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Corticosteroids, but not NSAIDs, are associated with less Alzheimer neuropathology

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Abstract

Objective—To test the hypothesis that corticosteroid and non-steroidal anti-inflammatory (NSAIDs) medications are associated with less global and regional Alzheimer's disease (AD) neuropathology.

Methods—This postmortem study was based on 694 brains of subjects from the Mount Sinai School of Medicine Brain Bank who did not have neuropathologies other than neuritic plaques (NPs), neurofibrillary tangles (NFTs), or cerebrovascular disease. Densities of NPs and of NFTs were assessed in several neocortical regions and in the hippocampus, entorhinal cortex, and amygdala. Counts of NPs in several neocortical regions were also assessed. For each neuropathology measure, analyses of covariance controlling for age at death and sex compared subjects who received only corticosteroids (n=54) or those who received only NSAIDs (n=56) to the same comparison group, subjects who received neither (n=576).

Results—Subjects receiving corticosteroids had significantly lower ratings and counts of NPs for all neuropathological measures, and NFTs overall and in the cerebral cortex and amygdala. In contrast, no measures were significant for subjects who received NSAIDs.

Conclusions—Use of corticosteroids was associated with approximately 50% less NPs and NFTs in most brain regions examined, compared to non-medicated subjects. In contrast, use of NSAIDs was not substantially associated with the reductions in hallmark lesions of AD. Since corticosteroids have anti-inflammatory as well as a myriad of other neurobiological effects, more direct studies in model systems could reveal novel therapeutic targets and mechanisms for AD lesion reduction.

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Keywords

glucocorticoids; corticosteroids; non-steroidal anti-inflammatory (NSAIDs) drugs; neuritic plaques; neurofibrillary tangles

Introduction

Several lines of evidence support a contribution of inflammation to the pathogenesis of Alzheimer's Disease (AD). Acute-phase proteins, cytokines, chemokines, and their receptors are up-regulated in AD brains (Weisman et al., 2006). An increase in the abundance of activated microglia is observed early in the course of AD (Eikelenboom et al., 2002) and in animal models (Grathwohl et al., 2009). Proinflammatory cytokines induce amyloid precursor protein (Brugg et al., 1995), and in turn, β amyloid ($A\beta$) can lead to further release of some cytokines (McGeer and McGeer, 2001). In addition, blood elevations of inflammatory markers have been associated with cognitive decline, AD, or dementia in observational studies^{e.g.} (Engelhart et al., 2004; Rafnsson et al., 2007).

Thus, there is substantial interest in determining whether at least some of the inflammatory changes are pathogenic (Lucin and Wyss-Coray, 2009) and whether anti-inflammatory medications can reduce the risk and the consequent neuropathology of AD. Epidemiologic evidence support a protective effect of non-steroidal anti-inflammatory drugs (NSAIDs) against AD (Hayden et al., 2007; Stewart et al., 1997; Zandi et al., 2002), but randomized clinical trials have not found such an effect (Aisen et al., 2002; Aisen et al., 2003; Martin et al., 2008). Further, NSAIDs were suggested to suppress plaque pathology in a mouse model for AD (Lim et al., 2000) but were not associated with reductions in the densities of diffuse plaques, neuritic plaques (NPs) or neurofibrillary tangles (NFTs)—the hallmark lesions of AD—or to global AD pathology in human brains (Arvanitakis et al., 2008; Halliday et al., 2000; Mackenzie and Munoz, 1998), or were even associated with increased NPs (Sonnen et al., 2010).

Among the classes of anti-inflammatory medications, corticosteroids offer the broadest anti-inflammatory/immunosuppressive effects. Despite their relationship with cognition and particularly with memory (Brown, 2009) {Roozendaal, 2009 1307/id}, they have been less studied in the context of AD, possibly because long-term use provokes several undesirable side effects, such as osteoporosis, weight gain, and increased susceptibility for infections (Gotsche and Johansen, 2004). Also, one clinical trial using low-dose prednisone found no significant results on a one year measure of cognitive decline (Aisen et al., 2000). However, consistent with studies in animals {Roozendaal, 2009 1307/id} a finding suggesting that higher dose steroids significantly decreased CSF amyloid beta peptide in a small group of non-demented subjects (Tokuda et al., 2002), and successful use of high-dose corticosteroids in the treatment of inflammatory diseases of the brain such as central nervous system (CNS) vasculitis and lupus cerebritis suggests that this group of medications might affect AD progression and risk.

