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Neuropeptide Y T1128C polymorphism: an independent predictor of hypertensive and cardiovascular diseases?

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Neuropeptide Y (NPY) is generally considered to play an important role in central and peripheral neural regulation, cardiovascular control and blood pressure homeostasis [1]. NPY is a 36-amino acid peptide that was initially isolated from porcine brain by Tatemoto *et al.* [2]. It belongs to a family of polypeptide hormones, including pancreatic polypeptides and peptide YY [2]. Because NPY is most abundant in the mammalian brain and peripheral sympathetic nerve terminals where it is colocalized with noradrenaline [3], it was classically viewed as a neuropeptide or neurotransmitter. However, following its discovery, NPY has been shown to exert diverse biological actions on central and peripheral neural regulation, cholesterol metabolism, appetite and behaviour, and cardiovascular and blood pressure homeostasis. The neural and cardiovascular effects of NPY and its possible role in hypertension have been the subject of several recent reviews [1,4–7]. *In vitro*, NPY exerts both postjunctional inotropic and chronotropic effects on cardiac tissue involving L-type Ca^{2+} currents and pacemaker currents by acting on specific pre- and postsynaptic receptors [1,7]. NPY also induces cardiac hypertrophy by stimulating cardiac myocyte growth, and angiogenic effects by promoting vascular sprouting and capillary tube formation by endothelial cells [7,8]. *In vivo*, the cardiovascular actions of NPY are more complex and appear to depend on the species and the site or mode of administration; these effects are often difficult to reconcile from one study to another [1]. There have been reports of NPY involving both an increase and decrease in cardiac output, both vasoconstriction and vasodilatation, and both an increase and decrease in blood pressure induced by NPY have been reported [1]. Thus, the precise role(s) and mechanism(s) of NPY with respect to cardiovascular regulation and blood pressure control in humans remain largely unknown. Against the vast literature on possible roles of NPY published to date, in the current issue of the journal, Wallerstedt *et al.* [9] report a significant association between a NPY gene T1128C polymorphism [Leu(7)-to-Pro(7)] and myocardial infarction and stroke in a Swedish hypertensive population. This study approaches NPY research from a clinical perspective, and its findings may contribute new information to our understanding of the potential role of NPY in human cardiovascular physiology and diseases.

Association analysis of gene polymorphisms and human diseases is a powerful tool for defining the effects of genetic factors on the development and progression of disease. Information derived from these studies may be useful in devising new strategies to prevent and treat human disease. Because of its potential effects on cardiovascular and blood pressure regulation [1,4,5,7], the association between NPY gene polymorphism and cardiovascular diseases has been the focus of several studies in animals and humans. Although the study by Wallerstedt *et al.* [9] was not the first attempt to identify an association between the NPY T1128C polymorphism and cardiovascular risks, their findings are the first to link the T1128C polymorphism to myocardial infarction and/or stroke in a hypertensive population. The human NPY gene was

first cloned in 1986 [10] and was assigned to chromosome 7 pter-q22 [11] or chromosome 7p15.1 [12]. Analysis of the NPY gene revealed that the transcription sequence spans approximately 8 kb pairs, with four exons separated by three introns [10]. DNA sequences located within 530 bases at the beginning of the transcription sequence appear to be important for NPY expression in neuronally-derived cells [10]. Early studies reported that a NPY locus on chromosome 4 appears to cosegregate with blood pressure in spontaneously hypertensive rats [13], but a NPY Y1 receptor polymorphism was not found to be associated with human essential hypertension in Caucasian individuals [14]. A significant NPY gene polymorphism, a thymidine (1128)-to-cytosine (1128) polymorphism (T1128C), which has been linked to increased cardiovascular risks, was identified in obese Finnish and Dutch subjects [15,16]. This polymorphism leads to a substitution of Pro(7) for Leu(7) in the signalling peptide sequence of pre-pro-NPY, thereby altering synthesis, processing and release of the active peptide. In this landmark study, Karvonen *et al.* [15] screened the entire coding region of the NPY gene in obese, non-diabetic Finnish and Dutch subjects and found a significant and consistent association between the Leu(7)-to-Pro(7) polymorphism and high serum total cholesterol and low-density lipoprotein (LDL) levels. Thus, this work provides the first genetic evidence that NPY may be linked to altered cholesterol metabolism and that the polymorphism producing Pro(7) in the NPY signalling peptide may be one of the strongest genetic factors influencing serum cholesterol and LDL levels in obese subjects [16]. Subsequently, the Leu (7)-to-Pro(7) polymorphism has been linked to both type 1 [17] and type 2 diabetes [18,19], atherosclerosis [20] and coronary heart disease [21]. These studies suggest that the NPY T1128C polymorphism may be a strong independent risk factor for various cardiovascular diseases.

