Butyrylcholinesterase Imaging Agents to Visualize Pathology in Alzheimer's Disease
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Background: Butyrylcholinesterase (BuChE) is an enzyme that, among other functions, catalyzes the hydrolysis of the neurotransmitter acetylcholine. Increased levels of BuChE are associated with the pathology of Alzheimer’s disease (AD). This association makes BuChE a suitable target for disease-specific imaging of this neurological disease. We propose that BuChE-specific radiopharmaceuticals can be used for brain scanning to detect this enzyme in vivo, and thus the pathology associated with AD. As a preliminary step towards this goal, imaging agents have been synthesized and evaluated in rodent and human brain tissues. Methods: BuChE-specific radioligands were administered to wild type and transgenic AD rodents as well as incubated with post-mortem normal and AD human brain tissues. The distribution of radioactivity was determined via autoradiography. BuChE inhibitors were used to confirm specificity of the radioligand binding to this enzyme. Results: Autoradiographic analysis of rodent and human brain tissues indicated accumulation of radioactivity in areas known to contain BuChE as determined by histochemical analysis. Furthermore, presence of a BuChE inhibitor attenuated accumulation of radioactivity. Preliminary results indicate that AD tissues can be distinguished from normal human brain. Conclusions: BuChE has previously been implicated in the pathology of neurological diseases. We have synthesized several BuChE imaging agents. Autoradiography, in experimental animal and human brain tissue indicates that these agents have the potential to provide a non-invasive means for early diagnosis and treatment monitoring of AD using brain scanning.

What do mouse models teach us about aging?
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Our lab studies the neurobehavioural changes in genetically modified mice as they age. There are three purposes for these studies. First, to understand the basic behavioural changes associated with aging. Second, to understand the neural and genetic mechanisms underlying these changes, and third, to use these mouse models to develop new treatments for age-related disorders. We have examined mouse models for glaucoma and Alzheimer’s disease. The DBA/2J mouse develops age-related glaucoma and is functionally blind by 12 months of age. We examined the effects of blindness on learning and memory in these mice and showed that treatment of glaucoma with Timoptic XE improved visual ability and performance on visuo-spatial tests of learning and memory. We are testing a number of mouse models of Alzheimer's disease and are finding that these mice have age-related visual and motor control problems as well as cognitive decline. For example, the double transgenic APPswe/PS1de9 mouse shows deficits in visual acuity but not in olfaction. One of our goals is to dissociate the sensory and motor deficits from deficits in cognitive function. Another goal is to examine sex and strain differences in the development of age-related disorders. Data will be presented on age-related behavioural deficits in the 3X-Tg and 5x FAD mouse models of Alzheimer's disease. The development of new drugs depends on a complete knowledge of the neurobiological mechanisms underlying diseases of aging and the goal of our research is to uncover these mechanisms. Supported by NSERC of Canada.

Discussant TBA