Neuron impairment or loss in brain may be responsible for type 2 diabetes and essential hypertension

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Type 2 diabetes and essential hypertension are both very common chronic diseases. Type 2 diabetes is often associated with hypertension, but the exact causes of them are unknown. Here, based on recent investigations, we will look at the pathogenesis of these two diseases in a new light.

Nowadays, the number of people diagnosed as type 2 diabetes has been over 150 million worldwide[1], and that of essential hypertension is about 1 billion[2], regardless of patients undiagnosed. Although having been researched for decades, the pathogenesis is not fully understood. The predominant theories consider type 2 diabetes as a metabolic disorder, which is characterized by insulin resistance. Insulin resistance can progress to type 2 diabetes, but its cause is now obscure, which may be food, genetic factors and some states of disease. If the pancreatic beta-cells cannot produce sufficient insulin in a condition of hyperglycaemia, insulin resistance has transited to type 2 diabetes[3]. Interestingly, even in the absence of hyperglycaemia, insulin resistance is correlated with obesity[4] and hypertension[5]. Some researches suggested that type 2 diabetes is a risk factor for hypertension[6], some others argued that insulin resistance and obesity might be the catalyst for each other[7], and a prevailing view considers obesity as a risk factor for both type 2 diabetes (or frank insulin resistance) and essential hypertension[8]。 An obvious question is posed: obesity and type 2 diabetes, who is the egg and who is the hen? Just recently, O'Rahilly reviewed the genetic researches on type 2 diabetes and obesity, and suggested that intrinsic biological but not environmental factors have a major role[9]. Although several genes have been targeted, the fundamental etiological factor of these two diseases has not been illuminated. We should notice that the managements for type 2 diabetes are now to aim directly at regulating blood glucose or blood pressure. Patients tried their best to avoid aggravation, but most of them still suffered severely from the disease especially when they get old. Therefore, the crucial biological factor deciding the onset of this disease has not been discovered. The same circumstances also exist in the research and therapy for essential hypertension[10]. A theory approved by many researchers relates the renin - angiotensin system to the pathogenesis of hypertension[11,12], but some hypertensive patients having low renin levels and the failure of therapy make this theory imperfect. In our opinion, type 2 diabetes and essential hypertension may share a common biological origin: neuron impairment or loss in brain. There have been documents raising the new point that the central nervous system should be the therapeutic target for type 2 diabetes or hypertension[13,14,15,16,17]. Our viewpoint is more radical, and we deem that the knowledge of type 2 diabetes and essential hypertension should be re-organized in order to improve the diagnosis and therapy. Before explaining our viewpoint, let's inspect the similarities of these two diseases.

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Similarities between type 2 diabetes and essential hypertension on risk factors

Some similarities on risk factors should be mentioned here for a better explanation later. (1) Obesity is found in at least 80% of patients diagnosed with type 2 diabetes[4], and for essential hypertension, the percentage is about 85%[18]. Now, obesity is regarded as a risk factor for both of these two diseases. (2) Chronic stress, which is related with high levels of corticosteroid[19], facilitates the pathogenesis of both diseases. In China, most patients diagnosed with type 2 diabetes and essential hypertension in 1990's are those engaged in job of high stress, for example, the executive of a large company. Nowadays, more and more city dwellers in China are affected by these diseases. Evidence suggested that high levels of corticosteroid will damage neurons in brain[20]. Sub-clinical Cushing's syndrome, which characterizes as cortisol excess, is also associated with type 2 diabetes and hypertension[21]. (3) Diets that are high in fatty acid increase the risk of insulin resistance and essential hypertension. Traditional viewpoints focused mainly on disorders of fat cell metabolism and the reduced compliance of blood vessels respectively. (4) Sympathetic nervous system activation exists in both diseases[7], and sympathetic excitation caused by sleep apnea increases corticotropin releasing hormone, cortisol production and inflammatory cytokines[22] which correlate with stress and fatigue. (5) Cigarette smoking is a known factor for the development of both diseases. (6) Both diseases are age related[23]. (7) Both diseases are heritable and may caused by more than one gene[9,24]. Although there are so many similarities on risk factors, researches on pathogenesis of type 2 diabetes and essential hypertension are separate from each other till now. We think that explaining the pathogenesis of these two diseases by a single reason may be more harmonized with the circumstances.

