Telmisartan Potentiates Insulin Secretion Via Ion Channels, Independent of The AT1 Receptor and PPARγ.

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Original investigation

Keywords: Telmisartan, Insulin secretion, AT1 receptor, PPARγ, Kv channel, L-type VGCC
Abstract

Background and aim: Angiotensin II type 1 (AT1) receptor blockers (ARBs), as antihypertensive drugs, have drawn attention for their benefits to individuals with diabetes and prediabetes. However, the direct effects of ARBs on insulin secretion remain unclear. In this study, we aimed to investigate the insulinotropic effect of ARBs and the underlying electrophysiological mechanism.

Methods: Islets isolated from Wistar rats or db/db mice were incubated with drugs under different glucose conditions for 30 minutes, then supernatant liquid was collected for insulin secretion. Intracellular Ca2+ ([Ca2+]i) levels of β-cells were measured by calcium imaging technology. Patch-clamp technology was applied to detect effects on action potential duration (APD), Voltage-dependent potassium (Kv) channels, and voltage-gated calcium channels (VGCC). In our in vivo experiment, the 8-week-old and 11-week-old db/db mice were separately administered acute oral acute oral telmisartan treatment (15 mg/kg), then the oral glucose tolerance test (OGTT) was performed to observe the insulinotropic effect of telmisartan at 2 hours following drug intake.

Results: Only telmisartan among the three ARBs—telmisartan, valsartan, and irbesartan—exhibited an insulin secretagogue role in rat islets. Independent of AT1 receptor and peroxisome proliferator-activated receptor γ (PPARγ), telmisartan exerted effects on ion channels including Kv channels and L-type VGCCs to promote extracellular Ca2+ influx, thereby potentiating insulin secretion in a glucose-dependent manner. Furthermore, we identified that telmisartan directly inhibited Kv2.1 channel on a Chinese hamster ovary cell line with Kv2.1 channel overexpression. Acute exposure of db/db mice to a telmisartan dose equivalent to therapeutic doses in humans resulted in lower blood glucose and increased plasma insulin concentration in OGTT. We further observed the telmisartan-induced insulinotropic and electrophysiological effects on pathological pancreatic islets isolated from db/db mice.

Conclusions: Our results establish an important insulinotropic function of telmisartan distinct from other ARBs in the treatment of diabetes.

Full Text

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Figures
Figure 1

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Figure 2

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Figure 3

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Figure 4

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Figure 5

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Figure 6

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Figure 7

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Figure 8

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