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Review

The pleiotropic functions of aspirin: mechanisms of action

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Abstract. Recent studies have suggested that aspirin and aspirin-like compounds have a variety of actions in addition to their well-studied ability to inhibit cyclooxygenases. These actions include inhibition of the uncoupling of oxidative phosphorylation, decreases in adenosine triphosphate stores, increases in extracellular adenosine, downregulation of the expression and activity of inducible nitric oxide synthetase, inhibition and/or stimulation of various mitogen-activated protein kinase activities and inhibition of nuclear factor binding κB site (NF-κB) activation. Moreover, aspirin-like compounds have recently been shown to have previously unappreciated clinical and biological effects, some apparently independent of cyclooxygenase. In this review we discuss the various mechanisms of action of aspirin-like compounds and their relevance to clinical disease and therapy.

Key words. Aspirin; prostaglandin; COX; signal transduction; NF-κB; NOS.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the earliest agents used in Western medicine. As early as the 4th century B.C., Hippocrates averred that chewing of willow leaves relieved the pains of childbirth. A millennium later, the Reverend Mr. Edmund Stone of Oxfordshire, England, again put the willow into our pharmacopoeia when, in a letter to the Royal Society, he commented that the bark of the willow *Salix alba* was 'a powerful astringent, and very efficacious in curing aguish and intermitting disorders.' By the turn of the 20th century the active ingredient in the bark, salicylic acid, had been identified, and acetylsalicylate, or aspirin, had been synthesized. However, it would remain until the 1970s—at least 23 centuries after its actions were first intuited—that the mechanisms of salicylate action began to be appreciated. Now, on the doorstep to the third millennium, it is becoming clear that the first mode of salicylate action to be identified—cyclooxygenase (COX) inhibition—is a major but probably not the only effect of salicylates. Moreover, a number of novel clinical uses of salicylates have recently been appreciated. In this paper we will review both the established, and the emerging, actions of salicylates and other NSAIDS.

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The classical mechanism of NSAID action: inhibition of COX 1 and 2

In the early 1970s Hamberg and Samuelsson identified the presence, in sheep seminal vesicles, platelets and other tissues, of an activity capable of converting

arachidonic acid (AA, supplied exogenously or liberated from membranes by phospholipase A_2) to a variety of prostaglandins (PGs) including PGE_2 and $PGF_{2\alpha}$ [1]. This activity, known variously as 'prostaglandin synthase', 'prostaglandin H (PGH) synthase' or COX, was shown to be the result of one or more heterobifunctional enzymes capable of catalyzing two sequential reactions: the bis-dioxygenation of arachidonic acid (COX activity) and the reduction of hydroperoxides to the corresponding alcohols (peroxidase activity) to form PGH_2. Series prostaglandins beyond PGH are then synthesized through a sequence of further enzymatic reactions [2]. PGs produced via COX appear to be important for a wide variety of homeostatic functions such as maintaining the integrity of the gastric mucosa, mediating normal platelet function, regulating renal blood flow, and participating in central nervous system mechanisms of thermoregulation [1]. In addition, it was quickly appreciated that stable prostaglandins of the E series regulate a number of processes critical to inflammatory responses, including an increase in vasodilation and vascular permeability, and mediation of peripheral pain. Moreover, although PGEs are generally proinflammatory, they also have several antiinflammatory effects, including suppression of adjuvant arthritis in rats [3], and inhibition of inflammatory signal transduction in human neutrophils ex vivo [4]. Thus, prostaglandins are critical to the regulation of both homeostasis and inflammation, and for many years these discrete functions were thought to be inseparable.

Recently, it has been appreciated that there are at least two isoforms of COX. The first (COX-1) is a constitutively expressed enzyme that has been shown to participate primarily in PG production for homeostatic functions. In contrast, COX-2 is the product of an 'immediate early' gene induced in response to interleukin-1β (IL-1β), lipopolysaccharide (LPS), tumor necrosis factor (TNFα) and other proinflammatory factors [1], and is therefore critical for the further propagation of inflammation. When expressed, COX-1 and COX-2 each demonstrates a broad tissue distribution [5], and each forms the same prostaglandin intermediates. Thus it is the timing and amount of expression, and the regulation of activity, that distinguish the effects of the two COXs.

