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The canine model of human cognitive aging and dementia: Pharmacological validity of the model for assessment of human cognitive-enhancing drugs

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Abstract

For the past 15 years we have investigated the aged beagle dog as a model for human aging and dementia. We have shown that dogs develop cognitive deficits and neuropathology seen in human aging and dementia. These similarities increase the likelihood that the model will be able to accurately predict the efficacy of Alzheimer's disease (AD) treatments as well as detect therapeutics with limited or no efficacy. Better predictive validity of cognitive-enhancing therapeutics (CETs) could lead to enormous cost savings by reducing the number of failed human clinical trials and also may reduce the likelihood of negative outcomes such as those recently observed in the AN-1792 clinical trials. The current review assesses the pharmacological validity of the canine model of human aging and dementia. We tested the efficacy of (1) CP-118,954 and phenserine, two acetylcholinesterase inhibitors, (2) an ampakine, (3) selegiline hydrochloride, two drugs that have failed human AD trials, and (4) adrafinil, a putative CET. Our research demonstrates that dogs not only develop isomorphic changes in human cognition and brain pathology, but also accurately predict the efficacy of known AD treatments and the absence or limited efficacy of treatments that failed clinical trials. These findings collectively support the utilization of the dog model as a preclinical screen for identifying novel CETs for both age-associated memory disorder and dementia.

Keywords: Acetylcholinesterase inhibitor; Aging; Alzheimer's disease; Ampakine; Cognition; Dementia; Dog; Pharmacological validity; Selegiline

1. Introduction

For the past 15 years, we have investigated the dog as a model of human aging and dementia. Initially, we developed comparable cognitive tasks to those used in non-human primate aging research. Our earliest results indicated that dogs demonstrate age-dependent cognitive decline on tests involving visual processing but not on tasks involving simple procedural learning (Milgram et al., 1994). We subsequently refined the model by developing novel tasks particularly suitable for dogs and by compiling data from over 250 animals (Adams et al., 2000a,b; Callahan et al., 2000; Chan et al., 2002; Cummings et al., 1996b; Head et al., 1995, 1998; Milgram, 2003; Milgram et al., 1994, 1999, 2002a,b; Tapp et al., 2003a,b). We also have collected data on neuropathological changes that occur in dog aging (Cummings et al., 1996a,c; Head et al., 1998, 2000, 2002; Head and Torp, 2002; Satou et al., 1997; Su et al., 1998; Torp et al., 2000a,b) and have identified changes, such as amyloid-β (Aβ) deposition, that correlate to some extent with cognitive decline (Cummings et al., 1996a; Head et al., 1998). Collectively, our data provide compelling support for

Abbreviations: Aβ, amyloid-β; AchE, acetylcholinesterase inhibitor; AD, Alzheimer's disease; CDS, canine cognitive dysfunction syndrome; CET, cognitive-enhancing therapeutic; DNMP, delayed non-match to position; FDA, food and drug administration; MAO-A, monoamine oxidase A; MAO-B, monoamine oxidase B; MCI, mild cognitive impairment; NMDA, *N*-methyl-D-aspartate; 3c-DNMP, three-component delayed non-match to position; 2c-DNMP, two-component delayed non-match to position.

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the aged dog as a model of human cognitive aging and dementia.

Animal models that exhibit isomorphisms with human cognitive aging and dementia are valuable for two reasons: (1) to generate and test hypotheses to further our understanding of aging processes, and (2) to identify therapeutics for clinical screening. The pharmacological validity of an animal model depends on its ability to accurately predict successful therapeutics in humans. The present review seeks to extend the utility of the dog model by establishing its pharmacological validity, namely its accuracy in predicting the efficacy of potential cognitive-enhancing therapeutics (CETs) in humans.

