

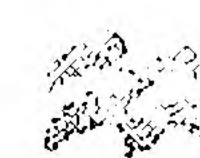
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Do K_{Ca} channels and carbonic anhydrase play a role in thiazide-induced hyperglycaemia?

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Summary:

Thiazide diuretics are widely used to treat hypertension, but their use is associated with impaired glucose tolerance. We propose that the diabetogenic action of thia-

zides may be due to their ability to open calcium-activated potassium (K_{Ca}) channels in pancreatic β -cells.

Keywords: thiazide diuretics; K channel; glucose; pancreatic β -cell; calcium

Thiazide diuretics are a widely used therapy for hypertension. However, glucose intolerance develops in about 3% of hypertensive patients treated with thiazides.^{1,2} The mechanism of this adverse effect is poorly understood. Glucose intolerance caused by thiazide diuretics is dose-dependent and usually reversible after discontinuation of treatment.^{1,2} It is functionally correlated with hypokalaemia and has been proposed to be secondary to it. In some studies prevention of the decline in serum potassium prevents hyperglycaemia² and hypokalaemia is associated with a reduced pancreatic β -cell response to glucose. However, it has also been suggested that hypokalaemia may be an aggravating factor rather than a primary stimulus.³ Besides the effect of thiazides on pancreatic cells, extra-pancreatic mechanisms have also been proposed to explain the diabetogenic action of the thiazide diuretics.^{4,5} We wish to propose a novel hypothesis regarding the diabetogenic effects of thiazides based on their action on a class of potassium (K) channels, which in turn may be related to their effects on intracellular pH (pH_i) through inhibition of carbonic anhydrase.

In the pancreas, depolarisation of the plasma membrane by closure of K channels and opening of cation and chloride channels leads to opening of voltage-dependent calcium channels and influx of calcium.⁶⁻⁸ The resultant increase of intracellular calcium ($[Ca^{2+}]_i$) is crucial to the process of insulin release; drugs which interfere with these mechanisms inhibit insulin release. It is known that diazoxide, a drug structurally related to the thiazides, hyperpolarises pancreatic β -cells by opening a spe-

cific class of ATP-dependent potassium channels (K_{ATP} channels) and that the consequent hyperpolarisation impairs insulin release,⁹⁻¹¹ and probably accounts for the diabetogenic effect of this drug. This effect of diazoxide can be inhibited by agents such as glibenclamide which block K_{ATP} channels and are used clinically as hypoglycaemic agents. It has also been proposed that diazoxide exerts direct vasodilator activity by activating the same, or a similar, K_{ATP} channel in vascular smooth muscle cells.¹²

Recently it has been found that hydrochlorothiazide also reduces insulin release. This action of hydrochlorothiazide was associated with a fall in glucose-stimulated $^{45}Ca^{2+}$ uptake in β -cells.¹³ As discussed above, influx of calcium is one of the most distal steps in stimulus-secretion coupling in pancreatic β -cells and is crucial to insulin release.⁷ We propose that the action of hydrochlorothiazide on calcium influx into the pancreatic β -cell may be by the same mechanism by which the drug inhibits calcium entry into vascular smooth muscle cells. Our group has previously shown that hydrochlorothiazide relaxes vascular smooth muscle cells through an inhibition of calcium influx.¹⁴ This effect of hydrochlorothiazide is associated with an increase in ^{86}Rb efflux, a marker of K^+ efflux,¹⁵ indicating that hydrochlorothiazide increases membrane permeability to K^+ ions, probably by opening K channels. The effects of hydrochlorothiazide on vascular tone, $[Ca^{2+}]_i$ and ^{86}Rb efflux were inhibited by charybdotoxin, a blocker of calcium-activated potassium (K_{Ca}) channels.^{14,15} In contrast, the K_{ATP} channel blocker glibenclamide did not affect hydrochlorothiazide-induced vasorelaxation or ^{86}Rb efflux.¹⁵ This is consistent with a previous report

showing that hydrochlorothiazide does not affect the opening of single K_{ATP} channels in the β -cell plasma membrane.¹⁶ These data suggest that the opening of calcium activated K channels (K_{Ca}) rather than K_{ATP} channels mediates the vasodilator effect of thiazides. Interestingly, electrophysiological studies have shown that cicletanine, a thiazide-like drug containing a furopyridine group, causes membrane hyperpolarisation in isolated canine femoral arteries¹⁷ probably by an action on K_{Ca} channels. K_{Ca} channels are present in pancreatic β -cells⁵ and by analogy with the potassium channel opening properties of diazoxide it is very likely that the effect of hydrochlorothiazide on K_{Ca} channels hyperpolarises the β -cell membrane, leading to a reduced insulin release. This effect could explain the inhibitory action of hydrochlorothiazide on insulin production.