Shortly after the discovery of COX activity, Sir John Vane and his associates proposed that the mechanism of salicylate action occurred via the inhibition of COX. They pointed out that almost all NSAIDs inhibited prostaglandin synthesis and that the dose required to inhibit 50% COX activity (ID_{50}) closely paralleled both their clinical potency and their effect in experimental animals; e.g. aspirin was anywhere from 1/40 to 1/200 as active as indomethacin and from 1/5 to 1/50 as active as ibuprofen [6].

Recent biochemical and X-ray crystallographic studies of both COX-1 and COX-2 have shed light on the mechanisms of COX inhibition by salicylates and other NSAIDs. Both COX-1 (a 70-kDa homodimer localized to microsomal membranes) and COX-2 possess an arachidonic acid binding site set within a molecular channel. Aspirin binds competitively and reversibly to the AA-binding sites of both enzymes, and subsequently irreversibly inactivates them by acetylating Ser 530 and blocking further access of AA to the active site. Thus, although the half-life of a single dose of aspirin in the bloodstream is of the order of 4 h, its effect on COX activity persists until turnover of the inactivated enzyme is complete. Other NSAIDs, such as ibuprofen and flurbiprofen, sterically hinder access of AA into the channel in which the active site is hidden but do not irreversibly block the enzyme, and their duration of action on COX is directly proportional to their half-life in the body. The gatekeeper of the channel in both COXs appears to be Arg 123, which interacts with the carboxylic acid group present in clinically useful NSAIDs. However, the channels are not identical. Whereas COX-1 contains an isoleucine at position 509, in COX-2 this amino acid has been substituted with valine, resulting in a somewhat larger channel, and raising the possibility that NSAIDS with appropriately oriented, bulky side chains might fit into the channel in COX-2 only. Consistent with this hypothesis, studies by Gierse et al. [7] showed that a single amino acid change of Val 509 to isoleucine conferred COX-2 selectivity to the class of SC-58125 inhibitors such as celecoxib. In contrast, traditional NSAIDS such as aspirin and indomethacin show little or no selectivity [7].

Interestingly, acetylation of COX-2 by aspirin appears to have metabolic and antiinflammatory consequences other than those related to inhibition of prostaglandin synthesis. Work from the laboratory of Serhan et al. has demonstrated that incubation of cocultures of neutrophils and endothelial cells or other cell types with aspirin—but not indomethacin or salicylate—results in the production of a class of 15-epi-lipoxins [8, 9]. The mechanism for 15-epi-lipoxin production appears to relate to the production of a 15(R)-eicosanoid intermediate by the endothelial cells in a manner dependent on novel enzymatic activity of acetylated COX-2 followed by conversion of the intermediate by neutrophil 5-lipoxygenase. Indeed, 15-epi-lipoxin production is enhanced by agents that upregulate COX-2. Lipoxins and 15-epi-lipoxins have inhibitory effects on neutrophils, including inhibition of stimulated neutrophil adherence to, and transmigration across, monolayers of human endothelial cells [10]. It should be noted that lipoxin compounds have proven as potent as dexamethasone in an in vivo, mouse ear model of leukotriene B_4-stimulated neutrophil infiltrations [11].

Lessons learned from COX-1 and COX-2 'knockout' mice

COX 'knockout' mice have generated results which are an eye-opener, because they not only confirm and explain the action of drugs, but also elucidate the compensatory position each one of these enzymes takes in the absence of the other. Furthermore, studies in these mice have provided insight into the pleiotropic action of PGE_2 and COXs.

