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Amyloid β and Alzheimer disease therapeutics: the devil may be in the details

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Alzheimer disease (AD) is characterized by the progressive accumulation of amyloid β protein (Aβ) in areas of the brain serving cognitive functions such as memory and language. The first of two separate reports (see the related articles beginning on pages 415 and 440) reveals that intrinsic T cell reactivity to the self-antigen Aβ exists in many humans and increases with age. This finding has implications for the design of Aβ vaccines. The second report demonstrates that a number of FDA- approved nonsteroidal anti-inflammatory drugs are capable of lowering Aβ levels in mice. The work suggests that further testing of the therapeutic utility of these types of compounds for the potential treatment of AD is warranted.

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Alzheimer disease (AD) has received a lot of recent attention, particularly in areas related to novel treatments. Recently, the potential therapeutic usefulness of the immune system has become apparent, leading to the question of whether it can be used to directly or indirectly influence AD-related pathology in beneficial ways.

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Nonstandard abbreviations used: Alzheimer disease (AD); amyloid β protein (Aβ); amyloid precursor protein (APP); cerebral amyloid angiopathy (CAA).

Active immunization with amyloid β (Aβ) peptides takes advantage of the immune system to generate antibodies that can somehow decrease Aβ-related pathology in mouse models of AD (1). Similarly, passive immunization involves direct administration of anti-Aβ antibodies, bypassing the need for an active immune response (2, 3). Since genetic, pathologic, and animal studies suggest that the buildup of Aβ in the brain leads directly or indirectly to cell dysfunction, cell death, and cognitive impairment, increased generation of anti-Aβ antibodies has the potential to prevent or treat AD by decreasing amyloid burden and its consequences in the brain. Though the first clinical trials for Aβ vaccination were halted due to CNS inflammation in a small subset of subjects, active and passive immunization strategies remain a viable potential therapy worth continued exploration. If positive effects can be seen in future trials, it will be important to minimize unwanted toxicity. In this issue of the *JCI*, Monsonego and colleagues (4) further characterize the innate immune response to Aβ in humans, thus revealing important details about how the elderly body reacts to Aβ, and opening new avenues to modify existing vaccination protocols. Also in this issue, Eriksen and colleagues (5) studied traditional NSAIDs that appear to have a nontraditional, COX-independent effect on decreasing Aβ42 production. While these drugs are often used to treat inflammation, they appear to have a novel effect on amyloid precursor protein (APP) cleavage, which is only now becoming apparent and which may be useful in the future as a therapeutic.

Aβ-reactive T cells increase with age

Monsonego et al. (4) found that some healthy, elderly individuals, as well as individuals with AD, contain elevated baseline levels of Aβ-reactive T cells. While the general trend is toward a diminished immune response with aging, this demonstrates a selective increase in Aβ-reactive T cells in older individuals with and without dementia. The reason for this selective expansion of Aβ-reactive T cells in elderly individuals remains unclear. It is often presumed that cognitively normal middle-aged and elderly individuals are similar in that they lack AD pathology; however, Aβ deposition in plaques appears to begin about 10–20 years prior to the onset of even the earliest symptoms sugges-

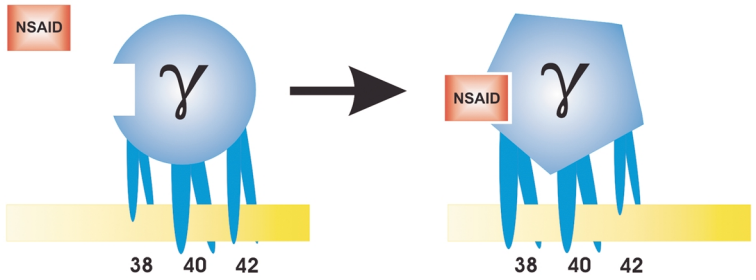

Figure 1
Model of how certain NSAIDs decrease Aβ42 production. NSAIDs may directly bind to the γ-secretase complex and alter APP processing to decrease Aβ42 production and also change production of other Aβ species.

tive of dementia due to AD (6). This means that some cognitively normal elderly subjects in this study likely possessed aggregated Aβ deposits in the brain, while it is also likely that most middle-aged individuals (younger than age 50) did not have AD pathology. One interesting possibility is that this change in T cell population is a response to the presence of Aβ aggregates even in the absence of dementia. The conformation of aggregated Aβ in AD is predominantly as β-sheets, whereas the soluble Aβ present in blood and cerebral spinal fluid has little or no β-sheet structure. Perhaps, this conformational change in endogenous Aβ stimulates a T cell response. Future studies will be necessary to determine if the peripheral T cell population correlates to CNS pathology or future AD symptoms (i.e., an antecedent bio-marker).

T cells, Aβ, and CNS inflammation

While speculative, individuals with elevated Aβ-reactive T cells may host a greater immune response to an active immunization with Aβ than someone who lacks this T cell change. The positive effects of Aβ immunization in mouse models (e.g., decreased plaque burden, behavioral improvement) appear to be mediated by antibodies, not the cellular response (7–10). Thus, augmentation of the production of anti-Aβ antibodies is likely to be beneficial. However, in the first trial of active Aβ immunization in AD patients, about 5% of individuals developed a side effect of CNS inflammation. There is evidence that this complication following active Aβ immunization is due to a T cell response (11). It therefore seems logical that minimizing certain aspects of T cell activation would decrease the likelihood of CNS inflammation. Consequently, it may be useful in future vaccination strategies to either exclude subjects that have already demonstrated a substantial T cell reaction to Aβ or to consider these subjects only for passive immunization. Monsonego and colleagues (4) found that the epitopes for Aβ-reactive T cells in humans are primarily amino acids 16–42. Interestingly, however, in studies of active immunization of humans and of mouse models of AD, the primary epitope to which antibodies are generated are amino acids 1–12 (12, 13). Because the cellular and humoral immune responses appear to have distinct, dominant epitopes, perhaps an antigen and adjuvant combination can be designed that favor a humoral immune response over a T cell response.