The current study was designed to test the hypothesis that the use of corticosteroids is associated with a reduction in the severity of the cardinal neuropathologic lesions of AD (NPs and NFTs) using a large series of postmortem brains from the Mount Sinai School of Medicine Department of Psychiatry Brain Bank. Since specific brain regions might be more or less sensitive to the use of anti-inflammatory medications (Sorrells et al., 2009), we examined regional as well as global neuropathology. The hypothesis that NSAIDs were associated with reductions in global or regional AD neuropathology was also examined.

Methods

Subjects

Postmortem brains, donated by the next of kin of deceased subjects participating in studies of aging and early dementia, were received over a period of 20 years by the Brain Bank. The vast majority of subjects (95%) were residents of local nursing homes and affiliated assisted living facilities from which detailed medical and cognitive histories could be obtained (Haroutunian et al., 1998). Medical charts were supplied by the primary care physicians of the community dwelling subjects, with their permission. This study was not intended to be an epidemiological survey of all cause dementia but rather of AD. Historically autopsy rates have been approximately 23% of all approaches and no obvious variable has distinguished those who have consented to autopsy from those who have not. The purpose of the study was to begin to understand the role of anti-inflammatory medications on neuropathological processes associated with AD. We therefore excluded that might confound conclusions regarding the role of these medications in mediating AD neuropathology. Thus, analyses were based on 694 brains of subjects who did not have major psychiatric disorders (e.g. schizophrenia) or neuropathologies (such as Pick or Lewy bodies) other than NPs, NFTs, or cerebrovascular disease. One hundred and fifty five subjects had a primary diagnosis of normal brain according to Consortium to Establish a Registry for Alzheimer's disease (CERAD) neuropathological criteria (Mirra et al., 1991), 267 had definite AD, 88 had probable AD, 68 had possible AD, and 116 had cerebrovascular disease. Diagnostic criteria were used exclusively for the inclusion and exclusion of subjects into the study cohort. Consent to autopsy was granted by the legal next of kin of each participant and all assessments were approved by governing institutional review boards including the Mount Sinai School of Medicine. Research staff—who were blind both to the hypotheses being tested and to the neuropathology findings—reviewed detailed medical records, which were available on all subjects, and whenever possible conducted in depth interviews and assessments with the subjects, and with staff and family caregivers to obtain information about ante-mortem medical, neurological, psychiatric, functional and cognitive status.

The Clinical Dementia Rating (CDR) scale assesses cognitive and functional impairments associated with dementia and provides specific severity criteria for classifying subjects as non-demented (CDR= 0), questionably demented (CDR= 0.5), or increasing levels of severity of dementia from CDR=1 to CDR=5 (Morris et al., 1997). A previously described (Haroutunian et al., 1998; Haroutunian et al., 1999) multi-step consensus approach was applied to the postmortem assignment of CDR scores based on cognitive and functional status during the last 6 months of life.

Assessment of anti-inflammatory medication use

Medication data was gleaned from detailed review of electronic pharmacy, and medical charts. Subjects with recorded prescribed anti-inflammatory medications since enrollment into the study, which averaged three years (SD=4.3) before death, were classified into two groups: non steroidal anti inflammatory (NSAIDs) medications (n=56) and corticosteroids (n=54). Although the precise duration of treatment could not be determined for most subjects, those who received steroidal ointments, eye drops, shampoo, or a local one-time or occasional injection were excluded (n=11). The primary indication for steroidal use (n=33) was for lung-related diseases (asthma, pneumonia, bronchitis, COPD, emphysema); all others used steroids for various reasons (eg. eczema, arthritis, polymyalgia rheumatica, aplastic anemia, Wegener's granulomatosis). NSAIDs were indicated primarily for pain management, most commonly with various arthritides (n=17) or following fractures (n=18), less often for other kinds of pain or fever. Half of the subjects on NSAIDs received aspirin,

23% received ibuprofen, and the rest received a variety of other NSAIDs. Of those receiving corticosteroids, 69% received prednisone, 19% dexamethasone, 10% hydrocortisone, and 1% prednisolone.

