Multifaceted clinical effects of acetazolamide: will the underlying mechanisms please stand up?

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IN THIS ISSUE, PICKERODT AND colleagues (7) showed for the first time that the acetazolamide (AZ) analog N-methyl acetazolamide (NMA), lacking carbonic anhydrase (CA) inhibiting activity, substantially reduced the acute hypoxia-induced increases in mean pulmonary arterial pressure [hypoxic pulmonary vasoconstriction (HPV)] and pulmonary vascular resistance in conscious dogs in vivo. Previously, they had shown that even the powerful sulfonamide CA inhibitors benzolamide and ethoxzolamide failed to reduce HPV (see references in Ref. 7). The study by Pickerodt et al. shows not only that AZ’s effect on HPV [note that, in humans, clinical oral doses of the drug substantially reduce HPV in acute hypoxia (see references in Ref. 7)] does not depend on CA inhibition (CAI), but that it is also a first important effort to identify the pharmacophore(s) that is able or needed to reduce or abolish HPV and thus may contribute to the elucidation of the vasoconstriction mechanism itself. In case of NMA, one hydrogen ion of the sulfonamide moiety is replaced by a methyl group and thereby loses its potency to block CA. In isolated pulmonary smooth muscle cells, AZ and NMA prevented the hypoxia-induced rise in intracellular Ca\(^{2+}\) concentration without influencing the membrane potential, voltage-gated potassium channels, and intracellular pH (see reference in Ref. 7), so the mechanism underlying AZ’s and NMA’s effects remains obscure.

AZ is used in a broad range of clinical settings. Without giving a comprehensive overview, I mention only a few of these. It is used as a mild diuretic, in eye disease (glaucoma), to reduce cerebrospinal fluid production, to treat metabolic alkalosis and sleep apnea, and to prevent and relieve the symptoms of acute mountain sickness. In addition, it is the first-choice pharmacological tool against episodic ataxia type 2 and forms the main treatment of hypokalemic periodic paralysis (6). AZ and other CA inhibitors have anticonvulsive properties and as such are used against epilepsy (5). Known side effects are depression, loss of libido, nausea, anorexia, paresthesias, fatigue, weight loss, and bad taste of carbonated beverages.

AZ has several important physiological effects, some of which may have clinical relevance. First, apart from having vasodilatory effects in animals, it causes vasodilation in the human forearm (see references in Ref. 7) and improves the ratio of oxygen supply to demand in the heart in hypoxia (8). Second, at low intravenous dose (but not with usual clinical oral applications), it reduces the ventilatory response to hypoxia (hypoxic ventilatory response; see references in Ref. 11) and thus could be useful in reducing the gain of the ventilatory control system in periodic breathing and apnea syndromes. Third, in animals, AZ potentiates the anti-allodynia effects of midazolam, promotes GABA\(_A\) receptor-mediated analgesia, and reduces formalin-induced and neuropathic pain (see references in Ref. 9).

How to explain this impressive variety of physiological and clinical effects? One reason could be that AZ is a nonselective inhibitor acting simultaneously on several of the 13 known human CA isoforms. An alternative explanation, however, may be actions independent from CAI. Indeed AZ emerges as a molecule with a variety of pharmacological actions of which I give a few examples. The attenuation of capsaicin and formalin-induced pain in mice is not shared by methazolamide (MTZ), a CA inhibitor with equal potency that is much more lipophilic, and may be explained by blocking (\(\alpha_{IE}\)-subunit-mediated) currents through R-type calcium channels and/or opening of Ca\(^{2+}\)-activated potassium (BK) channels (9). Its effectiveness in hypokalemic paralysis may be explained by a specific stimulating effect on BK channels that has been demonstrated in animal studies (see references in Ref. 6). An opening effect on BK channels may also be the underlying mechanism of AZ’s vasodilatory property, but whether this is a direct action or mediated by membrane hyperpolarization (caused by inhibition of an extracellular CA?) remains to be seen. Note, however, that, as mentioned above, the vasorelaxing effect in the pulmonary circulation, as reported by Pickerodt et al., does not seem to be mediated via BK channels. Respiratory muscle weakening as reported for humans (2) is also demonstrated in rabbits, where it is not shared by MTZ (3). The same applies to the reduction of the hypoxic ventilatory response in animals that is not seen with even high doses of MTZ (11). Whether this is due to opening of BK channels in the membrane of oxygen-sensing cells in the carotid bodies or rather to (BK channel-mediated?) local vasodilatation altering the arterial-to-carotid body Po\(_2\) relationship is unknown. An intriguing emerging new aspect of AZ’s pharmacological action is its ability to inhibit (the expression of) aquaporin-1 and other AP isoforms, which may at least partly account for its diuretic and possibly also its anti-inflammatory effects (10, 12) and provide it with a potential means to influence transepithelial fluid transport and brain water balance. Finally, AZ may have antioxidant properties that could contribute to its beneficial effects at high altitude (1).

From the above brief summary, it is evident that the physiological and clinical effects of AZ are extremely complex. Choosing the right dose (regimen) and administration route are of crucial importance. AZ does not easily penetrate into cells, but accumulates in renal proximal tubule cells that secrete it. Renal effects of AZ include diuresis, urine alkalosis, and increased sodium and potassium excretion and may result in acidemia (followed by stimulation of the peripheral chemoreceptors and a rise in ventilation) and fall in plasma K\(^+\).
concentration. Note that, at tissue concentrations $< 10^{-4}$ M, enzyme inhibition is incomplete and, therefore, ineffective (4). Physiological responses to AZ in the absence of renal effects may thus be mediated by mechanisms independent from CA, although inhibition of endothelial CA (CA IV) facing the vessel lumen cannot be entirely ruled out. Pickerodt et al. (7) used low concentrations and reported renal effects, but these were very small, supporting predominantly CAI-independent effects on HPV.

In conclusion, AZ may emerge as a suitable lead compound for the development of new vasoactive (dilating), analgesic, anti-inflammatory, anticonvulsant, neuromuscular, and even antioxidant drugs. The unsubstituted sulfonamide moiety is crucial for its CAI activity. The study by Pickerodt et al. (7) showing that replacing a hydrogen ion in the sulfonamide moiety by a methyl group does not affect the vasorelaxant activity of the analog on pulmonary smooth muscle cells is an interesting effort in that direction. Antioxidant properties may reside in the thiadiazole moiety (see references in Ref. 1). The 1,3,4-thiadiazole-sulfonamide moieties may account for the anticonvulsant properties, while substitutions of the alkyl moieties in the 5 position can result in compounds with appreciably higher anticonvulsant potencies (5). Studies are warranted to examine how the AZ molecule can be manipulated to see which moieties are necessary to act on molecular targets, such as membrane (including water) channels.

DISCLOSURES

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