PREVENTION

Effects of High Salt Intake on Blood Pressure and Cardiovascular Disease: The Role of COX Inhibitors

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ABSTRACT

Sodium has a bidirectional effect on blood pressure (BP) and cardiovascular disease (CVD). High sodium intake increases both BP and CVD, whereas low sodium intake decreases them. The significance of this association has been debated for years, mostly due to the inconsistency of data, but recently it has been revived due to new evidence about the harmful effects of sodium. Recent studies have indicated that high sodium intake was associated with an increase in BP and CVD, which in 2010 was estimated to have accounted for 1.65 million deaths worldwide. Based on this evidence, the American Heart Association has issued a Science Advisory statement regarding the significance of high sodium intake in relation to the incidence of hypertension and CVD. In addition to high sodium intake, experimental studies have shown that the coadministration of nonsteroidal anti-inflammatory drugs further aggravates the harmful effects of high sodium intake. The interrelationship of high sodium intake and nonsteroidal anti-inflammatory drugs will be discussed in this commentary.

Introduction

Sodium has a bidirectional effect on blood pressure (BP) and cardiovascular disease (CVD), and several studies have shown that high sodium intake increases BP and CVD, whereas low sodium intake decreases both BP and the incidence of CVD.[1–4] This subject has been debated over the years, mainly due to the inconsistency of the data; recently, it has been revived due to new evidence showing that high sodium intake is associated with increased BP and CVD, which in 2010 accounted for 1.65 million deaths worldwide.[4] To address this issue, the American Heart Association (AHA) issued a Science Advisory statement regarding the significance of high sodium intake as a major risk factor for hypertension (HTN) and CVD.[5] What is missing from this science report, as well as from the guidelines for the treatment of HTN, either alone or in combination with CVD and diabetes mellitus (DM),[6–8] is the role of high sodium intake combined with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). In both animals and humans, NSAIDs cause prostaglandin synthesis inhibition, leading to systemic and renal vasoconstriction, increase in sodium and water retention, and increase in BP.[9,10] This adverse effect of high sodium intake in combination with NSAIDs is very important, especially for older people, who routinely take NSAIDs for arthritis pain and inflammation; this could increase the incidence of heart failure (HF).[11] This commentary will focus on the current knowledge of the interaction of nonselective cyclooxygenase (COX) inhibitors with high sodium intake and the resulting effect on BP, CVD, and HF.

Interaction of Cyclooxygenase Inhibitors With High Sodium Intake: The Role of Prostaglandins

Prostaglandins are synthesized from arachidonic acid through the catalytic action of COX and serve an important function in regulating systemic and renal hemodynamics and the excretion of sodium and water from the kidneys.[12,13] There are 2 COX isoforms, COX-1 and COX-2, which have a similar biochemical action but different expression. COX-1 is constitutively expressed in all tissues of the body, whereas COX-2 is induced by inflammatory stimuli and is also constitutively expressed in the brain, lung, and kidney.[14–16] The main prostaglandins produced by COX-1 and COX-2 are (1) prostaglandin E_2 (PGE_2), localized in the kidney and responsible for renal blood flow regulation and sodium and water excretion; and (2) prostaglandin I_2 (PGI_2), or prostacyclin, mainly localized in the peripheral vessels and responsible for systemic vascular resistance and blood-flow regulation by opposing the vasoconstrictor and platelet-aggregatory effects of thromboxane A_2 (TXA_2). Blockade of prostaglandin synthesis with the administration of NSAIDs in patients on high sodium intake has been associated with increased BP and CVD.[17,18] Previous studies in our laboratory showed that spontaneously hypertensive rats (SHR) exposed to high salt intake (1% NaCL in

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Table 1. Hemodynamic and Histologic Effects of 3-Month Administration of High Salt Intake in Combination With Meclofenamate in Male SHR

	Control	Meclofenamate	*P* Value
No. of rats	8	8	NS
SBP, mm Hg	198 ± 8	248 ± 10	<0.005
DBP, mm Hg	138 ± 8	177 ± 7	<0.005
MAP, mm Hg	156 ± 6	201 ± 6	<0.005
HR, bpm	432 ± 43	475 ± 15	NS
LVW, mg	900 ± 30	1200 ± 30	<0.05
RVW, mg	240 ± 10	250 ± 10	NS
Hct, vol%	53.6 ± 2.6	54.0 ± 1.0	NS
GFR, mL/min/100 g	0.38 ± 0.02	0.28 ± 0.02	<0.05
ERPF, mL/min/100 g	1.06 ± 0.12	0.53 ± 0.06	<0.005
RBF, mL/min/100 g	2.34 ± 0.42	1.15 ± 0.15	<0.005
RVR, mm Hg/mL/min)	77 ± 20	195 ± 20	<0.005