2. Establishing pharmacological validity: importance of negative data

Most discussions of pharmacological validity focus on positive effects in animal models that predict positive effects in humans. By contrast, negative findings are generally ignored, likely because negative data is rarely published. However, the ability to predict that a compound will be ineffective has important pharmacoeconomic benefits. The estimated cost of bringing one CET to market is now 525 million dollars (Tufts Center for the Study of Drug Development, 2004). The most costly part of this total is incurred when carrying out ineffective clinical trials, which can be reduced in frequency with a model that accurately predicts negative results. This should result in decreased cost burdens to the end consumer—the patient.

In addition to the pharmacoeconomic benefits, utilization of multiple animal models is also potentially important for safety reasons. This was clearly illustrated in the AN-1792 clinical trials, which were initiated in human subjects as a result of positive evidence from the transgenic mouse model. The trials were suspended after 18 patients developed meningoencephalitis, some of which died. The preclinical screens did not predict this adverse event, likely because the Aβ vaccine targeted a foreign peptide in the transgenic mouse whereas it targeted an endogenous peptide in the human, causing an autoimmune response (Robinson et al., 2004). Perhaps this outcome could have been avoided if preclinical data also were obtained from primates or canines, which naturally deposit Aβ.

Currently, only four drugs are marketed for Alzheimer's disease (AD): three acetylcholinesterase (AChE) inhibitors and one *N*-methyl-D-aspartate (NMDA) receptor antagonist. None of the currently approved treatments significantly attenuate the progress of the disease; at best, they only attenuate the cognitive symptoms and even this may be limited (Courtney et al., 2004). Therefore the ability to detect true positives in animal models is limited by both the small number of approved drugs and by the absence of approved drugs that prevent or reverse the progression of the disease in clinical trials. Furthermore, the benefits of all four approved drugs are limited in duration of effect and are beneficial only in restricted subsets of the AD population. In many cases, positive effects depend on reducing the rate of cognitive decline, rather than reversing or halting the disease. Thus, the assessment of pharmacological validity should consider the accuracy of both positive and negative findings.

We have conducted numerous studies to evaluate the efficacy of purported cognitive enhancers on aged dogs. These have included, but were not limited to, AChE inhibitors, ampakine, selegiline (L-deprenyl), and adrafinil. This review first provides an overview of the evidence supporting the use of the dog as a model of human aging and dementia. The remainder of the review summarizes pharmacological work and, where applicable, briefly compares our efficacy studies in dogs with those conducted in humans, rodents and, where applicable, primates.

3. Dog model of aging and dementia—a brief overview

Cognitive functions include a set of higher-level mental processes that enable us to learn, remember, plan, and adapt our behavior to environmental changes. In aged dogs, cognitive decline is manifested in the development of impaired learning, depressed memory and reduced behavioral flexibility. Not all processes are equally affected; simple rule-based learning, simple discrimination learning and procedural learning remain largely intact (Milgram et al., 1994). By contrast, deficits in executive function and visuospatial function occur at high incidence in aged animals (Adams et al., 2000b) and can be detected in dogs as young as 6 years of age (unpublished data). Complex rule learning, such as non-matching working memory paradigms (Callahan et al., 2000; Chan et al., 2002; Head et al., 1995) and landmark discrimination (Milgram et al., 1999, 2002a), also is impaired in aged dogs. This pattern of cognitive decline shows many parallels to that seen in human aging and AD. Two of the earliest signs of cognitive decline in AD patients are impaired visuospatial function (Flicker et al., 1984, 1991; Freedman and Oscar-Berman, 1989) and delayed recall, which is dependent on executive function (Morris and Baddeley, 1988).

Canine aging is also similar to human aging in that both show extensive individual differences. Aged dogs can be characterized as successful agers, mildly impaired or severely impaired based on their cognitive test performance (Adams et al., 2000b). These categories are analogous to human successful aging, mild cognitive impairment (MCI) and dementia, respectively (Adams et al., 2000a). For a complete review of the cognitive aspects of the dog model of human aging and dementia, see Adams et al. (2000a).

The neuropathological changes that develop in dogs are similar to those seen in human aging and AD. Dogs are one of the few laboratory animals that naturally develop Aβ, a key feature of AD, also seen to a lesser extent in normal aging. Dogs predominantly accumulate the more neurotoxic