Neuropathological Assessment

The neuropathological assessment procedures employed have been described extensively^{e.g.} (Haroutunian et al., 1998; Haroutunian et al., 1999). Standardized representative blocks from superior and midfrontal gyrus, orbital cortex, basal ganglia with basal forebrain, amygdala, hippocampus (rostral and caudal levels with adjacent parahippocampal and inferior temporal cortex), superior temporal gyrus, parietal cortex (angular gyrus), calcarine cortex, hypothalamus with mammillary bodies, thalamus, midbrain, pons, medulla, cerebellar vermis, and lateral cerebellar hemisphere were examined using hematoxylin and eosin, modified Bielschowsky and modified thioflavin S. Any case showing evidence of Lewy body formation in the substantia nigra or locus ceruleus underwent anti-ubiquitin staining of representative cerebral cortical sections as well as anti- α -synuclein staining for ambiguous cases. Neuropathologists were blinded to the medication status of the subjects and to all dementia-associated clinical and psychometric data.

The extent of neuropathologic lesions was assessed using the CERAD neuropathologic battery (Mirra et al., 1991). Sections from each of the tissue blocks described above were rated for the extent of NPs and NFTs using the CERAD four-point scale of 0=none, 1=sparse, 3=moderate, or 5=severe, as described previously (Haroutunian et al., 1998). Additionally, quantitative data regarding the density of NPs were collected in five cortical regions using previously published methods^{e.g.} (Haroutunian et al., 1998): the mid-frontal gyrus (Brodmann area 9), orbital frontal cortex (Brodmann area 45/47), superior temporal gyrus (Brodmann area 21/22), inferior parietal cortex (Brodmann area 39) and calcarine cortex (Brodmann area 16). Five representative high power fields (0.5 mm²) were examined in each cortical region and a mean density score was calculated for each region as mean plaque density per mm².

NP and NFT ratings of the neocortical sections were summed into respective summary variables. The primary rating variables used in the analyses reported here were NPs and NFTs in the entorhinal cortex, hippocampus, amygdala and neocortex, and also totals of ratings of NPs and NFTs in these four regions. The five neocortical quantitative measures of NPs and their mean were also used for primary analyses.

Ancillary exploratory analyses revealed that the inclusion of NP and NFT density estimates from the subcortical fields assessed as part of the CERAD neuropathology battery did not substantively contribute to the results described (Haroutunian et al., 1998; Haroutunian et al., 1999). These brain regions were therefore not included in the final analyses.

Statistical analyses

Since the mechanisms of action and the indications for corticosteroids and NSAIDs are different, parallel analyses compared subjects who received only NSAIDs and those who received only corticosteroids, to the same comparison group—subjects who received neither NSAIDs nor corticosteroids. The 5 subjects who received both types of medications were excluded. Clinical and demographic characteristics of the three groups were compared by analysis of variance for continuous measures and by chi-square for categorical measures. Analyses of covariance controlling for age at death and sex were performed for the 16 neuropathological measures (11 NP measures and 5 NFT). The Holm multiple comparisons procedure (Holm, 1979) was performed to determine which measures, in the respective sets

of 11 or 5 measures, achieved an experimentwise significance level of 0.05. Uncorrected p-values are also presented for each measure.

Results

Table 1 presents the characteristics of the sample. Subjects averaged 83 years of age at death, a majority were females, and most were mildly to moderately demented at death. Subjects in the three groups did not significantly differ in age at death, sex ratio, or in the presence of arthritis, cerebrovascular disease, or the e4 allele of the APOE genotype. The groups differed significantly in dementia severity by CDR, with more severe dementia in the unmedicated group than either medicated group.

