

### Linking estrogen to Alzheimer's disease: An informatics approach

**Article abstract**—Epidemiologic studies suggest that estrogen protects against AD. We employ ARROWSMITH, a novel computer-assisted approach, to identify possible links between estrogen and AD that are not explicit in the biomedical literature, by searching for substances or processes that are known targets of estrogen action and that have also been separately studied in relation to AD. Several links appear particularly promising (e.g., estrogen's antioxidant activity) and merit attention by neuroscientists.

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Alzheimer's disease (AD) is characterized by a research effort of unusually broad scope; investigators must integrate observations across fields as diverse as peptide modeling, soil-water monitoring, and neuropsychological testing. Epidemiologic studies recently suggested that estrogen may protect against AD,<sup>1</sup> without elucidating which cellular actions of estrogen are involved. The problem is that estrogen exerts effects in many organ systems, resulting in an enormous and poorly integrated literature. It is no simple task to find and assess the studies that may be most relevant to AD, particularly those that have little or no cross-citation to neuroscience journals.

We have been working on information retrieval strategies for integrating knowledge across scientific specialties<sup>2,3</sup> and used a novel computer-assisted approach (ARROWSMITH) for identifying paths between two items in the biomedical literature to assess possible mechanisms by which indomethacin might be expected to affect patients with AD.<sup>4,5</sup> We now use the same approach to identify effects of estrogen that may be relevant to its protective effects on AD. One of these effects (estrogens exhibit antioxidant activity) seems particularly relevant and may have been overlooked by neuroscientists.

**Methods and Results.** Seventy records in MEDLINE, SCISEARCH, EMBASE, and BIOSIS databases mention both estrogen and AD directly (June 1995), discussing effects of estrogen on a relatively small number of factors such as choline acetyltransferase, growth factors,  $\beta$ -amyloid precursor protein, interleukin-6, tau, synaptic plasticity, and cerebral blood flow. We looked more broadly for indirect connections<sup>3</sup> showing that estrogen affects substances or processes "X" that have been separately studied in relation to AD. MEDLINE was searched to create a local computer file of 16,300 post-1974 titles containing the word "(o)estrogen\$" (\$ covers all variant endings) and a file of 8,200 post-1965 titles containing the word "Alzheimer\$." Records mentioning both estrogen and AD were excluded. The ARROWSMITH software was then used to perform two major functions. First, all words and phrases were identified that were common to the two sets of titles and that occurred in at least four titles in both sets. "Non-interesting" words were excluded with a precompiled 5,000-word stoplist<sup>2</sup> plus manual editing, leaving 194

"X-terms." Second, a printed display was prepared, for each X-term, of titles in which estrogen and X co-occurred; this list was juxtaposed with titles in which X and AD co-occurred. This format<sup>2</sup> allows the user to assess whether X might represent a plausible biological link between estrogen and AD; the user can then investigate further the relevant articles and carry out more extensive database searching.

Some of the X-terms are general (cDNA) or are discussed in the direct estrogen-AD literature (acetylcholine). However, several have been implicated in AD—yet have previously been examined, in the context of estrogen, primarily in organs other than brain and without explicit mention of AD. Estrogen regulates calbindin D28k, induces cathepsin D and other protease secretion, and alters superoxide dismutase in various non-neural systems. Estrogen inhibits apolipoprotein E (apoE) levels in plasma and enhances its cellular uptake; although estrogen and apoE co-occur in over 50 records, only one<sup>7</sup> relates this link to AD explicitly. Estrogen can enhance neuronal responses to glutamate and induce cytochrome c oxidase subunit III in rat hippocampus, but these effects have not been discussed in relation to AD. Estrogen receptor polymorphism has been examined extensively as a risk factor in breast cancer but has never been evaluated in AD. Most significantly, a substantial set of papers indicated that estrogen exhibits antioxidant activity (e.g., see reference 8).

**Discussion.** Although ARROWSMITH is operated as an experimental prototype, we envision that it may eventually become widely available as a supplement to current database search techniques. In effect, ARROWSMITH takes MEDLINE searching to a higher dimension, revealing relationships that cannot be gleaned readily by conventional searches or by reading review articles. This procedure identified indirect paths linking the title words "estrogen" and "Alzheimer," several of which are plausible targets of estrogen that have not been investigated in the context of AD.

In particular, we believe that the well-documented antioxidant activity of estrogen deserves attention. At the time this paper was submitted, we had not been able to find any published discussion of this effect as possibly relevant to AD, despite many suggestions that free radicals participate in the pathogenesis of AD and that antioxidants may be protec-

tive. This may represent an example in which information flow within the scientific community is hindered by fragmentation of the biomedical literature.<sup>2,5</sup> After this manuscript was submitted for publication, one paper did appear that mentions the estrogen-antioxidant-AD link explicitly,<sup>9</sup> and our attention was also called to a passing mention in the nonpeer reviewed (and nondatabase accessible) literature.<sup>10</sup> Thus, certain investigators were evidently cognizant of the link from their own expert knowledge of the estrogen field. These two papers underscore the utility of ARROWSMITH for information retrieval and verify that our search identified, before publication, links that experts consider promising and worthy of further consideration.

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## Hippocampal formation size predicts declining memory performance in normal aging

**Article abstract**—Hippocampal formation (HF) atrophy, although common in normal aging, has unknown clinical consequences. We used MRI to derive HF size measurements at baseline on 44 cognitively normal older adults entering a longitudinal study of memory function (mean age = 68.4 years, mean follow-up = 3.8 years). Only one subject became demented at follow-up. Multiple regression analyses controlling for age, gender, education, and diffuse cerebral atrophy revealed that HF size significantly predicted longitudinal change on memory tests previously found sensitive to decline in normal aging. These results indicate HF atrophy may be a risk factor for accelerated memory dysfunction in normal aging.

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Radiographically evident atrophy involving the hippocampal formation occurs in Alzheimer's disease<sup>1,2</sup> and also in nondemented elderly patients with mild cognitive impairment.<sup>3</sup> Nevertheless, lesser degrees of hippocampal atrophy may affect approximately one-third of elderly persons without any clinical evidence for cognitive dysfunction.<sup>4</sup>

In a recent study,<sup>5</sup> we obtained MRI derived measurements of hippocampal formation (HF) size on a group of cognitively normal elderly research volunteers. In this sample, there was a highly significant correlation ( $r = 0.49$ ,  $p < 0.001$ ), independent of diffuse cortical atrophy, between hippocampal size

and a composite index of delayed secondary memory performance. In this study, we analyzed the results of follow-up memory tests administered to members of this sample to determine whether longitudinal deterioration in recall performance would significantly correlate with the baseline hippocampal formation size measurements.

**Methods.** *Subjects.* Of all medically healthy and cognitively normal older adults participating in a study of memory impairment at the New York University Aging and Dementia Research Center, 101 individuals received clinical