FEATURED NEW INVESTIGATOR

Nonsteroidal anti-inflammatory medications are cytostatic against human vestibular schwannomas

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Vestibular schwannomas (VSs) are the most common tumors of the cerebellopontine angle. Significant clinical need exists for pharmacotherapies against VSs. Motivated by previous findings that immunohistochemical expression of cyclooxygenase 2 (COX-2) correlates with VS growth rate, we investigated the role of COX-2 in VSs and tested COX-2 inhibiting salicylates against VSs. COX-2 was found to be aberrantly expressed in human VS and primary human VS cells in comparison with control human nerve specimens and primary Schwann cells (SCs), respectively. Furthermore, levels of prostaglandin E2, the downstream enzymatic product of COX-2, were correlated with primary VS culture proliferation rate. Because COX-2 inhibiting salicylates such as aspirin are well tolerated and frequently clinically used, we assessed their repurposing for VS. Changes in proliferation, cell death, and cell viability were analyzed in primary VS cultures treated with aspirin, sodium salicylate, or 5-aminosalicylic acid. These drugs neither increased VS cell death nor affected healthy SCs. The cytostatic effect of aspirin in vitro was in concurrence with our previous clinical finding that patients with VS taking aspirin demonstrate reduced tumor growth. Overall, this work suggests that COX-2 is a key modulator in VS cell proliferation and survival and highlights salicylates as promising pharmacotherapies against VS. (Translational Research 2015;166:1–11)

Abbreviations: 5-ASA = 5-aminosalicylic acid; BrdU = 5-bromo-2′-deoxyuridine; GAN = great auricular nerve; COX-2 = cyclooxygenase 2; IκK = I kappa B kinase; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NaSal = sodium salicylate; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B; PBS = phosphate-buffered saline; PBST = phosphate-buffered saline with Tween 20; PTG = prostaglandin; *PTGS2* = gene encoding COX-2 protein; RIPA = Radioimmunoprecipitation Assay; S100 = Schwann cell/schwannoma cell marker; SC = Schwann cell; SD = standard deviation; SEM = standard error of the mean; VS = vestibular schwannoma

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AT A GLANCE COMMENTARY

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Background

Vestibular schwannomas (VSs) are the most common tumors of the cerebellopontine angle. Significant clinical need exists for pharmacotherapies against VSs.

Translational Significance

Cyclooxygenase 2 was found to be aberrantly expressed and active in human VSs. Well-tolerated and clinically relevant salicylates, namely aspirin, sodium salicylate, and 5-aminosalicylic acid, significantly reduced proliferation in primary human VS cultures. This work suggests that cyclooxygenase 2 is a key modulator in VS cell proliferation and survival and highlights salicylates as promising pharmacotherapies against VS.

INTRODUCTION

Vestibular schwannomas (VSs) are the most common tumors of the cerebellopontine angle and the fourth most common intracranial tumors.[1] Although VSs are histologically nonmalignant, they can lead to substantial morbidity, including sensorineural hearing loss, vestibular dysfunction, and facial nerve paralysis, because of their location within the internal auditory canal and the cerebellopontine angle.[1,2] Large VSs can cause additional paralysis of other cranial nerves, brainstem compression, and death.[2] Currently, patients with symptomatic or growing VSs can undergo surgical resection or radiotherapy. Both these procedures can result in serious complications. Surgical resection entails full or partial removal of the tumor via craniotomy and carries substantial risks, including sensorineural hearing loss, vestibular dysfunction, facial nerve paralysis, cerebrospinal fluid leaks, and meningitis.[3,4] Stereotactic radiotherapy entails delivering a radiation dose to the tumor and can be associated with severe adverse effects such as further exacerbation of the sensorineural hearing loss, vestibular dysfunction, and potential malignant transformation of the tumor.[5,6] Patients with nongrowing or asymptomatic VSs can undergo conservative management and follow tumor progression through serial magnetic resonance imaging, but because of the lack of biomarkers for VS growth and associated symptoms, conservative monitoring can be a risky approach.[7] Effective drug therapies that can limit VS growth would greatly advance health care for patients with VS.

Cyclooxygenase 2 (COX-2), a major inflammatory mediator, has been implicated in VS. Previous studies demonstrate that the expression level of COX-2 in VSs is correlated with tumor proliferation rates, as judged by the intensity of COX-2 immunostaining in VS specimens.[8] The COX enzymes catalyze the biosynthesis of prostaglandins (PTGs), hormone-like lipid compounds that can trigger the inflammatory response.[9] In contrast to COX-1, which is expressed constitutively as a homeostatic enzyme in several cell types such as platelets and gastrointestinal mucosal cells, COX-2 is expressed at sites of inflammation and neoplasia.[8,9] Specifically, COX-2 has been described to modulate cell proliferation and apoptosis in many solid tumors, such as colorectal, breast, and prostate cancers.[9]

Salicylates, a class of nonsteroidal anti-inflammatory drugs (NSAIDs) defined by their chemical structure, are attractive therapeutics because they are clinically relevant, well-tolerated, effective COX-2 inhibitors, commonly used against pathologies such as pain and arthritis.[10] Furthermore, in some cases, chronic intake of salicylates has led to a significant reduction in the incidence and burden of various tumors, such as colorectal cancer.[9] In our study, we assessed the efficacy of 3 different salicylates, aspirin, sodium salicylate (NaSal), and 5-aminosalicylic acid (5-ASA), against VS because they are clinically used and well tolerated. Specifically, aspirin has been confirmed to provide chemoprevention for multiple human malignancies, including colon, gastric, breast, and prostate cancer—reviewed in Thorat and Cuzick.[11] NaSal is a sodium salt of salicylic acid. It is used clinically as an analgesic and antipyretic and as an alternative to aspirin for people sensitive to aspirin. NaSal has shown effectiveness against myeloid leukemia cell lines.[12] 5-ASA is commonly used to treat inflammatory bowel disease including ulcerative colitis[13] and Crohn's disease,[14] and it can prevent colorectal cancer.[15] In addition to its anti-inflammatory properties, 5-ASA is thought to be an antioxidant that traps free radicals.[16] These 3 salicylates, although acting through similar mechanisms to inhibit COX activity, have nuances that can lead to differential therapeutic and toxic profiles.[10] We explored the expression of COX-2 in human VS and the therapeutic efficacy of salicylate-mediated COX-2 inhibition in primary VS cells. All salicylates tested were effective in selectively reducing proliferation and viability of cultured VS cells, accompanied by reduced secreted PTG levels. Our work suggests