In the murine chronic granulomatous tissue air pouch model of chronic inflammation, aspirin, a dual COX-1/COX-2 inhibitor, is more effective than the selective COX-2 inhibitor (NS-398) at inhibiting granuloma dry weight vascularity and COX activity [12]. These experiments suggest that COX-1 may play a role in inflammation. Moreover, whereas platelets of COX-1 knockout mice are unresponsive to AA, consistent with the new paradigm, these mice exhibit no spontaneous gastric or intestinal ulcers nor any renal dysfunction [13]. The absence of spontaneous gastric bleeding or erosion in these knockout mice leads to the conclusion that other cytoprotective mechanisms, such as synthesis of NO or calcitonin gene-related peptide (CGRP), compensate in the absence of PGs. The lack of renal pathology is consistent with previous finding that NSAIDs only cause dysfunction in already compromised kidneys, and suggest that this side effect is COX-2-dependent. However, PGs synthesized by COX-1 are apparently essential to the survival of fetuses, since the majority of the offspring born to COX-1 and -2 mice do not survive. The COX-2 knockout strain of mouse yielded similar unexpected results. These knockout mice do develop acute experimental inflammation induced by AA or phorbol ester. The female mice were infertile, for they did not ovulate [14, 15]. Recent studies by Kirtikara et al. have shown compensatory biosynthesis of PGE_2 in COX-1 and -2 null cells with respect to agonist-induced PGE_2 biosynthesis [16]. COX-1, $sPLA_2$ and PGE_2 production were significantly increased in COX-2-deficient cells. Thus, COX deficiency, regardless of whether it is COX-1 or -2, results in the enhanced basal and inducible expression of the remaining COX-isozyme as well as elevated expression of $sPLA_2$. These studies show the complex and compensatory mechanisms involved in PG production by these COXs. The use of specific COX-2 inhibitors may induce the basal levels of COX-1 and $sPLA_2$ to compensate for the PGs required for their homeostatic functions.

Is there a new class of COX-2s?

Previous studies have shown that COX-2 may be induced in various tissues and may also be constitutively expressed in tissues such as the brain [17]. The COX-2(s) may have preferential susceptibility to drugs and other modulators both at the tissue and subcellular level. Recent studies by Simmons et al. have shown that a class of COX-2s is induced by diclonfenac, which has reduced sensitivity to NSAIDS in macrophages [18]. Attur et al. and Patel et al. have shown the presence of a soluble cytosolic COX-2 (distinct from the membrane COX-2) that can be modulated by nitric oxide and tetracyclines [19, 20].

Toxic effects of aspirin: the COX-2 hypothesis

As noted above, COX-1 has been shown to participate in a wide variety of homeostatic functions. It should not be surprising, then, that NSAIDS that inhibit COX-1 are also capable of causing a wide variety of undesirable side effects. For instance, a major problem with NSAIDs at antiinflammatory doses is that they provoke gastritis and gastric ulceration. The irritation results from a requirement for endogenous prostaglandin production by the gastric mucosa in order to regulate the synthesis of the mucous barrier that prevents gastric self-digestion. Administration of an exogenous PGE_1 analogue (misoprostol) can help prevent NSAID-induced gastric ulcers [21].

In contrast to the gastrointestinal toxicity of NSAIDs, another side effect, inhibition of platelet aggregation, has both toxic and therapeutic attributes. Platelet inhibition by NSAIDs occurs via inhibition of production of thromboxane A_2, an effect that can be achieved both in vitro and in vivo at low, subanalgesic doses of aspirin or other NSAIDs [6]. The usefulness of the antithrombotic effect will be discussed below. On the other hand, patients on these drugs sometimes suffer untoward bleeding after tooth extraction, minor surgery or trauma.

Another side effect of NSAIDS that blocks COX is aspirin-sensitivity syndrome in genetically susceptible patients: wheezing (or exacerbation of asthma), sneezing and polyp formation. Although the mechanism for biosynthesis is poorly defined, it appears to relate at least in part to shunting of arachidonate into the 5-lipoxygenase pathway. Indeed, administration of aspirin results in an increase of leukotriene production in patients with aspirin-sensitive, but not-insensitive asthma [22, 23]. 5-Lipoxygenase products—including 5-hydroxyeicosatetraenoic acid (5-HETE) and the leukotrienes (LTs) A_4, B_4, C_4, D_4 and E_4—have a variety of proinflammatory effects. In particular, LTC_4, D_4 and E_4 have been implicated in aspirin sensitivity, and LTA_4 has been implicated in asthma [24]. Moreover, administration of 5-lipoxygenase inhibitors blocks both bronchoconstriction and LT production stimulated by aspirin in patients with aspirin-sensitive asthma [22, 23].

Similarly, elevations in LTB_4 have been postulated to account for NSAID-induced exacerbations of psoriasis, presumably via inhibition of COX-2 in inflamed skin. Tinnitus, a common side effect of high doses of salicylates, has been suggested by some to be due to inhibition of COX-1-dependent synthesis of PGEs by cells of the inner ear. Although conclusive data for this assertion are lacking, several studies have demonstrated the usefulness of PGE_1 analog misoprostal as a therapy for tinnitus [25, 26].

