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Review article

Epigenomic changes associated with impaired norepinephrine transporter function in postural tachycardia syndrome

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ABSTRACT

The postural tachycardia syndrome (POTS) is characterised clinically by symptoms of light-headedness, palpitations, fatigue and exercise intolerance occurring with standing and relieved by lying down. Symptoms occur in association with an inappropriate rise in heart rate in the absence of a fall in blood pressure with the assumption of standing. The pathophysiology of POTS is complicated and poorly understood. Plasma norepinephrine (NE) is often elevated in patients with POTS, resulting in consideration of dysfunction of the norepinephrine transporter (NET) encoded by *SLC6A2* gene. Whilst some studies have implicated a defect in the *SLC6A2* gene, the cause of reduced *SLC6A2* expression and function remains unclear. The search to explain the molecular mechanism of NET dysfunction has focused on genetic variation in the *SLC6A2* gene and remains inconclusive. More recent studies show epigenetic mechanisms implicated in the regulation of *SLC6A2* expression. In this article, we discuss the epigenetic mechanisms involved in *SLC6A2* repression and highlight the potential therapeutic application of targeting these mechanisms in POTS.

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1. Introduction

Postural tachycardia syndrome (POTS) is a clinical syndrome associated with orthostatic intolerance, characterised by symptoms of light-headedness, palpitations, fatigue and exercise intolerance occurring with standing and relieved by lying down. Symptoms occur in association with an inappropriate rise in heart rate in the absence of a fall in blood pressure with the assumption of upright posture. As norepinephrine (NE) levels are often elevated in patients with POTS, reduced neuronal NE reuptake activity has been implicated in the pathophysiology of POTS and has been attributed to decreased norepinephrine transporter (NET) gene, *SLC6A2* expression (Bayles et al., 2012; Jacob et al., 2000; Lambert et al., 2008; Shannon et al., 2000). Furthermore, pharmacological inhibition of NET in healthy individuals is consistent with a POTS-like phenotype (Schroeder et al., 2002). These studies support the idea that deficiency of NET may contribute to the pathophysiology of POTS.

The causes of reduced *SLC6A2* expression are poorly understood. Elucidating the genetic determinants, namely sequence variation has definitively identified a point mutation in one family (Shannon et al., 2000). However, follow up studies examining single nucleotide polymorphism (SNP) in the *SLC6A2* gene has questioned the genetic basis influencing the disease aetiology (Bayles et al., 2012; Ivancsits et al., 2003). There is now increasing interest in exploring how genetic variation could influence disease associated epigenetic variation.

DNA methylation is one of the best-studied epigenetic determinants, generally inversely associated with gene expression. Recent studies of *SLC6A2* promoter methylation show no difference between healthy individuals and patients with POTS (Bayles et al., 2012). Furthermore, there was no significant difference in DNA methylation pattern of *SLC6A2* promoter region between patients with major depression and panic disorder and healthy volunteers (Bayles et al., 2013). In contrast, the chromatin modifying events are associated with *SLC6A2* repression. Indeed, the binding of Methyl CpG binding protein 2 (MeCP2) and histone-modifications are thought to be associated with impaired *SLC6A2* expression in POTS as illustrated in Fig. 1 (Bayles et al., 2012). Furthermore, histone deacetylase inhibitors (HDACi) that are effective in experimental and clinical depression are shown to increase *Slc6a2* transcription *ex vivo* in mouse primary cortical cells, demonstrating the importance of histone modifications in *SLC6A2* gene regulation (Bayles et al., 2010). In this review we focus on the epigenetic mechanisms associated with *SLC6A2* repression and highlight the potential therapeutic applications of targeting these regulatory pathways.

