

ACQUISITION OF CONDITIONED TASTE AVERSION IS IMPAIRED IN THE AMYLOID PRECURSOR PROTEIN/PRESENILIN 1 MOUSE MODEL OF ALZHEIMER'S DISEASE

P. J. PISTELL^{a,b*} M. ZHU^a AND D. K. INGRAM^{a,b}

^a*Behavioral Neuroscience Section, Laboratory of Experimental Gerontology, National Institute on Aging, National Institutes of Health, Gerontology Research Center, 5600 Nathan Shock Drive, Baltimore, MD 21224, USA*

^b*Nutritional Neuroscience and Aging Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808, USA*

Abstract—Research into the underlying mechanisms of cognitive dysfunction in Alzheimer's disease (AD) has relied traditionally on tasks such as the water maze which evaluate spatial learning and memory. Since non-spatial forms of memory are also disrupted by AD, it is critical to establish other paradigms capable of investigating these deficits. Utilizing a non-spatial learning task, acquisition of conditioned taste aversion (CTA) was evaluated in a mouse model of AD. This line of transgenic mice encode a mutated allele of the human amyloid precursor protein (APP) and presenilin 1 (PS1) genes and exhibit extensive amyloid plaque deposition in the brain by 6–7 mo of age. Compared with wild-type mice, 10–17 month old APP/PS1 mice failed to acquire CTA to saccharin. Mice that only possessed one of the two mutations were able to acquire CTA to the saccharin. In 2–5 month old APP/PS1 mice acquisition of CTA was disrupted despite the lack of extensive plaque deposition. However, further analysis indicated a potential gender difference in both the CTA deficit and onset of plaque deposition with females showing greater conditioned aversion. Published by Elsevier Ltd on behalf of IBRO.

Key words: Alzheimer's disease, learning, transgenic mice, conditioned taste aversion.

Alzheimer's disease (AD) is one of the most prominent neurodegenerative disorders associated with aging. The hallmark symptom of AD is impaired learning and memory function that progresses from mild to severe. AD is characterized pathologically by extra-cellular deposition of beta-amyloid (A β) plaques and intra-cellular neurofibrillar tangles consisting of aggregates of hyperphosphorylated protein tau (Selkoe, 1989; Mandelkow and Mandelkow, 1998). The pathology is first observed in the hippocampal and cortical regions and has been shown to be correlated with deficits in learning and memory (Convit et al., 1997; De Leon et al.,

1997), although this linkage remains controversial (Morgan, 2003).

Over the past decade the use of mice expressing human familial mutations of AD has provided insight into the relationship between the pathological mechanisms and memory impairments (Ashe, 2001). Mice expressing mutations in amyloid precursor protein (APP), presenilin 1 (PS1), presenilin-2 (PS2), tau or apolipoprotein (apoE) have been generated to model various behavioral, physiological, pathological and biochemical aspects of AD (Corder et al., 1998; Ashe, 2000; Lewis et al., 2001; Gordon et al., 2002; Hwang et al., 2002; Jolas et al., 2002; Teter et al., 2002). The mice developed thus far to investigate the pathology and learning and memory associated deficits in AD do not include a mouse that possesses all of the pathophysiology of AD. However, even though they do not model all of the symptoms, these mice have proven useful tools for evaluating the contribution of specific genes to learning and memory deficits as well as potential therapeutics for alleviating these impairments.

The evaluation of learning and memory deficits in these mice to date has focused primarily on hippocampal-dependent spatial tasks, such as the water maze. However, the deficits associated with AD are not limited to spatial information (Pepin and Eslinger, 1989; Hom, 1992). A review of the human literature indicated AD patients display deficits in explicit memory as well as implicit memory deficits for verbal and visuoperceptual information (Carlesimo and Oscar-Berman, 1992). Therefore, it is important to evaluate if particular mouse models exhibit deficits on non-spatial learning and memory tasks involving brain regions other than the hippocampus.

Conditioned taste aversion (CTA) is a simple pavlovian conditioning paradigm evaluating non-spatial learning and can be rapidly acquired in even a single trial. CTA involves pairing the taste of a novel conditioned stimulus, such as a saccharin solution, with an aversive unconditioned stimulus such as nausea. One advantage of CTA is that the pathways for processing of the gustatory conditioned stimulus and unconditioned stimulus information are relatively well-known (for a detailed review see Welzl et al., 2001). Parallel processing of both the conditioned and unconditioned stimulus occurs at the nucleus of the solitary tract, parabrachial nucleus of the pons, parvocellular thalamic ventral posteromedial nucleus, amygdala and agranular insular cortex, indicating that an association between the conditioned stimulus and unconditioned stimulus could form at any of these locations. Other structures that have been implicated in the formation of a CTA include the

*Correspondence to: P. J. Pistell, Nutritional Neuroscience and Aging Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808, USA. Tel: +1-225-763-2739; fax: +1-225-763-0261.