Neuron impairment or loss in brain may be the primary pathological change

In our point of view, type 2 diabetes and essential hypertension are not just diseases of endocrine system and cardiovascular system respectively, but may substantially be a disease of central nervous system. Stress or other environmental factors make some neurons in brain unhealthy. And then, if the unhealthy stimuli persist and accumulate, neurons may die and be eliminated. This kind of neuron loss may happens firstly and mainly at solitary nucleus in brain stem, or amygdala in the limbic system for some unknown anatomical or physiological reasons. At the early stage, only a few neurons are impaired or lost, so the neurons alive can keep working as compensation. During this time, no clinical symptoms could be observed. If neurons continue to lose, the homeostasis will not be sustained, so the pathological changes get into infernal circle. From then on, several symptoms emerge. The neuron loss at solitary nucleus make the sympathetic system relatively predominate and overactive. Sympathetic excitation can raise the cardiac output. Simultaneously or at a later stage, it can also increase the total peripheral resistance. This may be the influence of neuron loss for cardiovascular system. On the other hand, sympathetic excitation increases adrenaline levels, which stimulate the release of corticosteroid, and then increases stress responses. So the insulin resistance is a result of persistent sympathetic excitation, but not just the metabolic disorders of fat cells, skeletal muscle cells or liver cells. Insulin resistance leads to raised pancreatic beta cell secreting, which may be exhausted, and the blood glucose will ultimately go out of control. This is our explanation of the pathogenesis of type 2 diabetes. The diagram of the complete process is presented in Figure 1.

Discussion about neuron impairment or loss at solitary nucleus or amygdala

Why is solitary nucleus or amygdala the suspected region of neuron impairment or loss? Documents of Researches on neuroanatomy and neurophysiology which are not new give us the clue. Solitary nucleus is a centre of parasympathetic system. There are glucose sensitive neurons at solitary nucleus which transmit satiate information to hypothalamus[25]. The glucagons-like peptidergic neurons at solitary nucleus are one of the target for leptin[26], which reduces food intake and lowers the body weight[27]. Solitary nucleus locates at the crossroad of nerve tract related to cognitive and autonomic modulation[28], and is vulnerable to reactive oxygen[29]. Furthermore, most neurons at solitary nucleus express glutamate receptor[30], and are innervated by excitatory afferent fibres[31], so they may be vulnerable to excitotoxicity[32]. An important gamma-aminobutyric acid (GABA) afference of solitary nucleus is from amygdala[33], which play a pivotal role in emotion and stress integration[34,28]. This inhibitory projection can be regarded as a protector as well as suppression for the neurons at solitary nucleus. In the condition of chronic stress, hippocampus and amygdala will be influenced under the control of cerebral cortex[20], and the solitary nucleus may be involved accordingly. The neuron impairment or loss at solitary nucleus will lead to attenuation of parasympathetic system and then the sympathetic system predominates. As the process of figure 1, persistent sympathetic excitation results in infernal circles. On the other hand, if the impairment takes place in neurons of amygdala (also because of chronic stress), the inhibitory projection to solitary nucleus is weakened, and the possibility of excitatory impairment for neurons at solitary nucleus will increase. So, neuron impairment or loss in either of solitary nucleus or amygdala can develop to the same outcome.