Results of the ANCOVAs for the comparisons of all neuropathological measures are presented in Figure 1 which provides p-values for each neuropathological measure and region. By the Holm criteria, brains of subjects receiving corticosteroids had significantly lower ratings and counts of NPs for all regions (p-values ranging from 0.001 to 0.029). NFTs were significantly lower overall (p=0.001), in the cerebral cortex (p=0.002) and in the amygdala (p=0.004), but the difference did not reach the Holm criteria in the hippocampus (p=0.032) and in the entorhinal cortex (p=0.083). In contrast, when comparing subjects who received NSAIDs to those who did not, all of the NFT measures were non-significant; none of the 11 NP measures were significant by the Holm criteria, although the uncorrected nominal p-values for the NP count measures were significant or near significance (p values ranged from 0.03 – 0.06).

Secondary analyses controlling for APOE4 genotype, for diagnosis of arthritis, or excluding the 116 brains of subjects with cerebrovascular disease left the results essentially unchanged. Since slower cognitive decline has been reported in APOE4 allele carriers who took NSAIDs (Hayden et al., 2007; Zandi et al., 2002), we also examined the interactions of the APOE4 genotype with NSAIDs and corticosteroids; APOE4 carriers and non-carriers did not differ significantly in their associations of neuropathology with either corticosteroids or NSAIDs. However, the small number of ApoE4 carriers in the medication groups (17 in NSAIDs group and n=12 in corticosteroids group) suggests the need for caution in interpreting this lack of significant association.

To address potential confounds related to physicians unwillingness to prescribe medications to more impaired individuals we repeated the analyses excluding subjects with moderate (CDR=2) or severe (CDR=3) dementia. For the corticosteroids comparisons, since the number of subjects decreased to 31, the p-values were smaller but the differences between the groups remained essentially unchanged (for example, cortical NP ratings were 2.1 (SE±.95) and 4.2 (SE±.38) for the corticosteroid and the comparison group (p=0.03, respectively). For the NSAIDs comparisons, the groups were either very similar or in some instances, the NSAIDs group had nominally more neuropathology than the comparison group (although none of the comparisons reached statistical significance).

Finally, to ensure that the results were not biased by exclusion of subjects who presented with other potentially dementing neuropathologies (such as Pick or Lewy bodies) in addition to AD neuropathology, we repeated the analyses including all brain bank cases who participated in our studies of aging and early dementia (corticosteroid group, n=76; NSAIDs group, n=74; control group, n=826). Results were very similar except for NFTs in the hippocampus that did not reach significance in this analysis (p=0.09) and NFTs in the entorhinal cortex that did reach significance (p=0.05). Note however, that the estimated marginal means for both comparisons were essentially identical.

Discussion

Use of corticosteroids was associated with approximately 50% lower densities of NPs and NFTs in most brain regions examined, except for NFTs in the hippocampus and entorhinal cortex where only nominal differences were apparent. NFT densities characteristically plateau in these regions early in the course of AD (Haroutunian et al., 1999) consistent with a weaker association. In contrast, use of NSAIDs was not substantially associated with the hallmark lesions of AD.

Consistent with the current observations, three studies that have examined the relationships between NSAIDs use and AD neuropathology (Arvanitakis et al., 2008; Halliday et al., 2000; Mackenzie and Munoz, 1998) did not find a significant association. The recent ACT study found that NSAIDs are associated with increased NPs (Sonnen et al., 2010). These negative or even deleterious reports are compatible with several clinical trials that found no advantage for NSAIDs or some evidence for a detrimental effect (Aisen et al., 2003; Martin et al., 2008). However, several observational studies suggest a protective effect of NSAIDs against clinically diagnosed AD (Szekely et al., 2008; Zandi et al., 2002) for which the marginal results for NP counts of the current study lend nominal support. If NSAIDs have a protective effect against AD, it might be through a non-A β mechanism of action, since NSAIDs use has been associated with less microglial activation (Mackenzie and Munoz, 1998).

Consistent with our result showing less AD neuropathology in subjects who received corticosteroids are recent findings suggesting that high cortisol levels are associated with slower rate of cognitive decline in mildly cognitively impaired subjects (Peavy et al., 2009). We are not familiar with any studies that examined the relationship of corticosteroids per se and the hallmark lesions of AD in human brains, or with epidemiological studies examining the effect of corticosteroids on cognitive decline and AD. It is possible that both types of studies have focused more on NSAIDs, since they are more commonly used than corticosteroids and may be used for longer periods of time. Also, corticosteroids are frequently used for diseases that increase mortality, such as COPD and autoimmune disorders, which might introduce selection bias. Thus, this group of medications might have received less attention in the AD context because of methodological limitations. Interestingly, year-long chronic glucocorticoid administration to nonhuman primates resulted in increased A β 42 relative to A β 40 levels, but without a change in overall plaque burden within the brain (Kulstad et al., 2005), suggesting an interaction of exogenous glucocorticoids with A β processing.

