In Vivo MRI Investigation of Decreased Neuronal Transport with Aging and in Brains Expressing Alzheimer's Pathology

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PURPOSE:

Axonal transport is an important physiological process crucial to neuronal function and viability. Projection neurons with long axons are selectively vulnerable in Alzheimer's disease (AD), and impairment of axonal transport has been implicated in AD pathophysiology[1,2,3]. Manganese enters neurons via Ca^{2+} channels and transported down the axon on microtubules[4,5]. We used manganese-enhanced MR imaging and parametric mapping analysis to investigate possible decreases in axonal transport of normal aged mice as well as mice transgenic for Alzheimer's pathology.

MATERIALS AND METHODS:

APPswe/PS1 double mutant transgenic mice (develop Aß deposits at 4–6 mos.) and age-matched controls (young control (YC),8-12 wks, n=5; young Tg (YT),8-10 wks, n=4; old control (OC), 43 wks, n=4 and old Tg (OT), 43-45 wks, n=4) were scanned under isoflurane gas anesthesia by a 1.5T MR scanner using a 3D-SPGR pulse sequence (TE=6.8 ms; TR=15 ms; FA=45 deg; 4 NEX). Serial MR scans pre- and post-injection of 5 µl $MnCl_2$ intranasally were performed at 1, 3, 6, 8, 10, 24, 36, 60, and 156 hrs. Images were coregistered, stereotactically aligned to the mouse atlas[6], and normalized (NEUROSTAT, U. of Wash.). VOI analysis of bulb and posterior olfactory tract were used to estimate 'time to peak' bulk transport using tracer dispersion modeling with bulb uptake as an input function. Pixel-by-pixel statistical subtraction converted to z-maps were generated to show group-wise changes in transport.

RESULTS:

Early olfactory bulb uptake of the aged mice (both OT and OC) was slower when compared to young mice (YC and YT). Peak uptake in young mice occured at 10 hrs and was significantly increased at 6, 8 and 10 hrs from old mice ($p \leq 0.05$) (Figure 1). Early transport into the anterior olfactory tract was decreased significantly ($p \leq 0.05$) at 8 and 10 hrs in OC versus YC, which persists to later time points at 24 and 36 hrs (Figure 2). Transport speed was estimated to be 20% decreased in old mice as compared to young. Group-wise statistical z-maps of anterior and posterior olfactory tract regions indicated decreased transport in all groups (YT, OC, OT) as compared to the young controls (Figure 3). Estimation of dynamic images for time-to-peak bulk transport in the posterior lateral olfactory tract indicated reduction in young transgenics versus young controls (0.89±0.34 mm/hr versus 1.74±1.18 mm/hr).

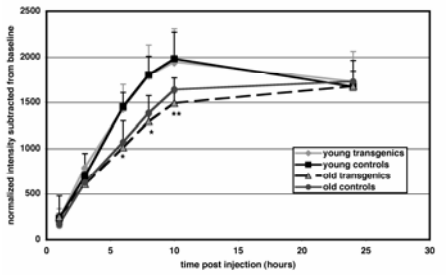

Figure 1. Dynamic curves of olfactory bulb uptake through 24hrs. * indicates significant decrease of both OT and OC as compared to YT and YC. ** indicates significant decrease of OT only as compared to YT and YC. ($p \leq 0.05$)

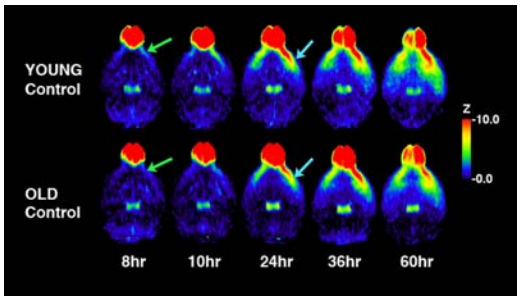

Figure 2. Bulk transport decreased in old controls. Statistical z-maps processed to indicate the maximum intensity projected into the transverse plane. Green Arrows indicate early transport decrease, blue arrows show later decrease

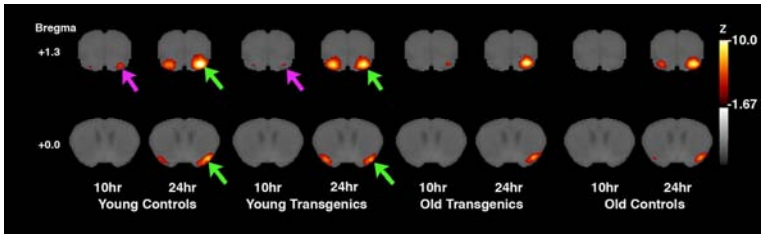

Figure 3. Decreased transport in transgenic and old mice. Group-wise statistical z-maps in coronal slices of the mouse brain at 10 and 24 hours post injection. Purple arrows indicate decreases in early transport. At 24 hours (green arrows), statistically significant decreases can be easily distinguished in the posterior olfactory tract. Slice distance from the bregma landmark in mm is indicated.

SUMMARY AND CONCLUSIONS:

This study indicates differences in both neuronal uptake (calcium channel activity) and neuronal transport between young and aged brains in controls as well as mice transgenic for AD pathology. Old mice, both control and Tg showed decreased rate and peak Mn^{2+} uptake in the bulb with highest uptake at 24 hrs as compared to young Tg and control that peaked at 10 hrs. Aged mice and young Tg showed decreased transport to posterior olfactory tract at 24 hrs. Parametric estimation for bulk transport indicated rate decreases in Tg as compared to control mice. Decrease in bulb uptake appears to be age-related, however decreased transport to the posterior tract was also seen in young transgenics with normal bulb uptake, therefore decreases in axonal transport are present prior to amyloid deposition in young AD Tg mice. This study may have important implications for the early pathophysiology and treatment of AD.

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