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FDG autoradiography reveals developmental and pathological effects of mutant amyloid in PDAPP transgenic mice

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Abstract

Transgenic mouse models of Alzheimer's disease (AD) show some characteristic features of the disease, and we aim to further bridge the gap between studies of humans with AD, those at risk, and these murine models by providing shared markers of disease which could be used to track progression and assess future interventions. Brain imaging measurements may prove useful in this regard. We previously found that the homozygous PDAPP mouse model of AD showed significant declines in glucose uptake with age in posterior cingulate cortex, an area homologous to the human posterior cingulate, which shows significant declines in AD and in those at risk for AD. To further evaluate this potential biomarker and its correlation across age, we used fluorodeoxyglucose autoradiography at two ages (2 and 12 months) in wildtype, heterozygous, and homozygous PDAPP mice. We found significant posterior cingulate fluorodeoxyglucose uptake declines again in homozygous PDAPP mice, but at both ages assessed. There was a strong effect of gene dose; homozygous mice showed larger and earlier effects. These results, in conjunction with our previous analyses, indicate a nonlinear progression stemming from synergistic effects of the overexpressed mutant gene, both developmental and pathological. The posterior cingulate is preferentially vulnerable to both effects of transgene in the PDAPP mouse, and both are independent of amyloid deposition.

Keywords

Alzheimer's disease; animal models; functional brain imaging; posterior cingulate cortex; fluorodeoxyglucose

Fluorodeoxyglucose (FDG) positron emission tomography (PET) studies find that persons with Alzheimer's disease (AD) characteristically show preferential and progressive neocortical reductions in measurements of the cerebral metabolic rate for glucose or FDG uptake, with the largest reduction found in the posterior cingulate cortex (PCC; Minoshima et al., 1994, 1997; Reiman et al., 1996). We have also examined the postmortem PCC and showed that the glucose

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uptake abnormalities may be related to decrements in mitochondrial oxidative energy metabolism in AD (Valla et al., 2001). In parallel to imaging studies in humans, we have mapped metabolic activity in the brains of transgenic mouse models of AD with the hope of providing a new surrogate marker of AD processes which could be used to help clarify disease mechanisms and screen candidate treatments. We previously reported (Reiman et al., 2000) a highly significant, preferential and progressive (i.e., found in 18-month-old but not 4-month-old mice) reduction in FDG uptake in the PCC of homozygous transgenic mice overexpressing human mutant β -amyloid precursor protein (PDAPP; Games et al., 1995). The finding in this region was enticing as the rodent PCC is generally homologous to the human, subserving similar functions, such as spatial (Vann et al., 2000) and associative/discriminative (Gabriel et al., 1987) learning.

We performed this study to further establish the time course of regional functional effects in the PDAPP mouse brain. Secondly, we sought to assess not only homozygous mice as before, but also the more widely-distributed and utilized heterozygous mice, for comparable effects despite their lower gene dose and expression level.

Experimental Procedures

The study was performed under guidelines approved by the Institutional Animal Care and Use Committee at the Harrington Research Center (Phoenix, Arizona, USA) where this work was completed. All mice were male and generously donated by Dora Games and Elan Pharmaceuticals (South San Francisco, CA, USA) after surgical sterilization and were received directly from the Elan colony at the prescribed ages. The transgenic mice contained the V717F APP mutation with a platelet-derived growth factor promoter (Games et al., 1995). Group characteristics are presented in Table 1.

Each transgenic group was blindly randomized with a same-age nontransgenic control group (2- and 12-month-old control groups were shared between +/- and +/+ PDAPP mice). However, blinding was confounded in part by white matter changes in the PDAPP mice (Gonzalez-Lima et al., 2001; Valla et al., 2006a). To generate the autoradiographic images, animals were processed as in Valla et al. (2006b) using 18 μ Ci/100g body weight [14 C]-fluorodeoxy-d-glucose (FDG). Tissue sections designated for autoradiography, along with 14 C autoradiography standards (Amersham), were apposed to Kodak Ektascan film in light-tight film cassettes and left undisturbed for a two-week exposure period; the films were subsequently uniformly developed in an automated processor. Regions selected for analysis correspond to the delineations of Paxinos & Franklin (2001) except that their retrosplenial gyrus was additionally subdivided anterior to posterior into posterior cingulate, posterior cingulate level 2, and retrosplenial. To investigate regions preferentially affected or spared in the transgenic mice independent of the variation in absolute measurements, regional data from each mouse was normalized to a whole brain value of 1000 nCi/g using the mean activity of all gray matter regions sampled in each respective mouse, as in our previous work. The randomized 2- and 12-month-old transgenic mice and controls were analyzed with a 2×3 ANOVA encompassing age and gene dose (0, 1, or 2), with each omnibus F assessed at $\alpha = 0.05$. Significant main effects of gene dose were followed by individual Student's t-tests between the three groups at reduced $\alpha = 0.01$. While the possibility remains that a portion of our results may be due to Type I error, the results correspond in part to previous studies, reducing the probability they are due to random fluctuations. Gene dose effects were assessed with a nonparametric Kendall's *tau*. In the subsequent study of older heterozygous mice, treatment was identical and regions were independently assessed in each cohort with Student's t-tests ($\alpha = 0.01$).