Wallerstedt *et al.* [9] further extend the previously reported association of the NPY T1128C polymorphism with increased cardiovascular risks in Swedish hypertensive patients with myocardial infarction and/or stroke. Their study is significant because it was based exclusively on a prospect study cohort with a large sample size (1032 hypertensive patients), including 174 patients with myocardial infarction, 170 patients with stroke and 688 matched hypertensive patients. This prospect study cohort was a subpopulation drawn from a CAPtopril Prevention Project (CAPPP), which studied the effects of captopril on morbidity and mortality in 10985 Swedish and Finnish hypertensive patients [22]. All patients had well-characterized cardiovascular phenotypes or end-points. The frequency of the NPY T1128C polymorphism was 8.4% in Swedish hypertensive patients with myocardial infarction and/or stroke (29 of 344) compared to 5.1% in control subjects without either myocardial infarction or stroke (35 of 688) [9]. The frequency of the T1128C allele in this study was somewhat lower than the 14% reported in obese Finnish subjects but higher than the 6% reported for obese Dutch subjects [15]. Nevertheless, the difference in the frequency of NPY T1128C polymorphism between hypertensive patients without or with myocardial infarction and/or stroke, although quite small, was significant even though all other cardiovascular risk factors were carefully adjusted ($P = 0.04$). No difference in the frequency of the T1128C allele was observed between subjects with myocardial infarction and stroke, suggesting that the allele carries a similar risk for cardiovascular and cerebrovascular complications. Surprisingly, the presence of the NPY T1128C allele did not affect other common cardiovascular phenotypes [blood pressure, total cholesterol, LDL and high-density lipoprotein (HDL)], apart from myocardial infarction and stroke outcome [9]. Thus, the important question that arises from this genetic association study is whether such a small difference in the frequency of the T1128C polymorphism between hypertensive subjects with or without myocardial infarction and/or stroke could be used to predict a possible occurrence of myocardial infarction and/or stroke in the hypertensive population.

Although a large number of studies have reported an association of the NPY T1128C polymorphism with various cardiovascular risks, the clinical relevance of this genetic variant

in normal cardiovascular regulation and clinical prediction and treatment of cardiovascular and hypertensive diseases remains to be determined. There are several reasons why we should be cautious when a potential association between the T1128C polymorphism and cardiovascular risks is reported and its implications are interpreted. First, the frequency of the T1128C polymorphism shows a strictly geographical distribution, with most if not all positive associations found largely in Nordic countries such as Finland, Sweden and the Netherlands [9,15–21]. In a recent retrospective study, Yamada *et al.* [23] were unable to find an association between NPY T1128C polymorphism and myocardial infarction in Japanese subjects although the frequency of T1128C allele is low in that country. Ding recently examined the distribution of the T1128C allele in 6626 subjects from Nordic Europeans, North Americans, South Americans, Asians and the Middle-East, and found a predominantly Nordic distribution [24]. Therefore, the effects of the T1128C allele on cardiovascular regulation and diseases are not likely to be relevant in populations other than the Nordic countries. Second, although Wallerstedt *et al.* [9] found a significant association between the T1128C polymorphism and myocardial infarction and/or stroke in Swedish hypertensive subjects, surprisingly, the polymorphism was not associated with other well-recognized cardiovascular phenotypes, such as smoking status, body mass index, systolic and diastolic blood pressure, diabetes, HDL, LDL or total cholesterol levels. Indeed, reports on the association between the T1128C polymorphism and cardiovascular phenotypes, especially total cholesterol, LDL and HDL, have been largely inconsistent [15,18,19,21,23,25]. Third, even though a positive association between the T1128C polymorphism and a specific cardiovascular phenotype is identified in a particular population, it is difficult to draw conclusions with respect to potential physiological or pathological roles of this polymorphism in cardiovascular control and development of diseases. For example, it is unknown whether this T1128C polymorphism translates into higher or lower levels of active polypeptide NPY because serum or tissue NPY levels were either not measured or vary to a great extent between studies. Pettersson-Fernholm *et al.* [17] found no differences in plasma NPY levels between type 1 diabetic patients with the T1128C allele and those with the wild-type genotype. By contrast, Kallio *et al.* [26] reported significantly lower plasma NPY levels in subjects with the T1128C allele in healthy subjects. Moreover, if the T1128C polymorphism indeed leads to changes in cardiovascular phenotype without altering circulating and tissue NPY levels, what are the possible mechanisms involved? Would subjects with T1128C allele respond to NPY in a more sensitive fashion than those with the wild-type allele? Or would they express higher levels of functional NPY receptors? NPY receptors belong to the family of heptahelical G-protein-coupled receptors with five subtypes, Y1 to Y5, coupled to a variety of signalling mechanisms, ranging from inhibition of adenylyl cyclase or the N-type calcium channel and mobilization of intracellular calcium [1]. However, Y1 and Y5 have been well studied in both central and peripheral nervous systems and are most likely important for neural regulation of vascular activity and cardiovascular function [1]. Clearly, to date, the mechanisms by which each NYP receptor subtype modulates cardiovascular homeostasis remain poorly understood due to the lack of subtype-specific potent antagonists. Thus, identification of an association between the T1128C polymorphism and cardiovascular risk factors may only be the initial step towards understanding the physiological and pathological roles of NPY in humans. More translational and basic studies are required to focus on the genetic impact of this polymorphism on normal cardiovascular and blood pressure control and the development of cardiovascular diseases, as well as the cellular and molecular mechanisms involved.

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