Finally, most NSAIDS including aspirin promote salt and water retention, especially when heart or liver disease compromises renal blood flow. In these cases, NSAIDS block the formation of renal vasoregulator PGI_2, resulting in decreased glomerular filtration. In more extreme cases it is not unusual to observe elevations in blood urea nitrogen (BUN) and creatinine, and NSAIDs should be used with particular caution in patients with renal compromise. In contrast to the role of COX-1 in gastric barrier maintenance, it has recently been appreciated that the kidney constitutively contains both COX-1 and COX-2; their respective roles in the regulation of renal blood flow remain to be determined. Based on the notion that inhibition of COX-2 but not COX-1 is critical to the antiinflammatory effect of NSAIDS, a number of pharmaceutical companies have recently begun to develop selective inhibitors of COX-2 with the intention of greatly improving the therapeutic/toxic ratio. By adding an appropriately localized bulky side group to NSAID-like structures, these agents are designed to block COX-2 while being sterically hindered from entering the COX-1 pocket. Preliminary data suggest that these agents do indeed preserve significant efficacy while reducing the risk of gastrointestinal and hemorrhagic complications. Celecoxib is the first of these agents to receive federal approval and is now available by prescription.

Non-prostaglandin-dependent effects of aspirin

A review of the clinical dose-response profile of aspirin suggests strongly that this agent has pharmacologic effects other than those related to COX inhibition (see table 1) [6]. At low doses (80–325 mg/day = aspirin I), aspirin inhibits platelet COX, and blocks thromboxane A_2 production. The lowest doses of aspirin appear to preferentially inhibit platelet thromboxane A_2 and may spare the production of antithrombotic prostacyclin by endothelial cells, an effect whose mechanism may be related to the ability of these low doses to acetylate platelets in the presystemic vascular bed, followed by first-pass metabolism leading to deactivation prior to entry into the systemic circulation [27, 28]. This platelet selectivity may be further amplified by the fact that, in contrast to endothelial cells, platelets are incapable of de novo production of COX and must therefore undergo replacement to restore thrombotic function. At intermediate doses (650 mg–3 m/day with serum concentrations < 20 mg/dl = aspirin II) aspirin globally inhibits COX and is not only antithrombotic but also analgesic and antipyretic. However, these aspirin II doses are insufficient to achieve maximal antiinflammatory effects. Rather, the use of aspirin in inflammatory diseases such as rheumatic fever and rheumatoid arthritis requires doses far in excess of those needed to inhibit COX (≥ 4 g/day, or 20–30 mg/dl or 1–2 mM = aspirin III). Consistent with the hypothesis that at least some high-dose aspirin effects are COX-independent is the fact that sodium salicylate—which is only 1/100 as effective as aspirin at inhibiting COX—is nonetheless an effective antiinflammatory agent at aspirin III concentrations. Moreover, it has long been appreciated that other NSAIDs also appear to have optimal antiinflammatory effects only at doses beyond those required for COX inhibition, suggesting that these agents, too, may have COX-independent properties. Some toxic effects of NSAIDs may also be COX-independent; for instance, aspirin inhibits synthesis of cartilage proteoglycan and bone metabolism (both in vitro and in vivo) by mechanisms that do not depend on inhibition of COX-1 or -2 [6]. A growing body of research now demonstrates a variety of salicylate effects on cellular signal transduction pathways other than those involving prostaglandins.

Effects on NOS

Nitric oxide synthase (NOS) is a family of at least three enzymes, including constitutive and inducible forms, that catalyze the synthesis of nitric oxide and have pleiotropic effects on vascular tone, inflammation and cell signaling. Aspirin (1–10 mM) has been reported to inhibit inducible NOS (iNOS) expression, including iNOS messenger RNA (mRNA) expression [29] and

Table 1. Differential clinical dose response profile of aspirin.

Type of dose	Dose	General effects
Aspirin I	80–325 mg per day	prevents coronary and cerebral thrombosis by virtue of its antiplatelet effects
Aspirin II	650 mg–3 g per day	analgesics and antipyretics
Aspirin III	>3 g per day	reduces redness and swelling of joints in rheumatic fever, gout and rheumatoid arthritis

translation into enzyme [30, 31]. The effects of aspirin on iNOS expression may be mediated, at least in part, via its effects on NF-κB [32, 33]. In addition to its effects on iNOS expression, aspirin (at 1 mM) has also been shown to inhibit NOS activity in vitro, an effect that has been proposed to be due to the ability of aspirin to acetylate iNOS and render it inactive [34]. The effects of aspirin on iNOS appear to be cell type-specific and may differ in different cells. Irrespective of the particular actions of aspirin on iNOS in a given cell type, the ability of this agent to inhibit NOS expression and/or activity is likely to contribute to its antiinflammatory activity.