Results

Results confirming the hypothesis of declines in cingulate regions are shown in Table 2. The groups did not differ significantly in absolute measurements of whole brain FDG uptake, absolute measurements of white matter (optic tract) uptake, or their whole brain to white matter ratio at any of the studied ages (Table 2), supporting the use of whole brain measurements to normalize regions for the variation in absolute measurements. As predicted, the ANOVA showed significant effects of the transgene as declines in normalized FDG uptake in each of the three posterior cingulate levels, with decreasing posterior cingulate FDG uptake significantly correlated with PDAPP gene dose in both the 2- and 12-month old mice (significant Kendall's *tau*, Table 2). However, we did not find an overall significant effect of age or an interaction between transgene and age in these regions between 2- and 12-month old mice (Table 2).

Exploratory findings in other regions are shown in Table 3. Similar to findings previously reported (Reiman et al., 2000), homozygous transgenic mice had significantly higher FDG uptake in the primary somatosensory cortex at 2 months, and this uptake was positively correlated to gene dose at both ages. Increases were also found in CA1 and the rostral and caudal caudoputamen at 12 months, again positively correlated with increasing gene dose. CA1 corresponds to the CA field here and not specifically to the molecular layer as in the original study. Mixed results were shown in the dorsal and ventral anterior pretectal areas. Heterozygous mice showed no significant differences from controls. Very few regions in this exploratory analysis showed significant main effects of transgene and age, and again, no significant interactions between age and gene dose were found.

In follow-up studies, we assessed two additional groups of heterozygotes aged to approximately 18 and 24 months. Again, there were no differences in whole brain or white matter activity versus controls, indicating no global changes between wildtype and transgenic. At 24 months, heterozygous PDAPP mice showed significant declines in the posterior cingulate level 2 ($p < 0.002$, -7.4% , 2-tailed t-tests) and retrosplenial ($p < 0.0005$, -12.0%) gyri, indicating that PCC deficits may still be progressive in heterozygotes, appearing later in life as compared to homozygotes. Other exploratory findings correspond in part to the initial analysis, with few other regions demonstrating significant differences (data not shown).

Discussion

PCC Metabolic Deficits Appear Before Amyloid Deposition

We have demonstrated that the homozygous PDAPP transgenic mouse model of AD (Games et al., 1995) reliably shows significant posterior cingulate hypometabolism, in agreement with previous studies (Dodart et al., 1999; Reiman et al., 2000). We did not find evidence in this analysis that the posterior cingulate metabolic deficits were progressive in the comparison of 2- and 12-month-old mice; where in contrast, our previous findings comparing 4- and 18-month-old homozygous PDAPP mice demonstrated a highly significant decline between those age points (Reiman et al., 2000). Our new data adds an interesting and potentially developmental dimension to the course of functional disruptions in the brains of these mice, as the simple effects due solely to increasing amyloid burden are logically excluded. A new interpretation of these findings is warranted, and one must consider the consequences of the mutant APP transgene outside of its intended role in simply, but profoundly, increasing soluble and deposited β -amyloid protein.

PDAPP Mutation Interferes with Development

Previously published work on these same cohorts (Gonzalez-Lima et al., 2001; Valla et al., 2006a) indicated persistent and profound congenital morphological alterations in the corpus callosum (CC) and hippocampal formation in homozygous PDAPP (and to a lesser extent, their heterozygous littermates). The most striking of these alterations is the absence or near-absence of commissural fibers in the posterior CC, which normally underlies much of the PCC. We have attributed this callosal defect to potential interference with APP's normal role in axonal growth cone motility (Sabo et al., 2003). Any developmental delay induced by mutant APP interfering with normal white matter development and thus regional connectivity would be expected to alter regional activity. Analysis of developing CNS white matter in rat pups indicated that the posterior CC matures later than all other assessed CNS tracts and may be only reaching a steady state at 60 days of age (Nair et al., 1999). Therefore, assuming a similar developmental time course in mice, the brain regions subserved by the undeveloped or circuitously-developing posterior PDAPP CC in the youngest cohort of our mice would show activity decrements, while other regions would be spared. Prior to significant amyloid deposition, this decrement may also show recovery as the developmental delay runs its course, as evidenced by the modest and statistically nonsignificant decline in 4-month-old PDAPP mice (Reiman et al., 2000).

