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Poster presentation

ANP mutation causes reduced proteolysis

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Background

A heterozygous frameshift (fs) mutation causing a 12 amino acid extension to the C-terminus of atrial natriuretic peptide (ANP) was recently genetically linked to patients with familial atrial fibrillation [1]. The frameshift product (fsANP), but not wild type ANP (wtANP), was elevated in the serum of affected patients, but the molecular basis for the elevated peptide concentrations was not determined. Here, we measured the ability of fsANP to interact with natriuretic peptide receptors and to be proteolytically degraded.

Methods and results

We comprehensively analyzed the function of the frameshift mutation by measuring its receptor interaction properties and its susceptibility to proteolysis. FsANP and wtANP bound and activated cognate cell surface receptors, NPR-A and NPR-C, similarly while fsANP had a slightly increased efficacy for human NPR-B. Proteolytic susceptibility was addressed with novel bioassays that measure the time required for human kidney membranes or purified neutral endopeptidase to abolish ANP-dependent activation of human NPR-A. Using human kidney membranes, we determined that the half-life of fsANP (4.5 min) was significantly longer than the half-life of wtANP (2.6 min). Additional membrane proteolysis studies indicated that wtANP and fsANP are preferentially degraded by neutral endopeptidase and serine peptidases, respectively.

Conclusion

These data indicate that the familial ANP frameshift mutation associated with atrial fibrillation has only minor effects on natriuretic peptide receptor interactions but markedly decreases peptide proteolysis.

References

1. Hodgson-Zingman DM, Karst ML, Zingman LV, Heublein DM, Darbar D, Herron KJ, Ballew JD, de Andrade M, Burnett JC, Olson TM: **Atrial natriuretic peptide frameshift mutation in familial atrial fibrillation.** *N Engl J Med* 2008, **359:**158-165.