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 adrenocortical 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 adrenocortical 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 digitalis affinities (eg, in references 2 and 6) is unsubstantiated in this respect. A few rodent species have α1-isozymes with low digitalis affinity, but it is not so in most species. The same high affinity of all isozymes for ouabain is the general rule for which there are few exceptions.9

Another important question is whether enough of the putative EDLF is produced to fulfill a regulatory role compared with the vast pool of Na⁺,K⁺-ATPase: A compound was isolated from plasma that was identified by its immunoreactivity to antiouabain, ie, an immunoassay for ouabain.2 According to Goto et al, this ouabainlike factor (OLF) satisfies all criteria required for EDLF. On the other hand, the secretion rate of OLF from adrenal glands of dogs with body weights of 21.5 kg was estimated at only 0.68 pmol/min.1 Assuming that 40% of the weight represents muscle tissue with a Na⁺,K⁺-ATPase concentration of 0.3 nmol/g·min and disregarding other tissues like nerve and kidney tissue with even 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 1

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 the large number of sodium pumps and therefore cardiotonic steroid receptors appears to necessitate that,
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