Peptides in Postural Orthostatic Tachycardia Syndrome

Players or Epiphenomena*

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Recently, increasing attention has been directed toward better understanding the physiological role and clinical importance of a wide range of endogenously released vasoactive peptides. The most well known of these are B-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) (1–4). However, others have also attracted attention, including C-type natriuretic peptide, vasoactive intestinal peptide, neuropeptide Y, the (uncertain in humans) Dendroaspis-type peptide, and adrenomedullin (ADM) (2–4). Although the sites of origin of these proteins differ and the triggers for their release vary, they nonetheless appear to play a role as endocrine/paracrine participants in overall cardiovascular hemodynamic control (1). Furthermore, gene expression and release of these peptides are affected by a wide range of disease states. In particular, the clinical relevance of BNP, ANP, and ADM as markers of disease severity has proved to be of special interest for prognostic assessment of patients with chronic heart failure or acute myocardial infarction (1,5–8).

Human BNP, ANP, and ADM are well-known vascular relaxation agents with diuretic properties (1–4,9,10). When the relative concentrations of peptide release and chamber weight are considered, BNP is predominantly of cardiac ventricular origin and ANP is mainly of atrial origin. ADM, on the other hand, has been identified in a wide range of organ systems including the adrenal medulla (hence the name), cardiac tissues, lungs, kidneys, and the gastrointestinal system (9,10). Like BNP and ANP, ADM is a vasodilator (acting through nitric oxide) and a natriuretic agent that increases glomerular filtration. Also like BNP and ANP, ADM production and release may be stimulated by, among other things, physical stress, and vasoconstrictors such as angiotensin II, norepinephrine, and endothelin-1. ADM mRNA is induced in vascular smooth muscle and cardiac cells by shear stress, stretch, hypoxia, and ischemia (9–12). Presumably, like BNP and ANP, ADM’s principal cardioprotective hemodynamic effect is a decrease in afterload (reduction of peripheral resistance); however, it also decreases preload by means of venous dilation and deters adverse cardiac remodeling by reducing cardiac hypertrophy and fibrosis.

Apart from their functional similarities, the manner in which BNP, ANP, and ADM are released from tissues also exhibit parallels. Each is released in the presence of cardiac volume overload and stretch (1–4,11–13). BNP, ANP, and ADM are each derived from larger precursor proteins and cleaved at the cell surface to produce an active peptide and, at least in the cases of BNP and ANP, a biologically inactive or less active amino-terminal fragment (N-terminal BNP, N-terminal ANP) (13). This processing step may be problematic in cardiac disease states such as heart failure. Recent findings, particularly with regard to BNP, suggest that the apparently increased BNP concentrations in heart failure and acute ischemia may be contaminated by unprocessed inactive/less active peptide (13,14). The result would be a greater proportion of reduced-activity peptide being released, thereby undermining the pharmacological effectiveness of the released hormone in terms of its cardioprotective actions. If that is the case in diseased hearts, one might predict that, were excess natriuretic peptide to be released, for perhaps unknown reasons, in healthy individuals, the released hormone would be composed of a complete complement of fully active processed peptide. The result, even if the excess peptide release were modest in amount, might be a greater natriuresis and vasodilation than would otherwise be expected; perhaps this is what occurs with ANP release during episodes of paroxysmal supraventricular tachycardia or atrial fibrillation (1–3,15).

Unlike BNP and, to a lesser extent, ANP the active form of ADM is difficult to measure in plasma due to both its short half-life and its tendency to bind nonspecifically to various proteins. Given this constraint, it is now widely accepted that measurement of the concentration of a more stable midregional fragment (MR-proADM) is a suitable surrogate for ADM concentration (7,8,12,16). The 2 proteins are presumed to be produced in equimolar amounts, and in previous studies, MR-proADM appeared to be a promising biomarker for predicting prognosis in heart failure and after acute myocardial infarction (7,8,12). On
the other hand, although potential disease-related problems with ADM precursor processing (analogous to that observed with BNP discussed earlier) remain to be addressed, the use of MR-proADM as a surrogate for the active peptide is likely acceptable in individuals without structural cardiac disease such as is the case with most postural orthostatic tachycardia syndrome (POTS) patients.

POTS remains a condition that has proved clinically very challenging. Its onset is usually without evident explanation, its pathophysiology is not adequately understood, its duration is entirely unpredictable, and there is no known effective therapy (17–20). Consequently, efforts designed to gain more sophisticated understanding of this mysterious affliction are welcome. In this issue of the *Journal*, Zhang et al. (21) investigated levels of circulating MR-proADM as a surrogate for ADM in children carrying a diagnosis of POTS. The authors report higher levels of MR-proADM in otherwise healthy children with a clinical diagnosis of POTS compared with normal controls. Further, they concluded that MR-proADM >61.5 pg/ml provided a useful cutoff to predict effectiveness of therapy with midodrine. With regard to the latter, this same group previously reported their experience suggesting that low-dose midodrine is beneficial in children with POTS, with success rates approaching 70% in a presumably unselected (at least from a vasoactive peptide consideration) population (22).