The schematic representation (Figure 2) of the role of solitary nucleus and amygdala in the nervous system may be helpful for comprehending their impairment in a view of evolution. Compared with other animals, the neocortex of human and some other higher mammals is extended greatly. The extended neocortex likes a new subassembly added to the old limbic system. It is this new subassembly that increases the pressure of the old autonomic nervous system. The complicated mental activity, which is related to the neocortex, may influence the autonomic nervous system through amygdala-solitary nucleus pathway. The vulnerability of this pathway may be a bottleneck of the brain evolution.

How do risk factors correlate with neuron loss?

We should now use the new viewpoint to re-inspect the risk factors for type 2 diabetes and essential hypertension.

Stress and corticosteroid level. Nowadays, chronic stress is very common for city dwellers all over the world. Neuronal impairments made by chronic stress may be crucial for the pathogenesis of type 2 diabetes and essential hypertension. Animal experiments link the stress condition with high levels of corticosteroids[19]. Early experiment found that the hippocampal CA3 pyramidal neurons is lost during chronic glucocorticoid administration[35]. Some researchers did not find the evidence for neuron loss, but verified that the total volume of hippocampus is reduced[36], and some neuronal processes are replaced by glial processes[37]. Rats receiving high doses of corticosterone for 3 weeks were found that their dendrites of layer II/III pyramidal neurons in the medial prefrontal cortex retracted compared to control animals[38]. These morphological evidences from hippocampus and cerebral cortex suggest that a high corticosteroid level is harmful for neurons in brain, including those at solitary nucleus. The detailed cellular and molecular mechanism for the

central nervous system impairment caused by stress was reviewed by Arnsten[20] and Goshen[39] recently. Amygdala is responsible for emotion and stress integration[34,28], whose total dendritic length and spinogenesis of pyramidal and stellate but not bipolar cells increase after exposed to restraint stress for 10 to 20 days[40]. Fortified input may over-excites the amygdala, which receives glutamatergic projection from widespread cortical areas. In the view of neuron loss, pathologic changes in amygdala or solitary nucleus then emerge.

Obesity. Obesity is very common all over the world. Although there are hypotheses about why obesity is related to type 2 diabetes and essential hypertension, the current explanations predominantly focus on the disorder of metabolism, but not that of central nervous system. In fact, many obese individuals have obstructive sleep apnoea syndrome[41], although sometimes they didn't aware. The hypoxia in sleep apnoea will cause a series of disorders, for example, activation of the sympathetic nervous system[7]. Evidence suggested that sleep apnoea is related to insulin resistance even in non-obese subjects[7]. Sleep apnoea is also related to disorders of cardiovascular system[42]. Furthermore, chronic sleep loss per se can alter the metabolic and endocrine functions[43]. Average sleep duration in 1960's is 8 ~ 8.9 h, which decreases to 6.9 ~7.0 h at the end of the 20th century[7]. On the other hand, the high fatty acid intake of some obese individuals affects the health of neuron (see below). So, Sleep loss and energy excess, which is very common worldwide, are both related to insulin resistance. If the neurons at solitary nucleus or amygdala are impaired or lost, the cardiovascular system will be involved, so the chronic raising of blood pressure and insulin resistance can coexist with each other. It is sound to explain the relation between obesity and type 2 diabetes or essential hypertension by the viewpoint of neuron impairment or loss in brain.

Taking food with high fatty acid. Evidence shows that the solitary nucleus represents the gate for central processing of vagally mediated afferent information related to fatty acid oxidation, and the central nucleus of the amygdala also plays a role in this mechanism[44]. If fatty acid is ingested, liver cell produced ketones will be released into circulation, and be utilized by nervous system as an energy source[45]. Food intake with high fatty acid leads to high levels of circulating ketones, so the probability of neuron injury in brain is increased. As discussed above, neurons at solitary nucleus or amygdala may be more vulnerable.

