Letters to the Editor

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Do Putative Endogenous Digitalis-like Factors Have a Physiological Role?

To the editor:

After approximately 20 years of fruitless search for endogenous digitalis-like factors (EDLF), interest has declined considerably among scientists occupied with theoretical aspects of the sodium pump and Na⁺,K⁺-ATPase. Among clinicians, however, judging from the great number of articles in clinical journals on endogenous ouabain and similar matters, the interest is undiminished. For years, little progress has been achieved in identifying EDLF. The number of publications on the topic, however, seems inversely related to facts and realities of the subject. The reason could be that EDLF do not exist.

Support for the concept that EDLF and even endogenous ouabain do play a role was provided by Hamlyn and coworkers,1,2 who claimed that ouabain is an adenocortical hormone. Speculations as to the pathophysiological role of endogenous ouabain in, for example, essential hypertension were recently reviewed by Blaustein.3 A commercial enzyme-immunoassay kit suitable for monitoring endogenous ouabain in plasma is now on the market.4 An independent confirmation and validation of anticipated endogenous ouabain was recently attempted by Doris et al.5 It appeared that they were unable to identify ouabain immunoreactivity in plasma from young healthy subjects or from medical intensive care unit patients as well as from adenocortical culture cells. I am surprised that sound reflections on the secretion rate of endogenous ouabain compared with the huge pool of receptors didn’t long ago bring the discussion to an end (see below). Goto et al6 listed a number of criteria that should be fulfilled for substances to be considered candidates for EDLF. Such criteria are much needed for discrimination among the vast number of EDLF proposed during the last 15 to 20 years. Obviously, inhibition of Na⁺,K⁺-ATPase does not suffice; in addition, a ouabainlike reactivity with Na⁺,K⁺-ATPase and positive inotropic effect on heart muscle should be possessed by serious candidates.7,8 According to Goto et al, EDLF immunoreactivity is not an adequate criterion per se and has even misled the search for EDLF.

One may ask whether circulating EDLF available for all sodium pumps would have any meaning in regulation of pump activity in individual organs with particular demands for pump activity. The frequent reference to isozymes of Na⁺,K⁺-ATPase with different tissue with a Na⁺,K⁺-ATPase concentration of 0.3 nmol/g and higher sodium pump concentrations, the muscles should contain a pool of Na⁺,K⁺-ATPase of 2.6 μmol. Occupation of this pool with OLF (ratio 1:1) would imply consumption of OLF corresponding to 7.2 years of production. Just 1% occupation of the Na⁺,K⁺-ATPase pool from muscle should likewise consume the production from 26 days. Since the half-life of Na⁺,K⁺-ATPase is a few days and that of the enzyme-ouabain complex is presumably of similar length, the absurdity of such a low production of OLF seems obvious.

My conclusion is that no physiological or pathophysiological role can be attributed to endogenous ouabain, since the published secretion rate is much too low compared with the vast number of receptors.

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References


Response

Dr Hansen's letter appears to be only tangentially directed toward my recently published work,1 and his letter does not take issue with, challenge, or debate any of my experimental findings or data interpretations. Dr Hansen seems to agree with me that adrenally secreted ouabain, or a stereoisomer of ouabain, is an unlikely candidate for an endogenous mammalian sodium pump inhibitor. Dr Hansen ascribes this to the low rate of adrenal secretion of "ouabain." Numerous other issues problematic to the acceptance of "ouabain" in this role have recently been discussed.2 I share his concern that the large number of sodium pumps and therefore cardiotoxic steroid receptors appears to necessitate that,
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