Hypothsis

Aldosterone, Sodium, and Hypertension
Lessons From Torcetrapib?

John W. Funder

On epidemiological grounds, inhibition of cholesterol ester transport protein (CETP), and, thus, blockade of transfer of cholesterol esters from high-density lipoprotein (“good cholesterol”) to other lipoproteins, represents a promising target in the prevention and treatment of atherosclerosis.1,2 The first large trial to test this hypothesis was the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) Trial, a major phase 3 secondary prevention morbidity and mortality trial in >15 000 subjects. ILLUMINATE compared the CETP inhibitor torcetrapib plus atorvastatin with atorvastatin alone. In an unanticipated outcome, the trial was terminated in December 2006 in the light of higher all-cause (cardiovascular and noncardiovascular) mortality in the torcetrapib arm.3

Three years later, the reasons for this increase in mortality remain uncertain. In addition to its undisputed effect on plasma lipoproteins, torcetrapib has been shown to raise blood pressure in humans4 and in rodents that lack CETP.5 In the ILLUMINATE Trial, subjects receiving torcetrapib showed highly significant increases in blood pressure (systolic: 4.0 mm Hg; diastolic: 2.0 mm Hg) after 3 months, as well as small but highly significant (P<0.001) elevations in serum [Na+] (0.58 milliequivalents/L) and [HCO3−] (0.27 milliequivalents/L) in the torcetrapib arm, and a decrease (0.14 milliequivalents/L) in serum [K+]. Similar blood pressure and electrolyte changes have been consistently reported in additional clinical trials of torcetrapib.6–10 Consistent with these blood pressure and electrolyte changes, which were maintained at the 12-month point, post hoc analysis of plasma samples from the ILLUMINATE Trial showed similarly small but significant increases in plasma aldosterone levels in the torcetrapib arm.

In a cohort the size of the ILLUMINATE Trial (>15 000 subjects), it comes as no surprise that even a modest increase in blood pressure or aldosterone levels might be implicated in increased mortality. Aldosterone excess can cause cardiovascular damage independent of blood pressure elevation, both experimentally11 and in normotensive subjects with familial hyperaldosteronism type 1, who have clear evidence of pathological cardiovascular change compared with matched controls.12 Given the documented increased morbidity and mortality in primary hyperaldosteronism compared with age-, sex-, and blood pressure–matched essential hypertensives,13 the default explanation for the increased mortality associated with torcetrapib appears to be that of its off-target action in elevating aldosterone levels in a high-risk, event-susceptible population, the modest magnitude and duration of exposure notwithstanding.

In vitro studies from Pfizer14 and Hoffman-La Roche15 have shown that in the H295R adrenal carcinoma cell line torcetrapib induces aldosterone release, consequent to increased expression of CYP11B2 (aldosterone synthase); unlike the relatively short-term effect of angiotensin II on CYP11B expression, that of torcetrapib appears to be maintained. In vivo studies in rats and nonhuman primates14 showed that corticosteroid release correlated with pressor activity across a range of CETP inhibitors. Simultaneously, studies from Merck Research Laboratories confirmed and extended these findings, changing the initial interpretation and posing anew the question of how torcetrapib raises blood pressure.

In these studies,6 torcetrapib, but not ancetrapib (a CETP inhibitor of a different chemical class), raised blood pressure acutely in both wild-type mice and mice expressing a cynomolgus monkey CETP transgene, which excludes the formal possibility that CETP inhibition is required to raise blood pressure. Blood pressure elevation does not appear to be a direct vascular effect, because torcetrapib did not increase perfusion pressure in the isolated perfused rat hindlimb. Torcetrapib raised blood pressure in pithed rats, evidence against a central mechanism; in dogs pretreated with prazosin or atenolol, no attenuation of the pressor response to torcetrapib was seen. Torcetrapib, but not ancetrapib, caused a rapid increase in aldosterone secretion when infused into conscious rats, and the pressor response to torcetrapib was abolished in adrenalectomized rats.

One additional study by Forrest et al.,5 however, brought the question of mechanism into a whole new focus. In conscious rats, aldosterone secretion in response to torcetrapib was completely inhibited by trilostane, an enzyme inhibitor that prevents conversion of pregnenolone to progesterone, an early step in corticosteroid synthesis. In contrast, the pressor effect of torcetrapib was completely unaffected. The trilostane study thus excludes aldosterone as the acute

Received November 1, 2009; first decision November 16, 2009; revision accepted December 3, 2009.
From the Prince Henry’s Institute of Medical Research, Monash Medical Centre, Clayton, Victoria, Australia.
Correspondence to John W. Funder, Prince Henry’s Institute of Medical Research, Monash Medical Centre, Clayton, Victoria 3168, Australia.
E-mail john.funder@princehenrys.org

Hypertension is available at http://hyper.ahajournals.org DOI: 10.1161/HYPERTENSIONAHA.109.146936
pressor agent, just as the prazosin/phentolamine studies similarly exclude torcetrapib acting via catecholamine release from the medulla.