Smoking. There are neurons at solitary nucleus that react to nicotine. The nicotinic and muscarinic actions can be detected in their membrane, both of which eliminate the reflex effect of pressure receptor at the aortic arch[46]. The nicotine in tobacco is distributed quickly through the bloodstream and crosses the blood-brain barrier into the central nervous system. The autoregulation function of neurons at solitary nucleus may be impaired by nicotine[47], and the blood pressure cannot be accommodated promptly. The solitary nucleus is an important centre of the autonomic nervous system, and its impairment will further influence the metabolism. In addition, nicotine can activate the sympathetic nervous system[48], and its metabolites[49](for example, cotinine) can also have an activating role. Furthermore, Tobacco smoke contains monoamine oxidase inhibitors[50], which significantly decrease MAO activity in smokers and delay the breaking down of monoaminergic neurotransmitters including adrenaline. So, smoking can be the risk factor for both type 2 diabetes and essential hypertension.

Pregnancy. Some pregnant women have the symptoms resembling the type 2 diabetes, which named gestational diabetes[51]. It occurs in less than one tenth of all pregnancies and may disappear after delivery. Many researches and therapeutic guidelines focused on preventing the damage for

health of the foetus or mother, but the pathogenesis is not clear. We should notice that women with gestational diabetes have a 17% ~ 63% risk of nongestational diabetes within 5 to 16 years after pregnancy[51]. This fact suggests that the neurons in brains of women at clinical risk may already be unhealthy, which are still competent reluctantly for their function. Changes on endocrine secretion during pregnancy may make the burden of these neurons heavier, and typical symptoms then manifest. If the neuron impairment exists at solitary nucleus, the hypertension in some pregnant women may share the same reason with gestational diabetes. Evidence showed that young adults with a very low birth weight have higher indexes of insulin resistance, glucose intolerance and higher blood pressure than those born at term[52]. This phenomenon suggests that the development which is not consummate may be a risk factor, and it is related to either the mother's temporary condition or the genetic background proper.

Aging and genetic background. The incidence of type 2 diabetes or essential hypertension increases with age. This age correlation also exists in Parkinson disease, Huntington disease and Alzheimer's disease, which are related to neuron degeneration[53]. On one hand, diseases of this kind usually affect aged people because it is difficult for senescent neurons to recover from impairment. On the other hand, these diseases have a strong genetic background[54,55,56]. Not everybody will be affected during aging. The genetic characteristics portray the process of pathogenesis. The genetic background of type 2 diabetes and essential hypertension is one of the most attractive domains of current research, but the achievement is still far from clinical application.

A special factor: lack of physical exercise. The sedentary lifestyle is a feature for whom work in an office. Type 2 diabetes and essential hypertension often affect these persons. Lack of physical exercise may be the reason. Plenty of evidence suggests that exercise can improve learning and memory[57] and can counteract the mental decline that comes with age[58]. Exercise can also amend apnoea in sleep, regardless of body mass index, age or gender[7]. A recent review focused on the relation between exercise and neuronal health suggested that brain derived neurotrophic factor (BDNF) may be a candidate for the saviour[59]. Exercise augments the effects of BDNF on synaptic plasticity trough its tyrosine kinase B receptor[59]. This may be a crucial mechanism for neurons to recover from stress. If the BDNF is not sufficient, neurons in brain may be more vulnerable. BDNF is expressed by many neurons of the central nervous system, and can promote the regenerative sprouting[60], so it can be regarded as a compensation for the bottleneck formed during neocortex expansion.

Cognitive dysfunction in type 2 diabetes and essential hypertension

Some patients with type 2 diabetes have cognitive impairment[61]. Type 2 diabetes now is implicated as a risk factor for age-related cognitive decline and dementia. Individuals with type 2 diabetes also more likely to develop to Alzheimer's disease or vascular dementia[62]. In the viewpoint of neuron loss, the projections originated from solitary nucleus or amygdale to widespread areas of neocortex is lost during the pathogenesis of type 2 diabetes. As a result, the autonomic feedback of neocortex and the emotional component of sensory input are weakened. The emotional component of cerebral function, which is related to attention, memory and judgment[63] will be impaired. After typical clinical symptoms' appearing, hyperglycaemia and some other metabolic disorders then make the condition worse. A phenomenon should be noticed that cognitive impairment is limited in patients with type 2 diabetes up to the age of 60 years, but a

study on the effect of cognition in the oldest old (up to the age of 85) did not find an association between diabetes and cognitive decline[23]. Biessels mentioned that this may be a survivor effect[23], and we agree with the point. The survivor effect can be explained by the genetic view.

