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Mechanisms and pharmacogenetic signals underlying thiazide diuretics blood pressure response

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Thiazide (TZD) diuretics are among the most commonly prescribed antihypertensives globally; however their chronic blood pressure (BP) lowering mechanism remains unclear. Herein we discuss the current evidence regarding specific mechanisms regulating the antihypertensive effects of TZDs, suggesting that TZDs act via multiple complex and interacting mechanisms, including natriuresis with short term use and direct vasodilatory effects chronically. Additionally, we review pharmacogenomics signals that have been associated with TZDs BP-response in several cohorts (i.e. *NEDD4L*, *PRKCA*, *EDNRA-GNAS*, and *YEATS4*) and discuss how these genes might be related to TZD BP-response mechanism. Understanding the association between these genes and TZD BP mechanism might facilitate the development of new drugs and therapeutic approaches based on a deeper understanding of the determinants of BP-response.

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Introduction

Hypertension (HTN) is a global public health burden affecting more than one billion individuals worldwide, and about one third of US adults [1,2]. It is a well-documented leading contributor to cardiovascular mortality, and a major modifiable risk factor for stroke, coronary heart disease, heart failure and end stage renal disease, making its management of critical importance [2]. Over the past five decades, thiazide (TZD) diuretics have been a mainstay in the treatment of HTN, and they are currently among the most commonly prescribed anti-HTN medications [3]. According to the current HTN guidelines in the US, this class of drugs is highly recommended as first line agents for most patients with uncomplicated essential HTN [4]. Despite their wide spread use, the underlying mechanism of BP lowering by TZDs has not been fully elucidated, and data have shown that only about half of TZD treated patients achieve BP control [5]. Understanding the mechanism underlying TZDs may help in identifying novel drug targets and therapeutic approaches, and have a measurable impact on the successful development of new drugs [6•], based on a deeper understanding of the determinants regulating BP-response. Thus, this review discusses the existing knowledge surrounding the BP lowering mechanisms of TZDs, the most compelling signals from TZD pharmacogenomics studies and the insights these findings may provide into TZDs mechanism of action.