Regulation of NF-κB activity

NF-κB is a transcriptional regulatory factor, implicated in cellular responses to inflammatory stress via transcription and translation of a wide range of cytokines and other proinflammatory proteins. Thus, the recent finding by Kopp and Ghosh [33] that sodium salicylate at relatively high doses ($\geq$ 20 mM) is capable of inhibiting NF-κB activation lends credence to the notion that the antiinflammatory effects of NSAIDs may not be due to COX inhibition alone. Subsequent studies have demonstrated that the findings of these authors may be generalizable to a variety of cell types [35]. Inhibition of NF-κB activation has direct effects on gene expression; for instance, aspirin suppresses LPS-induced NF-κB binding to an NF-κB-binding site in the TNF-α promoter [36], suppressing the induction of TNF-α mRNA production. Inhibition of NF-κB by aspirin-like drugs (1–10 mM) appears to depend upon the capacity of these agents to inhibit the activity of IκB kinase β (IKKβ) [37]. IKKβ has been reported to phosphorylate and cause the degradation of IκB, the stabilizing chaperone of NF-κB. Thus, inhibition of I$\kappa\kappa$B may result in failure of IκB degradation and inhibition of translocation of NF-κB to the nucleus. However, it should be noted that several NF-κB-dependent genes are not affected by aspirin-like drugs. For instance, COX-2 gene expression is not susceptible to sodium salicylate [38].

Regulation of MAPKs

The mitogen-activated protein kinases (MAPKs) are a family of serine/threonine kinases that share common sequence motifs, including an activation motif characterized by a dual phosphorylation site. Three families of MAPKs have been defined: the ERKs, which are activated in response to growth factors and play a role in mitosis and differentiation, and the JNKs and p38 kinase, which appear to play roles in cellular responses to stress. Recent studies have demonstrated the capacity of relatively high doses of salicylates ($\geq$ 20 mM) to inhibit ERK in cells stimulated with TNF-α but not epidermal growth factor [39], with potential antiproliferative consequences. Interestingly, ERK is also stimulated in postmitotic hematopoietic cells such as neutrophils, and studies suggest that rapid ERK activation in such cells is required in signaling for adhesion, a critical early step in inflammation [40]. As in mitotic cells, salicylates have been demonstrated to inhibit ERK activation in neutrophils, in a manner consistent with inhibitory effects on integrin-dependent adhesion [40]. In contrast to the effects of salicylates on ERK, studies of the other MAPKs have demonstrated that high doses of sodium salicylate can inhibit JNK but independently stimulate p38 kinase activation, with potential antiproliferative effects [41].

Other pharmacologic effects of aspirin-like drugs

A number of other COX-independent activities of aspirin-like drugs have been observed. In plants, the original source of salicylic acid—salicylates serve as host-defense molecules, and as signals to enhance the flowering of *Impatiens*. Indeed, salicylates induce the voodoo lily or skunk cabbage to undergo temperature rises of 12–16 °C in the course of their efflorescence: salicylates therefore not only reduce fever in humans but also produce it in plants. Aspirin and salicylates also inhibit anion transport across cell membranes, and uncouple mitochondrial oxidative phosphorylation [6, 42]. Moreover, NSAIDs have also been shown to cause increases in extracellular adenosine levels, with antiinflammatory consequences [43]. NSAIDS have been reported to inhibit adhesion or the activation of adhesion molecules on both lymphocytes and neutrophils, by mechanisms that may be COX-independent [44, 45]. Aspirin and aspirin-like drugs have also been reported to alter membrane viscosity (either directly or via alterations in the insertion of arachidonate into the plasma membrane) [46], to demonstrate antagonistic effects on G proteins [47], glucocorticoid and estrogen receptors [48], and to activate genes that code for heat-shock proteins in the lampbrush chromosomes of *Drosophila* [6]. Most recently, Lehmann et al. demonstrated the capacity of several NSAIDs to act as agonists of the peroxisome proliferator-activated receptors (PPARs) [49], an effect that Jiang et al. have implicated in the inhibition of cytokine production by monocytes [50].

