

THE EFFECTS OF CHOLINERGIC MANIPULATION IN THE DOG: PHARMACOLOGICAL VALIDATION OF A CANINE MODEL OF HUMAN AGING

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Aged dogs exhibit cognitive decline and amyloid pathology that parallels changes in human aging and dementia. To further validate the dog as a model for human aging, we examined the effect of pharmacological cholinergic manipulation on cognitive function using scopolamine, a non-specific muscarinic antagonist, and (-)-phenserine, a specific acetylcholinesterase inhibitor. Initially, a dose response study was used to determine the minimally effective dose of scopolamine for disrupting performance on a delayed visuospatial memory task in aged dogs. Subsequently, we tested that dose on a battery of cognitive tests in dogs ranging from 2-17 years of age. Scopolamine impaired performance in a task and age-dependent manner; performance of the visuospatial memory task was disrupted at a lower dose compared to semantic-like memory tasks and aged dogs were more sensitive than young to scopolamine impairment. No delay-dependent effects were detected on any test. We then examined the effect of (-)-phenserine on the visuospatial memory task and on an age-sensitive complex discrimination learning task. (-)-phenserine improved memory measures and prevented scopolamine-induced performance impairment at a short delay. (-)-phenserine also improved learning, but only when the task was sufficiently difficult. Our results demonstrate that cholinergic manipulation affects canine cognition similarly to that observed in humans; inhibition impairs and augmentation improves measures associated with memory in an age-dependent manner. Furthermore, cholinergic disruption produces a similar pattern of cognitive deficits as natural aging in dogs, which supports the suggestion that cholinergic function is naturally diminished with age in the dog. The absence of scopolamine-induced delay-dependent effects, and the improvement in complex learning following (-)-phenserine, support an attentional hypothesis of cholinergic function; however, the present results also support the hypothesis that attentional impairment can lead to deficits in m