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Breakthroughs and Views

Alzheimer's disease: Channeling APP to non-amyloidogenic processing

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Abstract

A good number of pharmacologic agents have over the years been touted as potentially beneficial in either preventing the onset or delay the progression of Alzheimer's disease. These include compounds such as non-steroidal anti-inflammatory drugs (NSAIDs) (HMG-CoA reductase inhibitors (statins)) and flavonoids. The underlying mechanisms for the beneficial effect of these agents are by and large attributed to their ability to reduce β-amyloid (Aβ) production and amyloid load in the brain, via inhibition of amyloidogenic γ-secretase activity. Recent reports have now provided mechanistic insights as to how non-amyloidogenic processing might also be enhanced by these seemingly unrelated treatments. Intriguingly, this appears to involve the inhibition of the activity of small GTPase Rho and its effector, the Rho-associated kinase, ROCK. Dietary caloric restriction (CR) also enhances non-amyloidogenic processing of APP, and this may be part of a more general anti-aging effect of CR mediated by gene expression changes downstream of the activity of the histone deacetylase SIRT1.

Keywords: Alzheimer's disease; β-Amyloid; Non-steroidal anti-inflammatory drugs; Rho; Rho-associated protein kinase; Statins

Proteolytic processing of the amyloid precursor protein (APP) can proceed via two opposing paths, with vastly different outcomes (Fig. 1, see [1] for a recent review). The amyloidogenic path involves sequential cleavages by β-secretase (BACE) and the γ-secretase complex, with the generation of β-amyloid (Aβ) fragments—the etiological agents of Alzheimic pathology. The non-amyloidogenic path, however, involves APP cleavage by α-secretases [2] at a site which will preclude BACE cleavage, and which releases a neuroprotective sAPPα fragment [3,4]. Much attention has been paid to BACE and γ-secretase in the development of anti-Alzheimic strategies. However, it has become clear in recent reports that the channeling of APP to the non-amyloidogenic pathway underlies at least part of the beneficial action of compounds such as non-steroidal anti-inflammatory drugs (NSAIDs) [5,6], HMG-CoA reductase inhibitors (statins) [7,8], flavonoids [9,10], as well as dietary caloric restriction [11]. Some recent reports also provided mechanistic insights as to how non-amyloidogenic processing might be enhanced by these seemingly unrelated treatments. Intriguingly, this appears to involve modulation of the activity of the small GTPase Rho and its effector, the Rho-associated kinase (ROCK).

The effect of NSAIDs and statins on the isoprenoid pathway, Rho/ROCK activity, and APP processing

The notion of a potential beneficial effect of NSAIDs on Alzheimer's disease has been around for some time [5,6]. While it is clear that NSAIDs' ability to lower $A\beta_{42}$ levels could be attributed to its direct modulation of γ-secretase activity [12,13], these drugs have also been shown to stimulate the secretion of sAPPα into the conditioned media of cultured cells [14]. Zhou et al. [15] had also recently demonstrated that NSAIDs may function by perturbing the isoprenoid pathway, particularly geranylgeranylation. In the authors' experiments,

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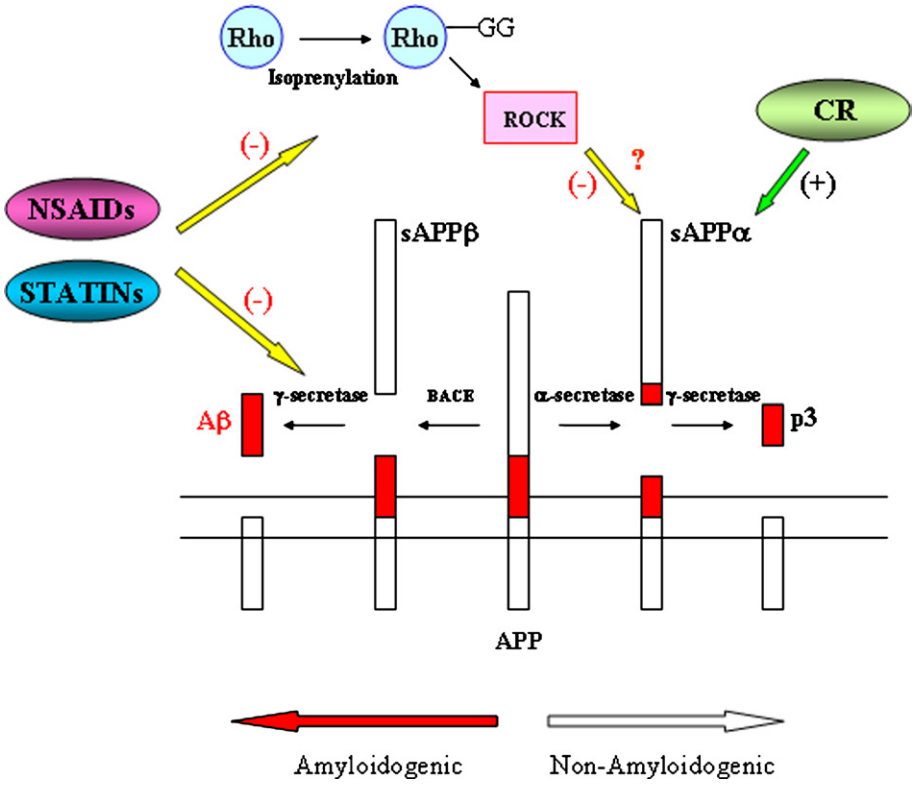