Emerging clinical applications of NSAIDs

In addition to their uses for pain and inflammation, salicylates have also been appreciated for their ability to dissolve corns on toes—a keratolytic effect, provoke

loss of uric acid from their kidneys—their uricosuric property and kill bacteria in vitro—their antiseptic action. In recent years, however, a number of other applications for aspirin and aspirin-like drugs have come under increasing use and scrutiny [6].

Thromboembolic disease

As noted above, the exploitation of aspirin's antithrombotic effects has constituted a major triumph of late-20th-century medicine. In particular, the observation that very low dose aspirin (aspirin I) has a selective effect on platelets, reducing thromboxane A_2 formation but sparing the endothelial cell and systemic COX-1, has permitted the use of aspirin as both prophylaxis and treatment for acute thrombotic syndromes such as stroke and myocardial infarction. In contrast to other NSAIDs, the unique capacity of aspirin to acetylate and permanently inactivate platelet COX-1, ensuring that the anticoagulative effects of a single aspirin will persist throughout the 7-day half-life of a platelet, has engendered confidence that the antithrombotic effects of aspirin will not wane throughout the dosing interval. Indeed, consumption of 1 aspirin daily may reduce the risk of heart attack and strokes by as much as 50% [51, 52].

Tumorigenesis

Accumulating epidemiologic data has suggested an association between NSAID consumption, particularly aspirin and sulindac [53], and a decline in colon cancer rates in population-based studies [34]. Subsequent studies have implicated COX-2 effects on cancer cells and, interestingly, suggested the possibility that NSAIDs may have antitumor properties. COX-2 has been reported to be upregulated 2–50-fold in 85–90% of colorectal adenocarcinomas [54]. Studies by Dubois et al. have shown that specific COX-2 inhibitors may inhibit metastasis of colon cancer [55], owing possibly to effects on angiogenesis or cell migration [56]. It should be noted, however, that the question of whether the possible antitumor effects of NSAIDs are due to COX inhibition remains controversial. For instance, studies by Chan et al. have suggested that tumor-suppressive effects of NSAIDs are not likely to be related to a reduction in prostaglandins but rather are due to the elevation of prostaglandin precursor AA [57]. Treatment of colon tumor cells with NSAIDs results in dramatic increases in AA, which in turn stimulates the conversion of sphingomyelin to ceramide, a known mediator of apoptosis. Similarly, aspirin has been reported to induce caspases, potentially leading to apoptosis. In this regard, the ability of salicylates to stimulate p38 activity may also be germane to antitumor effects, since Schwenger et al. have demonstrated that salicylate-induced apoptosis is p38-dependent [41]. Recent reports have suggested that a subset of human mismatch-repair (MMR) genes (hMLH1, hMSH2, hMSH6) are markedly reduced during exposure to aspirin. Thus, aspirin may induce genetic selection for microsatellite stability in a subset of MMR-deficient cells and may provide effective prophylactic therapy for hereditary nonpolyposis colorectal cancer [58]. Finally, aspirin has reported to inhibit UVB-induced AP-1 activity, possibly through its effects on ERK activation, suggesting that it may act as a chemopreventive agent for skin cancer [58].

Alzheimer's disease

A number of epidemiologic surveys, both large and small, have demonstrated an association between NSAID use and a decreased risk for Alzheimer's [59]. For instance, the Rotterdam Study compared the incidence of Alzheimer's in 365 NSAID users versus NSAID nonusers and observed a relative risk of 0.38 in the NSAID users; when adjusted for possible confounding variables, the relative risk remained lower in the users at 0.54 [60]. Such studies must be interpreted with caution, since the time course for onset of Alzheimer's is quite long, and NSAID use patterns vary widely. To date, no controlled, prospective study has been performed conclusively demonstrating the ability of NSAIDs to prevent Alzheimer's. In contrast, a number of in vitro studies have documented the ability of NSAIDs to modify nerve cell responses of potential relevance to Alzheimer's disease. For instance, NSAIDs have been shown to inhibit IL-1 β-induced IL-6 expression in astrocytes [61], to reverse the microglial response to amyloid β-protein [62] and to reduce levels of inducible neuronal NOS in LPS-stimulated glial cells [47]. Whether these, or any of the other antiinflammatory effects of NSAIDs, affect the course of Alzheimer's remains to be determined.

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