Reply to “Letter to the editor: ‘Why isn’t clinical experience with ouabain more widely accepted?’”

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REPLY: Fürstenwerth (12a) notes that my “Perspectives” on endogenous ouabain (EO) (2) didn’t mention the use of ouabain as a therapeutic and antihypertensive agent (true; see last paragraph); 2) didn’t consider the view that “(EO) is not ‘ouabain’” (21) [I cited an earlier version (32) and the refutation (24); my article (2) was published online 4 days before Lewis and colleagues’ (21); see our responses to Lewis et al. (2a, 14)]; and 3) called the 1993 discovery of ouabain-digoxin antagonism (27) “a surprise,” despite the 2010 report that ouabain antagonizes acute digoxin and bufalin cardiotoxicity (31).

Manunta et al. (26, 27) were, surely, the first to document that cardiotonic steroids (CTS) could antagonize one another and that all CTS do not have identical effects (e.g., ouabain, but not digoxin, causes hypertension). Thus this was “a surprise” in 1993. Nesher and colleagues (31) confirmed that ouabain and digoxin antagonize one another acutely but didn’t address the mechanism (41). The mechanism for antagonizing the chronic effects of ouabain (26, 27), not studied by Nesher, is apparently more complex (47).

Fürstenwerth cites the Lewis/Hilton/Nichols group (21) regarding “uncertainty on the identity of EO.” The repeatedly verified analytical (HPLC plus mass spectroscopy, nuclear magnetic resonance, and UV) evidence that mammalian (including human) EO is, in fact, “ouabain” (13, 16–18, 39, 42) is not mentioned, although this contradicts the Lewis et al. view (21). The latter had already been refuted twice (23, 24). Moreover, much additional, independent, but generally overlooked evidence confirms that the endogenous substance is chemically very “ouabain-like.” First, ouabain-resistant mutation of the α2 Na+ pump ouabain binding site abolishes the hypertensinogenic actions of ACTH and ouabain (10, 11, 22), proof that an EO-like ligand binds to this receptor. Second, prolonged subcutaneous administration of ouabain, but not digoxin, induces hypertension in rodents (15, 26, 44, 47). Ouabain’s effect has been replicated in numerous laboratories in the United States, Brazil, Canada, China, and Italy. Third, ouabain, but not digoxin, also increases expression of Ca2+ transporters, including Na+/Ca2+ exchanger-1 in arteries (47).

Similar upregulation of these arterial transporters occurs in many forms of hypertension (4, 35, 36, 46). Fourth, digoxin blocks both the ouabain-induced protein upregulation (47) and hypertension (15, 26, 27). Fifth, complexation of EO with Fab fragments that bind digoxin and ouabain with high affinity (37, 38) abolishes several forms of hypertension (4), including those induced by ACTH (10), ouabain (10, 15), and high dietary salt (15). Sixth, reduced expression of α2 Na+ pumps (the EO receptors), equivalent to α2 Na+ pump inhibition by nanomolar EO/ouabain, induces hypertension (5, 7, 45), whereas α2 overexpression lowers blood pressure (BP) (7, 34). Given these many related, consistent, and widely replicated observations, the burden is on the few groups (1, 9, 21) that have been unable to purify EO or to induce hypertension with ouabain to explain why not. Contradictory observations can’t both be correct, and negative results are not proof that EO is not ouabain. One must distinguish solid data from artifacts of experimental design and/or execution. It’s highly unlikely that EO spectra from five independent laboratories are all artifacts or that the >12 laboratories that have described ouabain-induced hypertension in rodents are all wrong.

Undoubtedly, EO has beneficial effects (30). Plasma EO is increased in normal pregnancy (16), and pregnant mice with ouabain-resistant α2 Na+ pumps have low BP (33). Plasma EO is also elevated during salt depletion (3, 25), and its acute and chronic vasotonic effects likely help minimize BP decline (3). Acutely, ouabain/EO can enhance cardiac and vascular (6, 20, 43) contractility. Nevertheless, acute intravenous administration of ouabain not only increases resistance to blood flow in humans (28) but, in hypertensive patients, may have devastating cerebrovascular and cardiovascular effects (19). Tests of oral ouabain clinical efficacy cited by Fürstenwerth are anecdotal. There are no controlled clinical trials and certainly none that compare efficacy to plasma ouabain level, a crucial problem, given the low and irregular absorption of oral ouabain (12). Indeed, ignorance of EO and lack of controlled trials continues to undermine all clinical studies of cardiotonic steroid efficacy [e.g., (8, 29, 40)]. Absent quality data, there is little rationale for discussing the clinical use of ouabain.

DISCLOSURES
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AUTHOR CONTRIBUTIONS
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REFERENCES