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Review

The potential antidepressant and antidiabetic effects of galanin system

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ABSTRACT

Epidemiological and clinical studies demonstrated that type 2 diabetes mellitus and depression are interconnected. Depression is an important risk factor for the development of type 2 diabetes mellitus, while patients with type 2 diabetes mellitus frequently have depressive symptoms. Despite many studies recently probed into the comorbid state of both diseases, so far the precise mechanism for this association is poorly understood. Experiments have demonstrated that neuropeptide galanin is involved in the pathogenesis of depression and type 2 diabetes mellitus. This review provides a new insight into the multivariate relationship among galanin, depression and type 2 diabetes mellitus, highlighting the effect of galanin system on the cross-talk between both diseases in human and rodent models. The current data support that activating central GalR2 attenuates insulin resistance and depressive feature in animal models. These may help us better understand the pathogenesis of both diseases and provide useful hints for the development of novel therapeutic approaches, i.e. to coadministrate GalR2 agonist with traditional antidepressive and antidiabetic medicines to treat depression and type 2 diabetes mellitus.

Contents

1. Introduction

Diabetes mellitus and depression are two chronic and prevalent diseases which affect millions of people all over the world. The major characteristics of type 2 diabetes mellitus are impaired insulin sensitivity and glucose intake in myocytes, hepatocytes and adipocytes via modification of the insulin signaling pathways, resulting in hyperglycemia and hyperinsulinemia (Taylor, 2012). There is a rapidly upward trend in the incidence of both diseases. In 2012, there are estimated 371 million people with diabetes in the world, which will expectedly rise to 552 million by 2030 (Guariguata, 2012; Whiting et al., 2011). Diabetes is responsible for about 1.256 million deaths globally in 2008 (Kaur et al., 2013).

Persons with major depression have limited social life and increased suicide risk due to their symptoms, including anhedonia, irritability, depressed mood, difficulty in concentrating, and abnormal appetite and sleep (Leone et al., 2012). Depression is an important and

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independent cardiovascular risk factor (Fontoura et al., 2012; Pinto et al., 2008, 2012). Depressive patients have low plasma levels of L-arginine and impaired intraplatelet nitric oxide and platelet hyperaggregability (Fontoura et al., 2012; Pinto et al., 2008, 2012). These implicate that there is an impairment of L-arginine–NO signaling pathway in platelets of depressive patients which may play critical roles in the multifaceted process of cardiovascular events. Depression is one of the most burdensome diseases worldwide frequently accompanied with suicide. Approximate 120 million people are currently affected by depression worldwide (Feixas et al., 2013). In 2001, depression was the fourth main cause of morbidity and could rise to second place by 2020, only after cardiovascular diseases (Feixas et al., 2013).

Both depression and type 2 diabetes mellitus are multifactorial diseases, caused by the complex interactions of genetic and environmental risk factors. A lot of mutual factors are involved in the pathogenesis of both diseases, including genetic, character, physical inactivity, stressful environment, psychological and social factors, as well as alterations in several neuroendocrine and immune systems (Qi et al., 2008). Recent studies have provided compelling clues that a lot of hormones, including galanin are implicated in the cross-talk between depression and type 2 diabetes mellitus.

Galanin, a 29-amino acid peptide hormone, was discovered in 1983 in the porcine intestine (Tatemoto et al., 1983). This peptide is widely distributed throughout the central and peripheral nervous systems as well as other tissues (Fang et al., 2012a) to modulate depression (Kuteeva et al., 2008, 2010), cognition, neuroendocrine, Alzheimer's disease (Lundström et al., 2005), neuronal differentiation (Agasse et al., 2013), pain threshold (Yu et al., 2013), food intake and energy homeostasis (Fang et al., 2012b). The galanin receptor family currently comprises three members, GalR1–3 (Webling et al., 2012). These different subtype receptors may be related to the different functions of galanin.

This article summarizes our recent studies and updated information obtained from researches on human and rodent models, to highlight the effects of galanin and its receptors on the cross-talk between type 2 diabetes mellitus and depression. These provide a new insight into the multivariate relationship among galanin, depression and type 2 diabetes mellitus, suggesting that galanin system is implicated in the cross-talk between both diseases.

2. The relationship between type 2 diabetes mellitus and depression

In 1684, the physician, Thomas Willis, first identified glycosuria as a sign of diabetes and suggested that diabetes resulted from long sadness, sorrow and depression (Leone et al., 2012; Rubin and Peyrot, 2002). In clinic, type 2 diabetes mellitus and depression are frequently paragenetic.