Progressive PDAPP Decline in Aging is Nonlinear

From 4 months of age onward, the homozygous PDAPP mice demonstrate declines in FDG uptake, ranging from the absence of significant reductions compared to WT mice at 4 months to modestly statistically significant reductions at 12 months to highly significant reductions at 18 months (Reiman et al., 2000). While we did perform thioflavin S staining to verify transgene status in older mice, we did not directly correlate our FDG measurements with amyloid expression or deposition. However, these FDG results correspond with the known increasing amyloid load, which becomes pronounced in all areas of the cortex, even in heterozygous mice (Games et al., 1995). Further, in these mice, diffuse amyloid deposition increases dramatically between 12 and 15 months of age (Reilly et al., 2003). Therefore, we suggest that suddenly accelerating amyloid deposition leads to a corresponding acceleration in functional decline. One caveat to consider, however, is that the glucose uptake changes are not as widespread as the known pattern of amyloid deposition. While plaque-associated metabolic decline in one region could be expected to drive changes throughout an interconnected network, it is clear from our results that amyloid deposition in a region will not directly reduce functional metabolism in that region. This observation is also supported by the lack of toxicity associated with early accumulation of amyloid plaques in the striatum in human PS1 mutation carriers (Klunk et al., 2007). There is also increasing support for the role of soluble and/or intracellular APP products in the disruption of cellular processes in AD (Gouras et al., 2005, for review) as well as in transgenic animal models (Galvan et al., 2006). A primary role for the mutant amyloid transgene in both the white matter changes (Valla et al., 2006a) and PCC FDG changes, developmental and functional, is supported by the significant Kendall's tau results, indicating significant PDAPP gene dose effects in both this and the previous study. An ultimate role for mutant amyloid expression causing functional decline in PCC is supported by our subsequent analysis of an alternative transgenic model (hPS1 $\times$ hAPP; Holcomb et al., 1998), where we localized similar FDG deficits in the absence of significant white matter changes (Valla et al., 2006b).

PCC Metabolic Deficits Relate to AD and Memory

In vivo imaging in humans has shown that the PCC is involved in memory retrieval (Nyberg et al., 1996; Cabeza et al., 1997) as well as in a network thought to underlie a 'default' mode of brain processing (Raichle et al., 2001) of which memory may be a large component. The

PCC in rats and rabbits is also involved in forms of learning and memory, such as spatial (Vann et al., 2000) and associative/discriminative (Gabriel et al., 1987) tasks. The PDAPP mice demonstrate both progressive (age- and amyloid burden-associated) and nonprogressive impairments in different aspects of spatial memory (Chen et al., 2000), which corresponds well to our findings: early nonprogressive performance deficits may be caused by persistent white matter disruptions and early developmental delays in PCC while subsequent progressive deficits may be related to increasing amyloid burden in interconnected circuits.

Conclusions

We have reproduced and extended our previous findings of PCC hypometabolism in homozygous PDAPP transgenic mice. The pattern of metabolism indicated by glucose uptake in this model resembles that seen in patients with AD (i.e., late aging-associated declines in association cortex and commensurate sparing or relatively increased activity in sensorimotor areas). However, we describe a potential indicator of developmental delay in very young mice, corresponding to congenital morphological alterations. Effects in both young and old were related to mutant APP overexpression (but not necessarily plaques), as indicated by a strong association with gene dose that has not previously been described. It is likely that these “bimodal” metabolic changes are reflective or contributive to, first, nonprogressive and developmental behavioral deficits that affect these mice from the youngest assessable ages, as well as to aging-related, burden-associated behavioral deficits existing later in this model (Chen et al., 2000).

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List of Abbreviations

AD, Alzheimer's disease; APP, amyloid precursor protein; CC, corpus callosum; FDG, fluorodeoxyglucose; PCC, posterior cingulate cortex; PET, positron emission tomography.

Table 1

Studied ages and weights of PDAPP homozygotes, heterozygotes and littermate controls.

