JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

Can we catch the second loach employing BACE1 inhibition, even as the first one might be escaping?

Obesity, diabetes and Alzheimer's disease (AD) are becoming increasingly common, especially in the aging population, and are adversely affecting the quality of life of patients and their families. These conditions have been shown to be interrelated, and AD has recently been referred to as type 3 diabetes, because neuronal insulin resistance underlies the pathophysiology of AD. Based on the amyloid-beta hypothesis, β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) is the most promising drug target for AD. BACE1 is a β-secretase that processes the amyloid precursor protein to generate amyloid β-42 (Aβ42). Recently, in consecutive publications, Meakin *et al.*[1,2] reported that the suppression of BACE1 in mice not only suppressed Aβ42 formation, but also prevented obesity, insulin resistance and vascular dysfunction[3]. Diet-induced obese (DIO) mice have higher Aβ42 levels in the bloodstream, as well as in their vessel walls. Systemic deletion of BACE1, as well as its inhibition by a specific inhibitor, reversed vascular dysfunction with recovery of nitric oxide (NO) production, which is also impaired in DIO. Inhibition of BACE1 enhances endothelial NO synthase activation by protein kinase B phosphorylation. In contrast, infusion of human Aβ42 at the pathophysiological level worsened endothelial dysfunction in normal mice. The authors also showed that blood Aβ42 levels correlate with vascular dysfunction, even in humans. They concluded that BACE1 inhibition is a promising treatment for vascular diseases, which are life-threatening complications of obesity and diabetes[3].

While their findings strongly suggest that Aβ42 is the cause of DIO-induced vascular dysfunction, it appears that bodyweight changes due to chronic treatment could be a confounder (Figure 1). Previously, the same authors presented clear evidence that BACE1 inhibition protects against DIO[1,2]. Consistently, the bodyweights of DIO mice were significantly increased by Aβ42 infusion and significantly decreased by BACE1 inhibitor treatment[3]. As 4 weeks of Aβ42 infusion significantly increased bodyweight, obesity induced by Aβ42 itself might be a partial cause of vascular dysfunction. Likewise, the decrease in bodyweight caused by the BACE1 inhibitor might reduce vascular dysfunction in DIO mice. Furthermore, all experiments were carried out at a relatively chronic stage (>4 weeks). It would be interesting to ascertain whether acute infusion of Aβ42 or BACE1 inhibition produces similar effects, because NO production and phosphorylation of endothelial NO synthase, protein kinase B and adenosine monophosphate-activated protein kinase might occur rapidly in response to such interventions. Experiments designed to detect earlier changes in vascular dysfunction, and pair-feeding to avoid effects attributable to bodyweight differences, might clarify these points in future studies.

There is a Japanese idiom stating that 'Sometimes, but not always, there is another loach under a willow tree where we have already caught a loach'. Here, BACE1 inhibitors might catch the second loach, vascular disease, by suppressing Aβ42 formation, in addition to the first loach, AD. By the way, is the first loach still in the bucket? In fact, phase III clinical trials of several BACE1 inhibitors were discontinued due to a lack of significant improvement or even worse outcomes in memory scores and non-negligible adverse effects[4]. The intracerebroventricular level of Aβ42 was significantly reduced by treatment with BACE1 inhibitors in these trials, indicating that the drugs worked as expected. However, it is still unclear why decreasing Aβ42 does not improve memory in AD. The possibilities are that: (i) the amyloid hypothesis, which has been considered highly plausible for ~20 years, is wrong, and that Aβ formation is not the cause of dementia in AD, but is instead just a marker; (ii) the intervention is too late to prevent AD progression and earlier inhibition of BACE1 might thus be effective; (iii) the off-target effects of BACE1 inhibitors mask the benefits; and (iv) Aβ42 has an important physiological function(s), and reducing its activity too strongly might be harmful[5]. An anti-Aβ antibody has just been approved by the US Food and Drug Administration, while the controversial results among studies are still being argued. Systemic deletion of BACE1 in mice induces mild impairments in memory. Some studies suggest that it would be better to target Aβ-independent molecules. Others suggest that targeting BACE1 more specifically, without affecting BACE2, would be more beneficial. These complicated situations make it difficult to simply claim that BACE1 inhibitors are a potential treatment for vascular diseases. As we already know that BACE1 inhibitors have some drawbacks, the way forward involves the identification of more inhibitors, specific only to the periphery, or

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Received 16 April 2021; revised 23 July 2021; accepted 27 July 2021

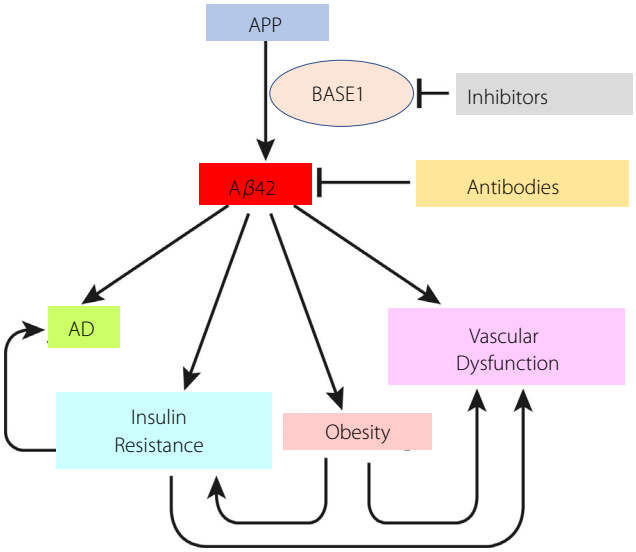

Figure 1 | β-Site amyloid precursor protein-cleaving enzyme 1 (BACE1), related molecules and their downstream phenotypes. BACE1 catalyzes amyloid precursor protein (APP) to generate amyloid beta-42 (Aβ42), which might cause not only Alzheimer's disease (AD) in the central nervous system, but also insulin resistance, obesity and vascular dysfunction in the periphery. Obesity, induced by Aβ42, secondarily causes insulin resistance and vascular dysfunction. Alternatively, the vascular dysfunction might be due to the insulin resistance. BACE1 inhibitors, as well as anti-Aβ42 antibodies, might become effective treatments if this schema is correct.

targeting other molecules involved in the target pathway.

However, this report presents intriguing findings. The authors showed elevated BACE1 levels in the arterial walls of obese people. They also showed BACE1 activation in patients with diabetes. If BACE1 is inhibited in the periphery by drugs that do not penetrate the blood–brain barrier, we might be able to treat vascular disease with such inhibitors without risking central adverse effects. In addition, blocking of Aβ might help treat obesity, for which effective new drugs are still eagerly awaited. Interestingly, neuronal BACE1 knock-in in mice reportedly resulted in the induction of both weight loss and diabetes[6]. Therefore, the effects of BACE1 inhibitors on weight loss might be augmented were this molecule to be inhibited only outside the brain. Future studies focusing on the peripheral inhibition of BACE1 might catch the second loach still waiting under the willow tree.

DISCLOSURE

Approval of the research protocol: N/A
Informed Consent: N/A
Approval date of Registry and the Registration No. of the study/trial: N/A
Animal Studies: N/A

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Doi: 10.1111/jdi.13640