Inasmuch as ADM is widely dispersed in various tissues, and particularly in vascular endothelium, Zhang et al. (21) propose that ADM may be a contributor to the pathophysiology of POTS. This aspect of the study is interesting and may open doors for further assessment of the role of vasoactive peptides in this condition. On the other hand, the observation that the POTS patients with the highest ADM levels responded best to the vasoconstrictor prodrug midodrine is more difficult to understand for several reasons. First, although it is possible that the handling of midodrine is different in Chinese children than in young persons in Western countries, the vast extent reported experience in the adolescent and young adult age groups does not tend to indicate that midodrine at modest doses (even in combination with salt and volume for that matter) is predictably effective for treating POTS. Second, in the current report by Zhang et al. (21), reliance for success is placed on symptom score improvement, whereas physiological measures such as heart rate changes with upright posture (their Table 4) were not substantially different between midodrine responders and nonresponders (Δ heart rate post-treatment: 32.6 ± 14.8 beats/min vs. 32.2 ± 10.4 beats/min, respectively) despite the p values. Thus, it is difficult to ascribe any benefit to cardiovascular physiological/pharmacological effects of midodrine. Third, the midodrine dose prescribed was very low (2.5 mg/day) and does not seem to have been administered either in divided doses as its pharmacology would dictate (23), or based on weight, as is common practice in pediatrics. In this regard, midodrine is a prodrug that is well absorbed, but its effect is delivered after conversion by hydrolytic cleavage to deglymidodrine. The latter has a somewhat longer half-life than midodrine (2 to 3 h vs. 0.5 h) with a maximum effect at 1 h and a duration of action of 4 to 6 h (23). Even allowing for some variability that may be found in dysautonomia patients and potential pharmacogenetic differences related to the Chinese patient population, it is difficult to conceive that the pharmacological effect could be long enough to be effective with once-daily dosing. Finally, based on their midodrine observations, Zhang et al. (21) suggest that the high ADM patients are the ones whose principal POTS pathophysiology is vascular dilation (i.e., the redistributive form), as opposed to the less common hyperadrenergic form, and thus would be the subset best treated with vasoconstrictor agents. This pathophysiological concept seems plausible. As noted earlier, the natriuretic peptides including ADM are known to be vascular relaxants and to reduce circulating volume by several mechanisms, including fluid transfer through vessel walls to the interstitium, diuresis, and redistribution, especially to the splanchnic bed (18,20). The latter is particularly large potential circulating volume “sink,” which is known to respond to nitric oxide in a manner that could fit one of the ADM modes of action. In combination then, increased ADM could account for the POTS clinical combination of orthostatic intolerance and increased vascular permeability with peripheral edema. Further, a net reduction of circulating volume may lead to decreased heart size and the need for more rapid heart rates to accommodate to posture and exercise (i.e., the tachycardia component of POTS) (24).

However, with all this having been said, one might have expected that the utility of any therapeutic vasoconstrictor agent would be more challenged, rather than less, in the presence of high levels of ADM; in other words, one might have predicted just the opposite effect than that reported in this issue of the *Journal* by Zhang et al. (21).

Excluding concerns related to the role of midodrine in POTS patients, the possibility that vasoactive peptides contribute to the pathophysiology of POTS is intriguing. As prime movers, such agents exhibit the pharmacological effects that may explain many of the clinical findings in POTS. However, the triggers (environmental, genetic, some combination) that would cause such peptides to be released in more than usual quantities are unknown. On the other hand, the increased circulating presence of ADM (and possibly other similar peptides) may simply be a secondary response to other POTS-related issues. Thus, although ADM does not appear to be much affected by exercise (25), the rapid sinus rates in POTS patients may trigger peptide release analogous to the case of ANP in supraventricular tachycardias. Similarly, enhanced norepinephrine and/or endothelin release as part of a physiological adaptation to maintain blood pressure during orthostatic stress could trigger increased circulating ADM. Finally, although probably unlikely, a small heart size with vigorous contraction may play a role through increased shear stress on myocardial tissues. With regard to the latter point, it has been suggested
(although debated) that heart size exhibits an inverse relationship with ADM concentrations (26).

In conclusion, the concept that vasoactive peptides may contribute to the clinical manifestations of POTS is potentially important. However, whether ADM and possibly other peptides are active players or simply epiphenomena in these patients will require considerable further study. At a minimum, natriuretic peptide concentrations may prove to be potentially useful markers of POTS severity that can be tracked in individual patients as treatments are introduced in an attempt to ameliorate the symptoms of this poorly understood condition.

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