and the consequences of traumatic brain injury.<sup>25</sup> Hallschmid et al<sup>26</sup> showed that CSF level of visfatin decreased with fat accumulation, which could indicate damage of visfatin transfer system across BBB. Visfatin might have unfavorable effects on CNS and promote damages to dopaminergic neurons and brain regions such as cortex and hippocampus. Visfatin induced pathological changes in the brain structures that would be accompanied with higher risk of neurodegenerative diseases including AD and PD.<sup>27</sup>

There are also other studies discussing the potential role of other adipocytokines including leptin and resistin in CNS. However, the data obtained from studies on adipocytokines in neurological disorders are still contradictory and unclear. Considering the increasing number of newly identified adipokines and adipocytokines, and their possible link with the onset or exacerbation of neurological diseases, is a great field of study to investigate the potential causative, diagnostic or therapeutic role of these adipose derived peptides in CNS disorders.

### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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