Abbreviations: DBP, diastolic blood pressure; ERPF, effective renal plasma flow; GFR, glomerular filtration rate; Hct, hematocrit; HR, heart rate; LVW, left ventricular weight; MAP, mean arterial pressure; NS, not significant; RBF, renal blood flow; RVR, renal vascular resistance; RVW, right ventricular weight; SBP, systolic blood pressure; SEM, standard error of the mean; SHR, spontaneously hypertensive rats.
Data are presented as mean ± SEM.

tap water) in combination with the nonselective COX inhibitor sodium meclofenamate (50 µg/mL) daily for 3 months developed significantly higher arterial pressure, renal vascular resistance, renal arteriolar changes, and larger left ventricular weight than SHR exposed to salt intake only.[19] In addition, the combination of high salt intake with sodium meclofenamate resulted in significantly lower effective renal plasma flow, renal blood flow, and glomerular filtration rate than SHR exposed to high salt intake only (Table 1). Similar findings also have been reported by other investigators.[9,20,21]

Clinical Impact of High Sodium Intake in Combination With Cyclooxygenase Inhibitors

Recent studies are fairly well convincing of the association of high sodium intake and the increased incidence of HTN, CVD, and HF.[1–4,11] According to a recent large multiethnic study (66 countries), daily sodium consumption of 3.95 g (range, 2.18–5.51 g/d) was responsible for 1.65 million deaths in 2010 from cardiovascular causes.[4] Several other studies have also shown that globally, the daily intake of sodium varies between 3 and 6 g (range, 7.5–15.0 g salt/d), which is much higher than the dietary reference intake (DRI) of 1.5 to 2.4 g sodium per day recommended by the guidelines.[22–24] In addition, the association of sodium intake with HTN, CVD, and HF is bidirectional, with high sodium intake increasing the incidence of these complications and low sodium intake decreasing them.[11,25–27] However, not all studies are consistent, and some have shown a J- or U-shaped curve of the association of sodium intake with HTN and CVD, suggesting that high as well as low sodium intake are associated with increased risk of HTN and CVD due to its effect on BP.[28,29] The J-curve demonstrates a relationship between a range of BPs and the incidence of CVD and stroke. When the BP reaches a point where the complications are the lowest (nadir), any further decrease or increase in BP from this point is associated with an increase in cardiovascular events. The J-curve effect is seen with various BP ranges, but it is mostly seen when the systolic BP falls to <130 mm Hg and the diastolic BP <70 mm Hg.[30] The heterogeneity of data regarding the adverse effects of low sodium intake has been attributed to several methodological issues of sodium intake based on dietary recall, urinary sodium excretion, and the inclusion of subjects with high cardiovascular risk, which could indicate a reverse causation,[1,5,29] although there is a pathophysiologic explanation for this effect. Sodium plays a critical role in normal human physiology, and sodium intake <3.0 g/d is associated with activation of the renin-angiotensin-aldosterone system, which has been associated with increased CVD and death.[31,32] These findings are at variance with the study by Mozaffarian et al,[4] who showed that lowering the definition of the reference sodium intake from 2.0 g/d (5.0 g salt/d) to 1.0 g/d (2.5 g salt/d) would have increased the deaths from cardiovascular causes by 40%, or 2.3 million deaths worldwide. Regardless of the amount of salt consumed, the administration of COX inhibitors increases salt sensitivity, especially in salt-sensitive subjects (eg, older, African American and diabetic subjects), and in addition interferes with the action of antihypertensive drugs and destabilizes previously controlled BP, thus increasing the cardiovascular complications of high sodium intake.[33,34] Therefore, older individuals, especially those with HF receiving NSAIDs for arthritis pain, inflammation, and other causes of pain, should be instructed to drastically decrease their sodium intake and even stop the use of NSAIDs.[11]

What, then, is a safe sodium intake? The old Institute of Medicine (IOM) guidelines set the daily DRI of sodium according to age, as follows: 1.5 g for ages <50 years, 1.3 g for ages 50 to 70 years, and 1.2 g for ages >70 years.[35] However, these restricted amounts of sodium were difficult to sustain and subsequently were revised upward to 2.3 to 2.4 g/d by the IOM and the Dietary Guidelines for Americans, regardless of age.[24,36] Due to increased salt sensitivity produced by the administration of NSAIDs, a daily sodium consumption between 2.3 and 2.4 g would be well tolerated and safe for older individuals receiving NSAIDs.

Conclusion

High sodium intake is associated with increased incidence of HTN and CVD. The coadministration of NSAIDs with high sodium intake potentiates the adverse cardiovascular and BP effects of high sodium intake, and people taking these drugs should decrease the amount of sodium consumed. Older people are more vulnerable than younger people, because a great majority of them receive NSAIDs for arthritis pain and inflammation. Older subjects with HF should be advised to drastically restrict sodium intake,

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and, if at all possible, avoid taking NSAIDs. Governmental agencies strive to change the American culture regarding the liberal amounts of sodium consumed and periodically issue guidelines recommending the amounts of sodium to be consumed by various age groups. The currently recommended DRI of sodium by the IOM and the Dietary Guidelines for Americans is between 2.3 and 2.4 g/d.

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