On-going studies in our department suggest that the K channel opening properties of hydrochlorothiazide may depend on changes in intracellular pH (pH_i). Effects of hydrochlorothiazide on pH_i appear to be associated with the ability of the drug to inhibit carbonic anhydrase activity.¹⁸ Interestingly others have shown that pre-treatment with acetazolamide, an inhibitor of carbonic anhydrase, caused decreased glucose tolerance in mice and decreased secretion of insulin by isolated pancreatic islets.¹⁹ These findings support the idea that inhibition of carbonic anhydrase activity may modulate pancreatic β -cell function and glucose tolerance. In addition, there are data indicating that bendroflumethiazide, which unlike other thiazide diuretics has minimal inhibitory effects on carbonic anhydrase at therapeutic levels, does not impair glucose tolerance in hypertensive patients^{20,21} and even improves glucose tolerance in the long term.²²

As a result of our studies we postulate that thiazide-induced hyperglucaemia is, at least in part, due to hyperpolarisation of the β -cell via an action on K_{Ca} channels. This effect may be caused by inhibition of carbonic anhydrase by hydrochlorothiazide resulting in an increase in pH_i. Opening of

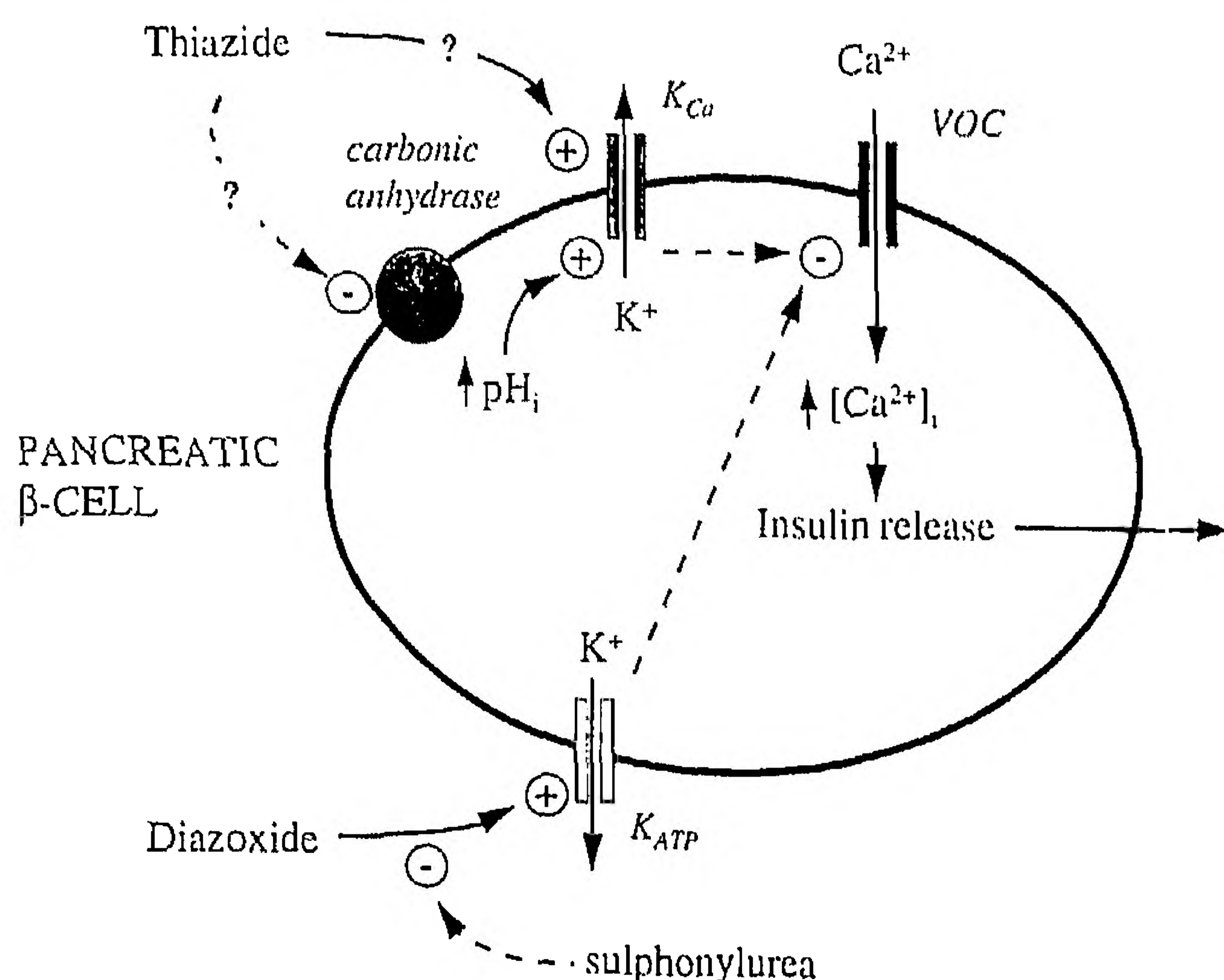


Figure 1 Diagrammatic scheme illustrating the proposed mechanism of inhibition of insulin release by thiazides. K_{Ca}-calcium-activated K channel, K_{ATP}-ATP-dependent K channel. VOC: voltage-operated calcium channel

K_{Ca} channels leads to hyperpolarisation of the cell membrane and closure of voltage-operated calcium channels, hence [Ca²⁺]_i decreases (Figure 1). In vascular smooth muscle this leads to vasodilation, whereas in pancreatic β -cells this leads to reduced insulin release and impaired glucose tolerance.

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