OFF-TARGET EFFECTS
OF TORCETRAPIB

The adverse off-target effects of the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib may be mediated by L-type calcium channels, shows a study published in the *Journal of Hypertension*.

Torcetrapib was found to be associated with increased mortality and morbidity in the ILLUMINATE trial. Although the mechanisms underlying the potential off-target effects of the drug are poorly understood, a link with increased aldosterone production and hypertension has been reported. Eric Niesor, from F. Hoffmann–La Roche laboratories, and colleagues have investigated this link in the H295R human adrenocarcinoma cell line and in spontaneously hypertensive rats (SHRs).

Similarly to the natural aldosterone agonist angiotensin II (Ang II), torcetrapib increased the levels of aldosterone in H295R cells. Gene expression analysis, however, showed that the gene cascade induced by torcetrapib is different from that triggered by Ang II. In particular, L-type calcium channel mRNA levels are upregulated only by torcetrapib, whereas Ang II acts on T-type calcium channels. The involvement of L-type calcium channels in the off-target effects of torcetrapib was also verified through RNA interference experiments. Furthermore, use of nifedipine, an L-type calcium channel antagonist, abolished the torcetrapib-induced increase in blood pressure in SHRs. Of note, CETP inhibitors structurally unrelated to torcetrapib, such as dalcetrapib, did not seem to have an effect on aldosterone production and blood pressure in SHRs.

These results reveal a putative primary target of torcetrapib. In addition to clarifying the off-target effects of the drug, these findings “may provide [a] tool to screen out undesirable compounds,” says Niesor. “Inhibition of the pathway or target used by torcetrapib will be a subject of further research,” he adds.

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