BP lowering mechanisms of thiazide diuretics

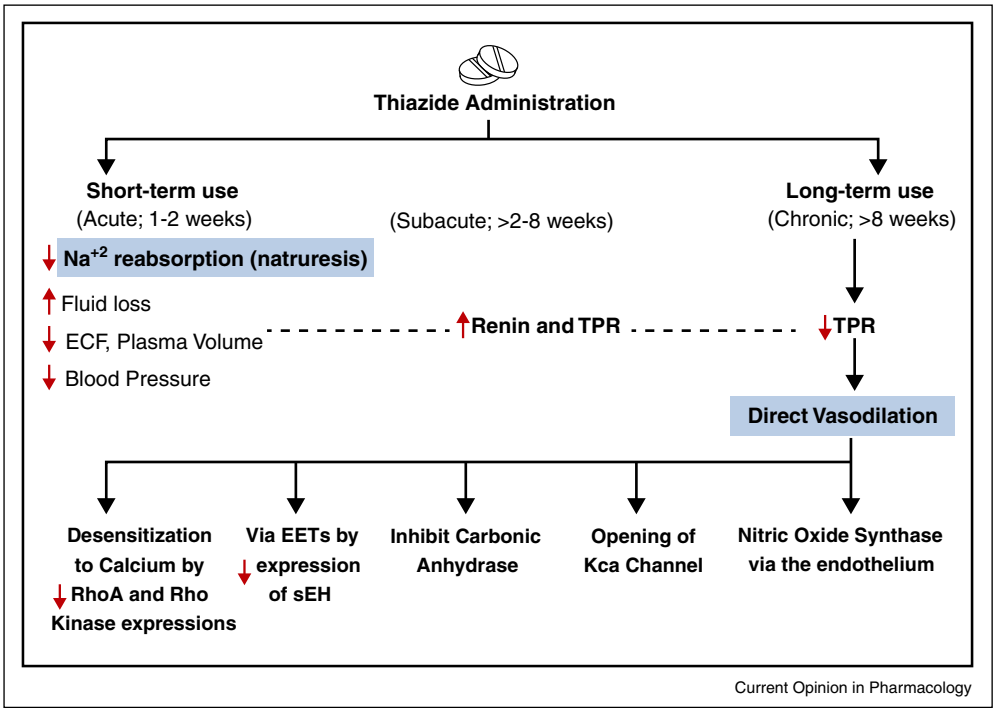
Short-term BP lowering mechanism

TZDs are well known to mediate their diuretic effects via inhibiting the Na^+/Cl^- cotransporter (NCC) in the distal convoluted tubule, which consequently increases fluid loss, leading to a reduction in the extracellular fluid (ECF), and plasma volume and eventually a decrease in cardiac output and BP [7]. Therefore, the anti-HTN mechanism of TZDs has long been hypothesized to be attributed to their diuretic effect and enhancement of sodium excretion. In support of this hypothesis, Bennett *et al.* have shown that adding 20 g of salt per day to the diet of HTN patients treated with hydrochlorothiazide (HCTZ) negated the anti-HTN effect of HCTZ. Additionally, TZDs have been shown to be ineffective in end stage renal disease, which supports the importance of natriuresis for the anti-HTN action of TZD diuretics [8]. However, other evidence contradicts this hypothesis. Specifically, chlorothiazide, a TZD diuretic, lowered the BP of patients with severe renal failure [9], suggesting the diuretic effects of TZDs might not be the driving mechanism underlying their BP lowering action. Consistent with this suggestion, studies have shown that after 4–6 weeks of TZD diuretic initiation, the ECF and plasma volumes return to normal levels, yet BP reduction is maintained [10,11]. Collectively, these studies suggest TZD BP lowering effects might be initially related to sodium regulation and reduction in plasma volume and cardiac output (Figure 1). However, it seems unlikely that this is the central mechanism underlying their chronic anti-hypertensive effect.

Long-term BP lowering mechanism

Over the past half a century, researchers have sought to define the mechanism underlying the chronic BP lowering effects of TZDs (Figure 1). Many have suggested this

Figure 1



Known and theoretical blood pressure lowering mechanisms of thiazide diuretics.

long-term mechanism is mediated via reduction in total peripheral resistance (TPR) [10,12]. However, the precise mechanism and factors underlying this reduction have not been fully elucidated [13]. Several studies have suggested that TZDs reduce TPR via a vasodilation effect [14–16]; yet the mechanism by which TZDs dilate blood vessels has been perplexing and controversial [17].

One hypothesized mechanism is that TZDs' vasodilatory effects might be mediated via the endothelium. This hypothesis was supported by an *in vitro* study showing that methaclothiazide, a TZD diuretic, inhibited the vasoconstrictive effect of norepinephrine and vasopressin in the aorta of spontaneously HTN rats, but not in Wistar Kyoto (non-HTN) rats [18]. Additionally, this effect was abolished by the removal of the endothelium or by using a nitric oxide synthase inhibitor, suggesting that TZDs' hypotensive effects might be mediated via a nitric oxide endothelium-dependent mechanism. On the contrary, another study showed that TZDs, at clinically therapeutic concentrations, inhibit the vasoconstriction effects of norepinephrine and angiotensin II in the presence or the absence of the endothelium [19]. This study also reported that TZD induced vasodilation was associated with a significant reduction in RhoA and Rho Kinase expression in the vascular smooth muscle, but no changes in cellular calcium levels were observed. The changes in expression observed were independent of endothelium, suggesting that TZDs act directly on the vascular smooth muscle and not the endothelium. The authors of this study suggested that the chronic anti-HTN effects of TZDs might be mediated via calcium desensitization that occurs over long term use of these medications. However, this hypothesis is based only on this study, and more research is needed to confirm this hypothesis.

Others suggest that TZD diuretics cause vasodilation via opening the calcium activated potassium channels (K_{CA}). This hypothesis was supported by results from an *in vitro* study showing that HCTZ dilates guinea pigs mesenteric arteries, and this effect was abolished by using charbdotoxin, an inhibitor of the K_{CA} [20]. Additionally, an *in vivo* study has also shown that HCTZ caused a vasodilatory effect when injected into human brachial artery, and this effect was abolished by using tetraethylammonium, a K_{CA} inhibitor [21]. Although this *in vivo* study has shown that the vasodilatory effects of TZDs may be mediated via K_{CA}, the TZD plasma concentrations measured in this study were ~10 times the plasma concentrations seen clinically in TZD treated patients [22], which brings into question if this vasodilatory effect underlies the BP lowering in the clinical setting.

Other researchers have proposed that the long term anti-HTN effects of TZDs are due to their carbonic anhydrase inhibiting properties, which produce alkalosis in the