Depression and its associated symptoms constitute a major risk factor in developing type 2 diabetes mellitus. Depression may accelerate the onset of diabetic complications and exacerbate the symptoms of diabetic patients through insufficient sleep, disturbed emotion, poor diet, little or no exercise and other factors relative to depression (Engum, 2007; Knol et al., 2006; Mezuk et al., 2008). Depressed subjects are less likely to conform to recommendations concerning their glycemic control and consequently impact the outcome of the disease therapy (Bassett et al., 2012; Masmoudi et al., 2013). Emotional and psychological disorders may reduce the quality of life of patients with diabetes. Next, depression may influence the secretion of several hormones, including serotonin, dopamine, norepinephrine and acetylcholine, which may contribute to insulin resistance and the development of type 2 diabetes (Golden et al., 2008; Luo et al., 1999). For example, a chronic increase in serotonin and norepinephrine contents in the ventromedial hypothalamus may produce hyperinsulinemia, insulin resistance and glucose intolerance (Luo et al., 1999). Last, depressive symptoms are also associated with activation of the hypothalamus–pituitary–adrenal axis, the sympathetic nervous system and the proinflammatory cytokines, which may interfere glucose metabolism and develop type 2 diabetes mellitus (Audet and Anisman, 2013; Masmoudi et al., 2013).

Similarly, the epidemiological studies have demonstrated that patients with type 2 diabetes mellitus are easy to induce depressive symptoms, two times more likely compared with nondiabetic individuals (Golden et al., 2008; Nouwen et al., 2010; Roberts et al., 2003). This may result from functional disability, dietary control, bothersome adherence to diabetes medication, diabetes complications and other psychological factors (Kaur et al., 2013; O'Connor et al., 2009; Rotella and Mannucci, 2013). Hyperglycemia and hyperinsulinemia increase the activity of the hypothalamic–pituitary–adrenal axis, which disturbs the function of the nervous system and consequently causes depression too. Adaptation to diabetes mellitus is a difficult and complex process. This necessitates several adjustments in the patient's lifestyle which may affect their emotional responses, resulting in withdrawal, loneliness, guilt feelings and hopelessness suicidal ideation.

The causal relationships underlying depression and diabetes are interconnected and complex. The monoaminergic theory may account for the link between both diseases. It has been shown that the norepinephrine mRNA expression levels are decreased in the locus coeruleus and other brain regions of experimental diabetic rats (Petrisic et al., 1997). The serotonin reuptake inhibitor, fluoxetine, may effectively reduce the severity of depression and improve glycemic control in patients with comorbid depression and diabetes after 8 weeks of treatment (Goodnick, 2001; Lustman et al., 2000), and a long-term treatment with milnacipran, a serotonin and norepinephrine reuptake inhibitor, results in significant improvement of both diseases (Abrahamian et al., 2009, 2012).

3. The antidepressant effect of galanin system

Pharmacological studies have demonstrated a role for galanin in regulating depression-like behavior in clinical and animal studies (Kormos and Gaszner, 2013; Kuteeva et al., 2010) (see Table 1). A high galanin expression level was found in the hippocampus and dorsal raphe nucleus of mice with chronic restraint stress-induced depression-like behavior (Zhao et al., 2013). The rats who received an intracerebroventricular injection of galanin significantly increased immobility, which was blocked by co-administration of galanin antagonist M35 in a forced swim test (Kuteeva et al., 2007). The injection of M35 alone produced a significant decrease in immobility in the forced swim test (Kuteeva et al., 2007). Galanin decreased motor activation and decreased appreciation of pleasurable stimuli (anhedonia) (Weiss et al., 1998). Galanin receptor agonist, galnon, was found to produce an antidepressant-like effect in the forced swim task (Lu et al., 2005). Interestingly, four-week treatment with the

Table 1
The effect of galanin on depression.

Species	Experimental model	Effect	References
Rat	FST (i.c.v. galanin)	Pro-depressive effect	Weiss et al. (1998)
Rat	FST (i.c.v. M35)	Antidepressant effect	Kuteeva et al. (2007)
Rat	FST (i.c.v. M617)	Pro-depressive effect	Kuteeva et al. (2008)
Rat	FST (i.c.v. M871)	Pro-depressive effect	Kuteeva et al. (2008)
Rat	FST (i.c.v. ARM1896)	Antidepressant effect	Kuteeva et al. (2008)
Rat	FST (i.c.v. SNAP37889)	Antidepressant effect	Swanson et al. (2005), Barr et al. (2006)
Mouse	FST/TST (i.v. J18)	Antidepressant effect	Saar et al. (2013a)
Mouse	TST (i.c.v. M1160)	Antidepressant effect	Saar et al. (2013b)
Mouse	GalR2 overexpressing mice	Antidepressant effect	Le Maître et al. (2011)
Mouse	GalR2 KO mice	Pro-depressive effect	Bailey et al. (2007)
Mouse	GalR2 KO mice	Pro-depressive effect	Lu et al. (2008)

M35, galanin receptor antagonist; M617, GalR1 agonist; M871, GalR2 antagonist; ARM1896, GalR2/3 agonist; SNAP37889, GalR3 antagonist; J18, GalR2 agonist; M1160, GalR2 agonist; KO, knockout; i.c.v., intracerebroventricular; i.v., intravenous; FST, forced swim test; TST, tail suspension test.