Certain NSAIDs decrease Aβ production

Many pathological studies have shown evidence of an inflammatory response (gliosis, increased cytokines) surrounding Aβ deposits in the AD brain. It is thought that this response may result in increased neuronal injury, which suggests the possibility that decreasing this response may be beneficial. In light of this, it is of interest that retrospective, epidemiological studies show that NSAID use is associated with a decreased risk of developing AD. Herein, Eriksen and colleagues (5) further define a different molecular mechanism that may be relevant to this relationship. It appears that certain NSAIDs, potentially in a novel, direct interaction with the γ-secretase complex, can alter APP cleavage and the subsequent species of Aβ produced. Eriksen et al. screened 18 NSAID compounds, including several enantiomers that do not inhibit COX. Interestingly, though structurally similar, these compounds can have different effects on what species of Aβ is produced; some decrease Aβ42, while others decrease Aβ40. The mechanism may be via a direct effect on the γ-secretase complex, which presumably causes a subtle conformational change and alters APP cleavage (Figure 1). In future studies, it will be important to investigate the molecular details of the NSAID/γ-secretase complex interaction. In addition, the drugs most effective in decreasing Aβ levels in humans will need to be determined.

Eriksen and colleagues (5) have focused on decreasing the more aggregation-prone Aβ42 species in order to potentially treat AD. Another potential treatment avenue, however, is to decrease both Aβ42, as well as other species such as Aβ40, the peptide that builds up extensively in cerebral amyloid angiopathy (CAA). If an NSAID compound, or derivative, could be designed to decrease both pathological species of Aβ, it may benefit both diseases. While an important aim is to find a drug to decrease Aβ42, it will be important not to increase Aβ40 levels as a consequence. This could potentially lead to increased risk for developing CAA and its consequences such as hemorrhage.

These studies provide exciting new insights and avenues for AD treatment by suggesting improvements in current vaccination strategies or by furthering our understanding of how NSAIDs alter Aβ42 production. While it is not going to be easy, there remains much hope that the amyloid hypothesis of AD will be tested and that truly effective therapies for AD can be developed.

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Endocannabinoids and the regulation of body fat: the smoke is clearing

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Endocannabinoids, endogenous ligands of cannabinoid receptor type 1 (CB1), have emerged as novel and important regulators of energy homeostasis. A report in this issue (see the related article beginning on page 423) demonstrates reduced body weight, fat mass, and appetite in CB1$^{-/-}$ mice. Examination of the underlying mechanisms reveals a dual role for endocannabinoids as they affect both appetite and peripheral lipolysis.

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Chronically elevated energy expenditure without a corresponding increase in energy intake leads to wasting and death. Almost all species in the wild, and the great majority of the human race, struggle with such negative energy balance in their daily battle for survival. In sharp contrast, however, modern industrialized societies are threatened by the exact opposite: chronically increased energy intake without a respective increase in energy expenditure. This constellation leads to obesity and diabetes as well as a variety of life-threatening consequences of such diseases, such as cancer and cardiovascular diseases (1, 2). While it appears intuitively obvious that in the majority of cases, positive energy balance should be corrected by changes in lifestyle and/or diet, the impressive dynamics of the spreading obesity epidemic (3) certainly suggests that, in modern industrialized civilizations, an efficient and safe pharmacological approach to treat obesity would be useful. In light of this, it is not surprising that within the past decades, increasing attention has been paid to central and peripheral regulatory components of energy metabolism to develop pharmacological modulators of appetite and energy expenditure. From this perspective, one of the great, and surprising, discoveries of the past decade was the revelation of an endocannabinoid system and its influences on appetite and metabolism (4–8).

Cannabinoids and endocannabinoids act via G protein–coupled receptors. The strongest effects of endocannabinoids on behavior, including those related to food intake, appear to be mediated by cannabinoid receptor type 1 (CB1), which is the predominant receptor type in the CNS. The molecular cascade triggered by CB1 activation has been studied in depth (reviewed in ref. 8). In short, the dominant G protein subtypes activated by CB1 belong to the $G_{i/o}$ family; these in turn alter electric properties of membranes, second-messenger systems, and immediate-early genes. CB1 activation inhibits voltage-gated L, N, and P/Q Ca^{2+} currents, while activating K^+ currents; and while agonists of CB1 induce the inhibition of adenylyl cyclase, they also induce the activation of focal adhesion kinase and MAPK. CB1-associated activation of G proteins also underlies the stimulation of NO synthase. Current ideology suggests that the activation or inhibition of CB1 (mainly by fatty acid ethanolamides) influences the aforementioned subcellular events and results in changes in neurotransmitter release at the level of axon terminals (7). However, to date, the phenotype of neurons in the hypothalamic appetite center that are directly affected by cannabinoids has not been elucidated. In this issue of the *JCI*, a report by Cota et al. (9) greatly advances our understanding of this critical issue by pinpointing those neuropeptide systems in the hypothalamus that most likely mediate cannabinoid-induced changes in energy homeostasis.

Cannabinoids and metabolism

Anecdotal evidence regarding the robust effect of the recreational drug marijuana (*Cannabis sativa*) on appetite and food intake has been widely known for centuries (10). However, it was the discovery of marijuana's main psychoactive component, Δ^9-tetra-

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Nonstandard abbreviations used: cannabinoid receptor type 1 (CB1); corticotropin-releasing hormone (CRH); cocaine-amphetamine–regulated transcript (CART); melanin-concentrating hormone (MCH).