Essential hypertension is also related to dementia in older patients[64]. The pathogenesis of this kind of dementia, which is now not clear, may be similar to that of type 2 diabetes.

Regarding the complications

There are typical complications for type 2 diabetes and essential hypertension. Some of these complications, for example the disorders at kidney, retina and distal part of feet, may correlate to hyperglycaemia or disorders of microcirculation, which are explained well by traditional theories. Most of the complications generate after the neuron impairment or loss in brain, but in our opinion, the collapse of sexual functions[65] and pain[66] seen in some patients with type 2 diabetes may be related primarily to the pathogenesis of the disease. Unfortunately, based on the present reports of researches, the underlying mechanism still cannot be well elucidated.

Significance, prospect and problems to solve

According to the viewpoint of neuron impairment or loss, the pathogenesis of type 2 diabetes and essential hypertension can be now associated for a better prevention and cure. As expounding above, when diagnosed with either or both of these diseases, it is too late. The traditional treatments for type 2 diabetes focus on controlling of blood glucose, blood pressure and lipids to minimize the risk of long-term consequences, and those for essential hypertension aim at depressing the blood pressure. All these treatments do not catch the point, but postpone the aggravation of the symptoms. We suggest that prevention is far more effective and may be the exclusive way to cure both diseases. Modified lifestyle and neurotrophic medication may be the candidates for individuals with a definite genetic background. The valid prevention can protect neurons in brain, so the consequent symptoms will not emerge. If it is the case, millions of people will avoid the harassing of these two common chronic diseases, and resources of public health will not be wasted.

Although having a new light for the future research, there is still a distance from practice. First, the structure and function of human neocortex is far more complicated than that of some model animals. Therefore, there are difficulties in replicating chronic stress exactly. Technically, the complexity of surrounding structures of solitary nucleus and amygdala increases the difficulty for experimental analysis. So it is necessary to design experiments more carefully and rigorously in order to find the exact location and molecular mechanism of neuron impairment or loss. We have not approached the question that whether the over-activated inhibitory projection from amygdala per se is harmful to neurons at solitary nucleus, which is worthy of being deeply researched in future. The current focus of researches is on the hypothalamus[67,15], but we don't think this hypothalamus-centred view can well explain the pathogenesis of type 2 diabetes and essential hypertension. Second, because of the complexity of the anatomy and function of the brain, whether an individual is vulnerable to risk factors of theses two diseases may be decided by the postnatal developmental process. The process is regulated by more than one gene. This viewpoint is being confirmed by current researches[9,11]. That is to say, there is still a great deal of works to do for revealing the genetic regularities. Third, patients who have been diagnosed with type 2 diabetes (and some with intractable essential hypertension) have missed the opportunity for

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Figure 1 | Process of the pathogenesis of type 2 diabetes and essential hypertension. Risk factors and the disease state are displayed in frames of ellipse, and the pathological changes are in the frames of rectangle. Neuron impairment or loss is the primary change of the whole process, and is responsible for the genesis of both type 2 diabetes and essential hypertension.

Figure 2 | The schematic representation of the amygdala-solitary nucleus pathway. The amygdala belongs to the limbic system, which closely related to the neocortex. The solitary nucleus is one of the centres for the autonomic nervous system, and regulates the parasympathetic function. The amygdala-solitary nucleus pathway coordinates the psychical and visceral activities. The expansion and plastic changes of the neocortex may make the burden of the amygdala-solitary nucleus pathway too heavy.