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Adenosine and Clinical Forms of Neurally-Mediated Syncope



Central or peripheral baroreceptor reflex abnormalities, alterations in neurohumoral mechanisms, or

both, are thought to play a role in causing neurally-mediated syncope. Because adenosine and its receptors are involved in some forms of syncope (1-3), we evaluated the purinergic profile of 4 common forms of syncope: typical vasovagal syncope (VVS); situational syncope (which occurs in specific circumstances after micturition, defecation, coughing, swallowing, or gastrointestinal stimulation); carotid sinus syncope (CSS); and syncope without prodromes or with very short (2 to 3 s) prodromes and a normal heart (no prodromes). We compared patients with neurally-mediated syncope with healthy control subjects to test the hypothesis that the adenosine profile differs with the different clinical presentation.

The purinergic profile included an assay of the baseline adenosine plasma level (APL) and characterization of A_{2A} adenosine receptor (A_{2A} R) expression and single nucleotide c.1083 C>T polymorphism (SNP), which is the most common SNP in the A_{2A} R gene. The method was previously described (1-4). Clinical and biological characteristics of patients and control subjects are given in Table 1.

Thus, these findings demonstrate an association between adenosine plasmatic levels and unexplained syncope in patients without prodromes, CSS, and VVS, who have profiles different from normal control subjects. The clinical manifestation of adenosine depends on its concentration, on adenosine receptor expression level, and on the presence of receptor reserve. However, the causal role of this interplay in the mechanism of syncope is yet to be determined. Conversely, adenosine is not associated with situational syncope, which is mainly triggered by well identifiable afferent neural reflexes. Patients with situational syncope showed APL values similar to those in normal control subjects, although they had high A_{2A} R expression and a higher rate of the TT variant. The purinergic profile of situational syncope patients was never investigated.

Syncope without prodromes and CSS (which is a similar form of syncope without prodromes or very short prodromes and an absence of known triggers) have a similar distinct profile. In these 2 forms, the role of adenosine may potentially be important in causing syncope. When APL values are very low, as in these clinical forms, and are mainly below or approximately at the K_D value for A_{1A} adenosine receptor (A₁ R) of 0.7 μM, even a modest acute increase in APL may recruit a sufficient number of A₁ R, which is known to be located within the sinus node and in the atrioventricular node. Their activation causes sinus bradycardia and/or atrioventricular block.

For patients with typical VVS, a combination of neural outflow and purinergic activation is likely.

TABLE 1 Clinical Characteristics of the Study Population and Purinergic Profile

	No Prodromes, Normal Heart (n = 57)	Carotid Sinus (n = 9)	Situational (n = 23)	Vasovagal (n = 30)	Control Subjects (n = 40)
Age, yrs	64 ± 15*	74 ± 10*	56 ± 18	45 ± 17*	53 ± 15
Women	36 (63)	2 (22)	8* (35)	18 (60%)	23 (57)
Total number of syncopes	3 (2-5)	2 (2-3)	4 (2-6.5)	8† (4-15)	—
Duration of symptoms, yrs	1 (1-3)	1 (1-2)	4 (1.5-10)	10† (3-22)	—
APL, μ M	0.18* (0.12-0.36)	0.16* (0.10-0.31)	0.60 (0.43-0.70)	0.85* (0.59-1.90)	0.60 (0.50-0.69)
APL \leq 0.36 μ M‡	45* (79%)	8* (89%)	5* (22%)	2 (7%)	1 (2%)
A _{2A} R expression, arbitrary units	0.5* (0.3-0.6) (n = 16)	0.5 (0.4-0.5) (n = 6)	0.9* (0.9-1.0) (n = 7)	0.8* (0.7-1.0) (n = 11)	0.7 (0.5-0.8) (n = 40)
SNP:TT/TC/CC variants	2/20/5	1/4/3	12/5/2*	0/5/9	7/20/13
Tilt table test, hypotension + bradycardia response	13/56 (23%)	2/6 (33%)	8/23 (35%)	22/30§ (73%)	—

Values are mean ± SD, n (%), or n (ranges). *p < 0.05 compared with control subjects; †p < 0.05 vasovagal compared with no prodromes and carotid sinus; ‡Value corresponding to the best receiving-operating characteristic curve discriminant [see Deharo et al. (2)]; §p < 0.05 vasovagal compared with each other group.
APL = adenosine plasma level; A_{2A} R = adenosine A_{2A} receptor; SNP = single nucleotide c.1364 C>T polymorphism.

The high APL values in VVS patients are compatible with the activation of low affinity A_{2A} R activation (K_D 1.8 μ M) and desensitization of high affinity A₁ R. Low affinity A_{2A} R is located in the vessels and causes vasodilation. Thus, syncope may be related to the vasodilatory effect of the A_{2A} R activation, which acts synergically with the blunted sympathetic nervous activity. Interestingly, these patients also showed a high incidence of positive tilt tests. It is known that a positive tilt test denotes susceptibility to hypotension (5).

In conclusion, particular purinergic profiles, which are genetically predetermined, characterize different common forms of neurally-mediated syncope that can be classified as low, normal, and high adenosine syncope; this classification might have therapeutic implications.

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Early Repolarization

A Risk Factor in Brugada Syndrome



Conte et al. (1) reported their long-term results of implantable cardioverter-defibrillator therapy in Brugada syndrome (BS). The investigators noted that 4 patients experienced an electrical storm and 1 (Patient #3) had a “fragmentation of the QRS complex (f-QRS).” In fact, this patient’s electrocardiogram (ECG) showed a spike mainly at the terminal portion of all QRS complexes. After ajmaline challenge, a coved-type ECG was induced, and the spike disappeared, unmasking an S wave in leads V₄ to V₆.

We believe that the terminal QRS spike may signify early repolarization (ER) rather than f-QRS in this BS patient. Unlike in myocardial infarction, f-QRS has