2. Postural tachycardia syndrome (POTS)

POTS is a condition of orthostatic intolerance primarily affecting females (Garland et al., 2007). It is characterised by an increase in heart rate of 30 beats per minute or more within 10 min of standing that is not accompanied with orthostatic hypotension (Freeman et al., 2011). POTS individuals have impaired cognitive function especially during standing and head-up tilting and poor health related quality of life with increased depression and anxiety (Anderson et al., 2014). POTS is associated with multiple symptoms including light-headedness, fatigue, palpitation, chest discomfort, shortness of breath and nausea (Raj, 2006). Other features may include migraine like headaches on standing (Khurana and Eisenberg, 2011) and symptoms of gastrointestinal abnormality such as nausea (Zarate et al., 2010). Some patients may show an increase in standing blood pressure (Grubb, 2008). Although POTS is a heterogeneous condition, the increase in heart rate on standing is the key diagnostic feature of the condition. The increase in heart rate with symptoms of orthostatic intolerance, which improve on recumbency, persisting for more than 6 months define this syndrome (Raj, 2013). POTS is an uncommon disorder, most commonly presenting in the late teens and early twenty's with a reported population prevalence of 0.2%, approximately 75% of whom are female (Benarroch, 2012; Sheldon et al., 2015). Although POTS has not been associated with increased mortality, there can be significant morbidity as a result of the associated functional impairment (Raj, 2013).

Identification of the underlying pathophysiology of POTS has been challenging due to the existence of multiple causes. Several pathophysiological mechanisms have been proposed, categorized as neuropathic, hypovolemic and hyperadrenergic. Neuropathic POTS is characterised by decreased adrenergic vasoconstriction either in the lower limbs or in the splanchnic vasculature. This was associated with venous pooling in the lower limbs, splanchnic and/or pelvic circulation (Stewart et al., 2003). Consistent with this finding, evaluation of sympathetic nervous system function in POTS patients performed using three separate stimuli – the cold pressor test, nitroprusside and tyramine resulted in elevated NE spillover in the arms of patients and control individuals but failed to increase NE spillover in legs of patients alone (Jacob et al., 2000). The neuropathic condition is also characterised by reduced release of NE in lower limbs in response to orthostatic stress, and loss of sweating in the feet on thermoregulatory sweat test and quantitative sudomotor axon (Thieben et al., 2007). More recent studies have shown reduced cardiac sympathetic innervation in POTS using radioactive *meta*-iodobenzylgaunidine (MIBG) neuroimaging (Haensch et al., 2010, 2014). MIBG is a ligand for NET, which mediates uptake into adrenergic neurons. Quantification of sympathetic innervation *in vivo* by scintigraphy using MIBG measures the relative distribution of adrenergic neurodensity and function. Myocardial MIBG uptake was reduced in 20% of POTS patients, indicative of diminished postganglionic adrenergic innervation (Haensch et al., 2010). In a subsequent study, intraepidermal nerve fiber (IENF) density and MIBG uptake were measured in 84 POTS patients (Haensch et al., 2014). IENF density was examined using protein gene product 9.5 (PGP9.5) immunohistochemistry in skin biopsies. Skin biopsy using anti-PGP9.5 immunohistochemistry is used for morphological analysis of autonomic nerve fibers in peripheral neuropathies (Lauria et al., 2010). IENF density was slightly below the normal range in 45% of patients whereas 21% of patients showed reduced uptake of MIBG. Low IENF density was correlated with decreased cardiac uptake of MIBG, indicating a subset of neuropathic POTS patients show small fiber neuropathy of the skin associated with the reduced myocardial postganglionic sympathetic innervation (Haensch et al., 2014).

Some studies have reported reduced blood volume including red cell and plasma volume in POTS (Raj et al., 2005; Stewart et al., 2006). The renin-angiotensin aldosterone system (RAAS) plays an important role in blood volume regulation (Bollag, 2014). Hypovolemia usually increases RAAS activity, activating sodium retention to restore extracellular fluid volume. POTS individuals have compromised RAAS activity as well as reduced aldosterone levels (Raj et al., 2005). Hyperadrenergic POTS is characterised by increased adrenergic vasoconstriction. Some studies report POTS patients with high systemic plasma NE when compared to healthy individuals whereas conflicting results have been reported (Furlan et al., 1998; Jacob et al., 2000, 1999; Lambert et al., 2008). This is probably because of the heterogeneous nature of POTS. Excessive tachycardia in the hyperadrenergic state on postural change is thought to associate with increased release (Goldstein et al., 2002) or decreased clearance of NE (Esler et al., 1990; Jacob et al., 2000, 1999; Lambert et al., 2008). Decreased clearance of NE is attributed to dysfunction

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