One clinical trial randomized 138 AD patients to 20mg prednisone daily for four weeks tapered to 10mg daily for one year or placebo, but the two groups did not differ in 1-year rate of cognitive decline (Aisen et al., 2000). However, two single doses of dexamethasone 4mg suppressed amyloid angiopathy, reversed white matter changes, and restored cognitive function in a patient with cerebral amyloid inflammatory vasculopathy (Harkness et al., 2004). It is possible that higher doses of corticosteroids, as more commonly used in other inflammatory diseases of the brain such as lupus cerebritis and CNS vasculitis, may have an effect on AD neuropathology. The known adverse side effects of high dose exogenous glucocorticoids preclude their routine use for prevention or treatment of cognitive compromise and AD. However, the present results suggest that the study of the mechanisms through which administration of such medications directly to the CNS—as is now being examined for insulin for similar reasons (Benedict et al., 2007)—affect NPs and NFTs may provide insights into novel therapeutic avenues.

The effects of synthetic corticosteroids on the CNS are particularly complex, among other reasons because multidrug resistance transporters reduce their ability to cross the blood brain barrier (BBB)(De Kloet et al., 1998). Thus, in vivo studies using these medications to produce central effects must utilize high enough doses to overwhelm these transporters. The strongly significant results for corticosteroids attained in the current study suggest that the various doses employed were sufficient. Seventy percent of the subjects taking corticosteroids were receiving either prednisone or prednisolone, both of which are better able to penetrate the BBB(Bannwarth et al., 1997; Karssen et al., 2002) than dexamethasone, for which penetration is low(Meijer et al., 1998). Indeed, results remain essentially unchanged when comparing subjects taking only prednisone to those who did not take anti-inflammatory medication, despite the smaller numbers (data not shown).

Numerous studies demonstrate that under some circumstances glucocorticoid signaling via glucocorticoid receptor makes neurons less capable of surviving a variety of insults(Sapolsky and Pulsinelli, 1985). Contrary to the general anti-inflammatory properties of glucocorticoids(McEwen et al., 1997), in the context of brain insult—such as from β -amyloid—there is an increase in glucocorticoid-induced inflammation in the CNS that might contribute to this increased neuronal injury(Sorrells et al., 2009). However, a growing body of literature(Lucin and Wyss-Coray, 2009) suggests that a robust inflammatory response may be essential to degrading/reducing brain insults and promoting repair. This is particularly relevant to the very elderly(Katsel et al., 2009), who constitute the vast majority of the sample in this study. Thus, it is likely that like so many other systems, the effects of glucocorticoids on neurobiology are complex, dose- and age-dependent. The striking association of systemic glucocorticoid therapy with lower neuropathological lesions of AD in the current study suggests that direct studies of cause and effect relationships are warranted and might provide clues for novel therapeutic approaches to dementia and AD.

Subjects receiving corticosteroids were less severely demented, as measured by the CDR, than subjects not receiving these medications. It is possible that physicians are less prone to medicate more severely demented subjects with these types of medications. Since CDR and neuropathology are highly correlated(Schnaider et al., 2008) it could be that the observed lower AD neuropathology might simply reflect less demented subjects. However, this argument seems less plausible given the differential effects of corticosteroids and NSAIDs on AD neuropathology in subjects who did not differ significantly with respect to dementia severity ($p=0.37$) as well as other demographic and clinical characteristics as shown in Table 1. Additionally, analyses limited only to non-demented or mildly demented subjects left the differences between the corticosteroids and the comparison groups essentially unchanged. Although consistent with disease progression, this cross-sectional approach cannot confidently address the question of differential brain region vulnerability as a function of disease progression. More definitive conclusions must await longitudinal studies with sensitive and validated biomarkers.

