Heavy metal to lower the pressure?

Ralf Köhler*

Aragon Institute of Health Sciences I+CS and ARAID, Unidad de Investigación Translacional, University Hospital Miguel Servet, Paseo Isabel la Católica, 1-3, Zaragoza 50009, Spain

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This editorial refers to ‘Tungstate activates BK channels in a β-subunit- and Mg²⁺-dependent manner: relevance for arterial vasodilatation’ by A.I. Fernández-Mariño et al., pp. 29–38, this issue.

Activation of the large conductance, Ca²⁺-dependent K⁺ channel [KCa1.1-β-subunits, generally known as the Big K (BK) or maxi K channel] is an important negative feedback on depolarization and Ca²⁺-induced contraction of smooth muscle and thus arterial vasoconstriction (Figure 1). Intriguingly, altered function of BK and/or polymorphism in human BK α- and β-subunit genes have been associated with hypertension, and, from the therapeutic perspective, it is generally believed or hoped that improving BK channel function helps to ease vasodilatation and to lower blood pressure in hypertension. The study by Fernández-Mariño et al. demonstrates that the heavy metal salt tungstate has vasodilator capabilities by stimulating BK activity (Figure 1). At the molecular level, the authors showed that this positive gating modulation is conferred by the β1-subunit of the BK channel complex and interactions with the magnesium control of channel activity. Hence, the study makes a significant contribution to a better understanding of the regulation of BK channels by a heavy metal salt. From the translational perspective, the study fosters the potential utility of tungstate as a new type of antihypertensive ‘drug’, perhaps as food additive or component of the daily diet.

The pharmaceutical industry has developed fairly selective and potent BK openers (e.g. Neurosearch with the rather non-selective NS1619, or the newer more potent NS11021, BMS204352 by Bristol Meyer Squibb, and NS8 by Nippon Shinyaku; for review, see Köhler et al. and Wulff and Zhorov). Also, nature has provided us with some compounds: for instance, DHS-I, a B1-subunit-dependent positive gating modulator (present in Desmodium adscendens from the bean family which is used for bronchodilating asthma therapy in traditional African herbal medicine). Moreover, unsaturated fatty acids such as arachidonic acid and docosahexaenoic acid (ω-3 fatty acids) act as positive gating modulators. Despite our knowledge of these synthetic and natural modulators for considerable time (5–15 years), none of the small molecules has been developed further for antihypertensive therapy or related clinical applications; the reasons for this are unclear. Nonetheless, it is still remarkable that two BK openers (BMS204352 and NS8) entered clinical trials although they failed because lack of efficacy (BMS204352 for neuroprotection after ischaemic stroke; NS8 for overactive bladder). Blood pressure-lowering actions of the compounds in humans have not been published. Another BK opener, Andolast, has been considered for the treatment of asthma. A drawback to their possible utility as antihypertensive drugs could be their mode of action (favouring hyperpolarization and closure of L-type Ca²⁺ channels; Figure 1), which is in principal not much different from a Ca²⁺ channel blocker, of which we already have a few. Also, the safety profile may be problematic because of potential interactions with BK channels in neurons or other tissues that may give rise to multiple side-effects. In summary, a complicated setting makes it difficult to convince the pharmaceutical industry to undergo risky and costly endeavours.

According to the study by Fernández-Mariño et al., nature may provide us with some cheaper solutions such as tungstate diets or tungstate as food additives. Hence, in the late 1990s, tungstate was shown to have blood pressure-lowering efficacy by inhibition of endothelial xanthine oxidase (reduced ROS production) and to promote vasodilatation in the SHR model of hypertension. Moreover, tungstate has been considered as an anti-obesity drug because it reduced weight in obese rats. However, oral sodium tungstate at 200 mg per day failed in a phase II clinical trial (TROTA-1, NCT00555074) to reduce body weight, and the treatment apparently did not lower blood pressure in these obese but normotensive volunteers. Another possible reason for the disappointing outcome might be that it is difficult to reach relatively high—therapeutically meaningful—concentrations over a longer period, which may be due to its fast elimination via the kidney.

How much tungstate do we need to consume and for how long? Is this safe over time? Well, nobody knows, but I feel a slight discomfort consuming high amounts of a heavy metal. Even so, tungstate is considered harmless—over years or decades as it would apply to hypertensive subjects. As already mentioned above, BK is also expressed in other tissues like the kidney and the brain, and high dosage or long-term intake—albeit hypothetical at present—may also cause side-effects on the central and neurovegetative systems and in the kidney. Here it should be noted that some of the blood pressure-controlling actions mediated by BK channels are presumably related to channel function in the renal tubular system.

In conclusion, the present work by Fernández-Mariño et al. has the potential to be incentive to provide proof for in vivo efficacy and safety of tungstate treatments in hypertensive subjects. This should be relatively quickly accomplished in the case of tungstate. One may also consider tungstate as an adjuvant, e.g. in combination with the classical...
drugs such as ACE and angiotensin II receptor antagonists and β-blockers, although not with Ca^{2+}-antagonists (same mode of action) or with diuretics because they further accelerate tungsate’s elimination via the kidney. So, we will wait and see whether tungsate may serve for improving health standards in our cardiovascular-morbidity societies beyond its usage as wire in light bulbs and as electrodes for the physiologist. Regardless of these general considerations that apply, of course, to all new ideas and attempts to improve treatment standards, the study by Fernández-Mariño et al. is important because the authors envision novel molecular and pharmacological mechanisms and strengthen translational perspectives to exploit an important molecular player in the arterial system to counteract and/or to prevent hypertension and ensuing cardiovascular and ischemic disease by cost-effective dietary means.

Conflict of interest: none declared.

References