	Wildtype	Heterozygotes	Homozygotes
2 Month-old	N = 8	N = 7	N = 8
age (days)	58.5 ± 0.9	55.6 ± 3.3 ^a	52.3 ± 1.0 ^{ab}
weight (g)	34.2 ± 2.7	31.0 ± 4.1	30.6 ± 2.4 ^a
12 Month-old	N = 8	N = 8	N = 7
age (days)	374.0 ± 1.1	373.8 ± 1.0	374.4 ± 1.0
weight (g)	42.2 ± 3.0	41.2 ± 3.4	36.3 ± 2.5 ^{ab}

Superscripts indicate statistically significant (but likely not meaningful) differences across transgene dose (Student's t-tests, with $\alpha = 0.05$)

^a significantly different from same-aged WT

^b significantly different from same-aged heterozygote.

Table 2

FDG uptake in control and cingulate regions.

	2-Month-Old		WT	12-Month-Old		WT	<i>tauP</i>	Dose	ANOVA P Age	Int
	WT	+/-	+/-	+/+	+/-	+/+	<i>tauP</i>			
Optic tract	244 ± 94	300 ± 100	282 ± 95	0.573	337 ± 113	251 ± 73	314 ± 78	0.778	0.365	0.119
Whole brain	493 ± 113	560 ± 187	506 ± 126	0.778	663 ± 127	519 ± 143	561 ± 110	0.159	0.635	0.088
Whole brain / Optic tract	2.34 ± 1.23	1.93 ± 0.21	1.86 ± 0.29		2.12 ± 0.71	2.10 ± 0.39	1.81 ± 0.16		0.227	0.688
Cingulate gyrus, retrosplenial	1207 ± 107	1073 ± 114	1003 ± 79 ^a	0.002	1160 ± 71	1086 ± 98	1049 ± 54 ^a	0.011	<0.001	0.350
Cingulate gyrus, posterior 2	1265 ± 50	1210 ± 102	1097 ± 91 ^a	0.002	1257 ± 86	1224 ± 109	1106 ± 74 ^a	0.007	<0.001	0.938
Cingulate gyrus, posterior	1249 ± 35	1294 ± 58	1214 ± 60	0.284	1249 ± 77	1281 ± 45	1160 ± 71 ^b	0.071	<0.001	0.424
Cingulate gyrus, middle	1185 ± 40	1250 ± 56	1204 ± 68	0.416	1257 ± 85	1264 ± 54	1193 ± 76	0.128	0.063	0.208
Cingulate gyrus, anterior	1079 ± 44	1061 ± 67	1112 ± 88	0.260	1071 ± 59	1110 ± 47	1075 ± 58	1.00	0.705	0.168

FDG uptake mean ± standard deviation from wildtype (WT), heterozygous (+/-), and homozygous (+/+) PDAPP mice, along with P values from the Kendall's *tau* and omnibus F-tests. There were no statistically significant interactions (Int) between transgene dose and age. Superscripts indicate significant post hoc results across transgene dose (Student's t-tests, with reduced $\alpha = 0.01$)

^a significantly different from same-aged WT

^b significantly different from same-aged heterozygote. Retrosplenial and posterior cingulate activity declines in significant correlation to gene dose, but not age. Region labels correspond to the stereotaxic atlas of Paxinos and Franklin (2001), except cingulate gyrus was subdivided as follows: middle—Bregma -0.5; posterior—Bregma -1.4; posterior 2—Bregma -2.1; retrosplenial—Bregma -2.6.

Table 3

FDG uptake in additional cortical and subcortical regions.