Strengths of the study were a relatively large sample size, systematic independent rating of the extent of regional AD pathology, and quantitative counts of NPs in the cortex in addition to the qualitative CERAD neuropathological rating. In addition, since subjects were primarily residents of nursing homes and assisted living facilities, medications were administered under direct medical staff supervision. Thus, the confidence in the reliability of medical records is significantly higher than for self report or even visual inspection of prescribed medications. Moreover, it is likely that prescribed anti-inflammatory medications reflected actual use, and that the problem of non-reported medications was relatively limited. Also, good information on the indication for such use was available to us. Limitations of the study are the lack of information on incidental non-prescribed NSAID use which might have occurred in all three groups, on the use of anti-inflammatory medication

before study enrollment (which averaged three years before death), incomplete information on duration and dosage, and lack of antemortem levels of cortisol and inflammatory markers, all of which might modulate the effect of anti-inflammatory medications on the neuropathology of AD. Although results were very similar when including all brain bank cases who participated in our aging studies (i.e., including those with other than AD neuropathology), since the sample is primarily of institutionalized subjects, extrapolation of the results to community dwelling elderly requires caution. For example, the rate of NSAID use in the neuropathological sample of the ACT population-based study was much higher (70%) than in our sample (Sonnen et al., 2010).

Since medications were administered and taken under direct medical staff supervision, the medication records and the confidence in their reliability is significantly higher than in studies that rely on self report or even studies that utilize visual inspection and inventory of prescribed medications

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Figure 1. Comparison of the extent of AD neuropathology in subjects who had a history of corticosteroids use (n=54) to controls (n=576) or of NSAIDs use (n=56) to controls

Upper Panel Legend (p-values for corticosteroids comparisons; p-values for NSAIDs comparisons): NP Hippo-neuritic plaque CERAD ratings in the hippocampus (0.002;0.25); NP EC- neuritic plaques in the entorhinal cortex (0.017;0.39); NP Amyg- neuritic plaques in the amygdala (0.029;0.49); NFT Hippo- neurofibrillary tangles CERAD ratings in the hippocampus (0.032;0.86); NFT EC- neurofibrillary tangles in the entorhinal cortex (0.083;0.74); NFT amyg- neurofibrillary tangles in the amygdala (0.004;0.68).

Lower Panel Legend (p-values for corticosteroids comparisons; p-values for NSAIDs comparisons): NP cortex- sum of CERAD ratings of neuritic plaques in four cortical regions (0.001;0.26); NP sum- sum of CERAD ratings of NPs in the hippocampus, entorhinal cortex, amygdala, and cortex (0.001; 0.26); NFT cortex- sum of CERAD ratings of neurofibrillary tangles in four cortical regions (0.002; 0.20); NFT sum- sum of CERAD ratings of NFTs in the same regions as in NPsum (0.001; 0.55).

*p 0.05; **p 0.005

Table 1

Sample characteristics by anti-inflammatory medication status

	No anti-inflammatory medication	NSAIDs	Corticosteroids	Statistics F (2, df), p or χ^2 (2), p
N	576	56	54	
Age at death	82.9 (10.2)	83.9 (9.6)	80.2 (9.3)	F (2,691)=2.47, p=0.09
Sex (%F)	64.2	51.8	53.7	χ^2 (2) =5.24, p=0.07
CDR	2.4 (1.7)	1.8 (1.3)	1.5 (1.5)	F (2,683)=11.36, p=0.001
% APOE4 genotype	30.1	30.4	22.2	χ^2 (2) =1.51, p=0.47
% Arthritis	22.6	35.7	22.2	χ^2 (2) =4.93, p=0.09
% CVD *	24.7	28.6	26.4	χ^2 (2) =0.46, p=.80
Mean NP count	7.6 (8.8)	4.8 (5.7)	3.9 (6.6)	F (2,674)=, p=0.001
Mean NP rating	13.3 (11.6)	11.6 (10.3)	7.2 (9.2)	F (2,649)=, p=0.001
Mean NFT rating	11.5 (9.4)	10.6 (8.5)	6.6 (6.8)	F (2,647)=, P=0.001

* Cerebrovascular disease-primary or secondary CERAD diagnosis