One possible explanation for this conundrum, a pressor effect abolished by adrenalectomy but not by trilostane, may be that torcetrapib increases the secretion of endogenous ouabain (EO) from the zona glomerulosa of the adrenal. Although there is still ongoing debate about EO,16,17 and the details of its biosynthesis from cholesterol in the zona glomerulosa remain to be established,18,19 there is increasing evidence supporting both its endogenous origin and (patho)physiological roles.20 Levels of EO are reported to be elevated in various forms of experimental hypertension20–22 and clinically in essential hypertension and primary aldosteronism.23,24 Circulating EO levels rise in response to chronic sodium elevation,25 to adrenocorticotropic hormone (ACTH),26 and to angiotensin II via angiotensin type II receptors.27 Although some early studies reported that EO raised blood pressure in rats, others showed no effect, a difference attributed to experimental variables, including method of blood pressure measurement, strain, and sodium intake.28 More recent studies from Zhang et al29 on wild-type and mice heterozygous (+/−) for null mutations in the genes coding for the α1 or α2 subunit of the Na+ pump have shown that ouabain raises blood pressure and myogenic tone by reducing α2 Na+ pump activity and promoting Ca2+ entry via Na+/Ca2+ exchange.

In parallel studies on ACTH-induced hypertension from Dostanic-Larson et al,26 the α2 isoform was made resistant to ouabain; in contrast with wild-type mice, which show a progressive elevation of blood pressure to a plateau 25 mmHg above control after 4 days of ACTH treatment, the mutant mice showed no elevation in blood pressure in response to ACTH. Under resting conditions, no difference was seen between strains, suggesting no apparent role in the maintenance of basal blood pressure. Infusion of the Glaxo-Smith-Kline antibody Digibind completely abolished ACTH-induced hypertension, as did KB-R7943 (Tocris), an inhibitor of the reverse mode of the Na/Ca2+ exchanger. It would be of considerable interest if infusion of Digibind or KB-R7943 could be shown to block acute torcetrapib-induced blood pressure elevation in experimental animals.

EO is clearly not the only noncorticosteroid, noncatechol secretion product of the adrenal but has a now well-defined action on the vasculature to raise blood pressure. As shown in the Figure, both EO and aldosterone secretion are responsive to angiotensin II; in contrast, however, whereas added sodium rapidly lowers aldosterone secretion, that of EO is elevated in high-sodium states.25 One intriguing note, as also illustrated in the Figure, is that canrenone, a potent mineralocorticoid receptor antagonist, is commonly used in studies on EO as a

---

**Figure.** Control of aldosterone secretion (A) and EO (B) as part of sodium and blood pressure homeostasis. Distortion of negative feedback of control of aldosterone secretion by torcetrapib (C) and possible combinatorial effects of torcetrapib on aldosterone and EO secretion (D).
partial agonist/predominant antagonist. In terms of homeostasis, the physiology of the elevation of EO secretion in response to sodium loading may be to raise blood pressure and to produce a pressure natriuresis. The responses to torcetrapib include a rapid, direct effect on the zona glomerulosa to raise plasma levels of aldosterone and, putatively, of EO. This latter may be an acute effect only, and, as noted previously, the chronic elevation of blood pressure seen clinically with torcetrapib may be solely attributed to increased levels of aldosterone. It may, however, also involve a continued EO secretory response, amplified in response to aldosterone-induced sodium retention.

A persisting enigma has been why aldosterone levels inappropriate for sodium status are so damaging in the cardiovascular system, whereas much higher levels in chronic sodium deficiency are not damaging but are homeostatic. The answer may lie in the zona glomerulosa, in that EO secretion is stimulated by a sodium load, squarely opposite to that of aldosterone. It may thus be that the enigma posed by torcetrapib sheds light on a more basic enigma, that of how sodium status stochastically modifies tissue responses to mineralocorticoid receptor activation by aldosterone.

Disclosures

None.

References

5. Forrest MJ, Bloomfield D, Briscol RJ, Brown PM, Cumiskey AM, Erhart RF. Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone. Br J Pharmacol. 154:1465–1473.
Aldosterone, Sodium, and Hypertension: Lessons From Torcetrapib?

John W. Funder

Hypertension. 2010;55:221-223; originally published online January 4, 2010;
doi: 10.1161/HYPERTENSIONAHA.109.146936

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/55/2/221

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/