Fig. 1. Schematic diagram depicting the inhibition of Rho-ROCK axis as a possible underlying cause of NSAID and statin effects on the proteolytic fate of APP. The drugs could inhibit the isoprenylation of Rho, therefore its membrane attachment and ability to activate its downstream effector ROCK. Inhibition of the Rho-ROCK axis enhances the generation of sAPPα via indirect, unknown mechanisms (indicated as ?). These drugs may also have a direct inhibitory effect on the amyloidogenic pathway by inhibiting γ-secretase. The net effect is a channeling of APP processing towards the non-amyloidogenic pathway and a decrease in β-amyloid (Aβ) production. Caloric restriction (CR) enhances the production of sAPPα, probably via an increased expression of α-secretase (see text).

geranylgeranyl pyrophosphate (GGpp) (but not farnesyl pyrophosphate) treatment of SH-SY5Y cells expressing the Swedish APP mutant resulted in an increase in $A\beta_{42}$ production. This increase is blocked by the NSAIDs sulindac sulfide and ibuprofen. The downstream factor targeted by the drugs is delineated and narrowed down to the small GTPase Rho, as only the dominant-negative form of Rho, but not Cdc42 or Rac1, caused a decrease in $A\beta_{42}$. Inactivation of Rho by C3 transferase also reduced $A\beta_{42}$. In addition, treatment of both APP-expressing cells and mice with the ROCK inhibitor Y-27632 also reduced $A\beta_{42}$ both in vitro and in vivo. Furthermore, there is a clear correlation between the ability of individual NSAIDs to negatively regulate Rho activity and their $A\beta_{42}$ lowering capacity.

Pedrini et al. [8], on the other hand, demonstrated that the α-secretase-mediated shedding of sAPPα induced by statins in Swedish APP-expressing N2a mouse neuroblastoma cells is modulated by ROCK. A farnesyl transferase inhibitor, FTI-1, promotes sAPPα shedding in a manner that is synergistic with statins. Contrastingly, arachidonic acid, which activates ROCK, reduced sAPPα shedding. A constitutively active ROCK mutant diminished sAPPα shedding from both untreated and statin-treated cells, whereas a kinase-dead ROCK mutant on its own activated sAPPα shedding. It appears, therefore, that both NSAIDs and statins might enhance sAPPα production through the attenuation of a signaling pathway that is modulated by Rho and ROCK. Since sAPPα production implicates an increase in α-secretase processing, such preclusion of amyloidogenic, β-secretase processing could at least partly explain the ability of NSAIDs and statins to reduce $A\beta_{42}$ levels.

NSAIDs and statins may also affect brain inflammation through the isoprenoid pathway and Rho/ROCK

The benefits of NSAIDs and statins in countering the progression of Alzheimer's go beyond reducing $A\beta_{42}$ production by neurons. Alzheimer's is often viewed as a neuroinflammatory disease and $A\beta_{42}$ is a potent activator of microglia-mediated CNS tissue inflammation [16,17]. The anti-inflammatory action of NSAIDs is of course well known, but statins could also suppress neuronal inflammation. A recent report by Cordal and Landreth [18] showed that statin robustly inhibited Aβ-stimulated expression of interleukin-1β and NO production in microglia and monocyte cells. This inhibition is apparently linked to the suppression of the isoprenoid