	2-Month-Old		12-Month-Old		<i>tauP</i>	Dose	ANOVA P	
	WT	+/-	+/+	+/-			Age	Int
Posterior parietal cortex	1061 ± 73	1045 ± 68	1071 ± 83	1103 ± 62	0.612	0.855	0.005	0.472
Primary somatosensory cortex	1059 ± 54	1106 ± 56	1142 ± 57	1080 ± 80	0.003	0.004	0.273	0.866
Primary somatosensory, barrels	1124 ± 115	1126 ± 77	1212 ± 52	1105 ± 52	0.955	0.070	0.179	0.429
Secondary somatosensory c.	1101 ± 96	1084 ± 83	1126 ± 50	1057 ± 52	0.430	0.284	0.351	0.729
Primary visual c., monocular	1034 ± 80	976 ± 80	1037 ± 99	1020 ± 81	0.822	0.367	0.260	0.241
Primary visual c., binocular	1037 ± 75	974 ± 86	1038 ± 94	1025 ± 97	0.236	0.236	0.254	0.396
Secondary visual cortex	1029 ± 78	954 ± 74	1051 ± 61	1021 ± 103	0.910	0.499	0.384	0.537
CA1	756 ± 40	761 ± 26	796 ± 42	742 ± 41	0.143	0.001	<0.001	0.075
CA3	738 ± 20	707 ± 39	746 ± 50	751 ± 35	0.778	0.128	0.055	0.511
Dentate gyrus	872 ± 37	854 ± 70	871 ± 48	888 ± 26	0.822	0.130	0.373	0.617
Subiculum	883 ± 36	922 ± 36	895 ± 52	906 ± 40	0.430	0.693	0.088	0.949
Anteroventral thalamus	893 ± 64	926 ± 100	916 ± 64	947 ± 112	0.430	1.00	0.962	0.738
Reticular thalamus	913 ± 45	965 ± 50	955 ± 43	956 ± 53	0.091	0.735	0.202	0.291
Paratenial thalamus	988 ± 88	992 ± 83	993 ± 62	1080 ± 68	0.866	0.128	0.456	0.347
Reuniens thalamus	778 ± 53	770 ± 34	824 ± 68	848 ± 59	0.236	0.955	0.625	0.240
Ventromedial thalamus	1199 ± 55	1185 ± 50	1194 ± 62	1229 ± 79	0.955	0.159	0.336	0.598
Ventrolateral thalamus	1252 ± 63	1203 ± 75	1240 ± 71	1223 ± 53	0.822	0.735	0.315	0.693
Lateral posterior thalamus	1078 ± 45	1052 ± 63	1027 ± 69	1108 ± 66	0.236	0.215	0.098	0.966
Parafascicular thalamus	1074 ± 87	1123 ± 97	1027 ± 81	1095 ± 53	0.573	0.778	0.081	0.565
Lateral habenula	886 ± 96	966 ± 62	894 ± 120	928 ± 107	0.910	0.693	0.461	0.407
Paraventricular hypothalamus	648 ± 40	615 ± 42	678 ± 45	701 ± 23	0.215	0.464	0.018	0.821
Rostral caudoputamen	1029 ± 63	1132 ± 94	1104 ± 83	999 ± 25	0.114	0.001	0.001	0.171
Caudal caudoputamen	760 ± 102	656 ± 68	755 ± 92	694 ± 41	1.00	0.055	<0.001	0.133
Subthalamus	914 ± 46	969 ± 77	904 ± 41	934 ± 55	0.778	0.778	0.251	0.466
Zona inserta	925 ± 65	949 ± 62	957 ± 47	1007 ± 64	0.195	0.195	0.900	0.238
Nucleus accumbens	917 ± 71	853 ± 82	918 ± 84	870 ± 77	1.00	0.114	0.013	0.501
Nuc. of vertical diagonal band	832 ± 27	812 ± 72	855 ± 53	864 ± 69	0.612	0.778	0.483	0.839
Anterior pretectal area, dorsal	1139 ± 67	1207 ± 35	1138 ± 41	1159 ± 35	0.114	0.081	0.018	0.161
Anterior pretectal area, ventral	1185 ± 65	1230 ± 80	1134 ± 41	1143 ± 37	0.260	0.398	0.006	0.639
Dorsolateral geniculate	936 ± 41	884 ± 39	880 ± 54	922 ± 53	0.091	0.499	0.011	0.622
Superior colliculus, deep gray	892 ± 51	890 ± 72	888 ± 35	849 ± 61	0.236	0.955	0.909	0.907
Superior colliculus, superf. gray	952 ± 83	932 ± 122	895 ± 74	952 ± 77	0.195	0.338	0.678	0.950
Red nucleus	1060 ± 58	1133 ± 96	1065 ± 51	1039 ± 52	0.866	0.535	0.185	0.321
Nucleus of III	1129 ± 58	1177 ± 70	1115 ± 62	1120 ± 52	0.215	0.535	0.198	0.822
Pontine nuclei	885 ± 68	940 ± 60	908 ± 41	836 ± 47	0.284	0.024	0.022	0.383
Inferior colliculus, central	1360 ± 196	1299 ± 279	1409 ± 145	1072 ± 344	0.430	0.955	<0.001	0.695
Periaqueductal gray	697 ± 90	744 ± 92	738 ± 40	720 ± 74	0.003	0.338	0.362	0.791

Listing of additional regions analyzed and FDG uptake mean ± standard deviation from wildtype (WT), heterozygous (+/-), and homozygous (+/+) PDAPP mice, along with P values from the Kendall's *tau* and omnibus F-tests. There were again no statistically significant interactions (Int) between transgene dose and age. Superscripts indicate significant post hoc results across transgene dose (Student's t-tests, with reduced $\alpha = 0.01$)

a significantly different from same-aged WT
b significantly different from same-aged heterozygote. Region labels correspond to the stereotaxic atlas of Paxinos and Franklin (2001).