E-mail address: Paul.Pistell@prbc.edu (P. J. Pistell).

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; A β , beta-amyloid; CTA, conditioned taste aversion; PS1, presenilin 1.

hypothalamus (Roth et al., 1973), basal forebrain (Lopez-Garcia et al., 1993) and potentially the noradrenergic system (Dunn and Everitt, 1987). Lesions of the hippocampus impact CTA only mildly, or not at all (Best and Orr, 1973; Murphy and Brown, 1974; Yamamoto et al., 1995). Therefore, CTA appears to be an ideal paradigm for evaluating non-spatial forms of learning, not dependent on hippocampal function, in mouse models of AD.

A recent study investigating CTA in TgCRND8 mice with a double mutation in human APP genes (Janus et al., 2004) found that TgCRND8 mice exhibited a deficit in the acquisition of CTA. Another study reported no acquisition deficits in CTA in P301L transgenic mice exhibiting neurofibrillary tangles by 6 months of age; however, they did not accelerate extinction of the CTA (Pennanen et al., 2004). More recently a study has shown that mice with reduced levels of neprilysin, a major A β degrading enzyme, exhibit weaker CTA that extinguished faster than age-matched controls (Madani et al., 2006). Given these findings, CTA may be a useful model for assessing learning and memory deficits in mouse models of AD, but may depend on the AD-related genes involved.

To further validate CTA as a model to evaluate learning and memory deficits in mouse models of AD, we conducted a series of experiments to evaluate CTA in another mouse model of AD. The mice utilized were double transgenic mice expressing a human familial mutation in both APP_{SWE} and PS1 _{Δ E9}. These mice exhibit A β deposition as well as learning and memory deficits by 6 months of age (Savonenko et al., 2005). The initial experiment was designed to replicate the findings reported by Janus et al. (2004) utilizing 10–17 month old mice after the reported onset of A β deposition. The second experiment examined the contribution of each transgene alone in 9–17 month old mice to assess if the deficit in CTA could be attributed to a single mutated gene, and the final experiment evaluated CTA in mice 2–5 months of age, prior to reported plaque deposition, in an attempt to assess if a deficit in CTA was correlated with A β deposition.

EXPERIMENTAL PROCEDURES

Animals

The mice used for this study were male and female APP_{SWE}/PS1 _{Δ E9} dtg (+/+), heterozygous for APP (+/–) or PS1 (–/+), or wildtype (–/–) mice on a mixed strain background (primarily C57BL/6 and C3He/J), derived from founder mice originally developed and donated by D. Borchelt and colleagues at the Johns Hopkins School of Medicine, Baltimore, MD, USA (Borchelt et al., 1997). The mice were raised in the vivarium at the Gerontology Research Center under controlled experimental conditions (22 \pm 1 °C, 70 \pm 10% humidity) with a 12-h light/dark cycle. All of the procedures were approved by the Animal Care and Use Committee of the Gerontology Research Center and followed the NIH guidelines for the Care and Use of Laboratory Animals. Every effort was made to minimize the number of animals used and their suffering.

Conditioning procedures

At the initiation of the experiments, mice were moved to individual hanging wire cages with solid Plexiglas inserts placed on

the bottom of the cage, and paper bedding was provided to cover the bottom of the cage. The mice had *ad libitum* access to food for the duration of the experiment. Water was provided through two 15 ml tubes attached to the outside of each cage. Access to water was limited to 7 h each day from 08:00–15:00 h. The water intake of mice for the first 30 min was measured, and on average the mice consumed around 1 ml of water during the first 30 min each day. The mice were also weighed each day prior to the bottles being attached to the cages. After 6 days of habituation where only water was provided, mice were given a conditioning day where a 0.5% saccharin solution serving as the conditioned stimulus (saccharin sodium salt, Sigma Chemical Co., St. Louis, MO, USA) was provided in one bottle during the first 30 min period. For the remainder of the 7-h period, water was available in both bottles. The location of the saccharin bottle on the conditioning day was counterbalanced across experimental groups. One hour after the saccharin solution was removed, mice were given an i.p. injection of either lithium chloride (LiCl: 0.14 M, 2% of the body weight; Sigma Chemical Co.: L7026), or a corresponding amount of saline. The LiCl served as the unconditioned stimulus by producing a behavioral malaise. The following day consisted of a recovery period where mice had normal access to water in both bottles. Two days following conditioning, mice were given a two-bottle choice test in which the 0.5% saccharin solution was presented in one bottle with water in the other. The location of the saccharin on the cage was pseudo-randomized across experimental groups and the location of the saccharin solution on the conditioning day. Saccharin intake was expressed as a percentage of the total fluid intake (ml saccharin/(ml saccharin+ml water) \times 100).

The group numbers for the three experiments were: experiment 1 (10–17 month old APP/PS1 or wild-type mice; mean age=14.1): APP/PS1–saline ($N=13$; mean age=13.6); APP/PS1–LiCl ($N=13$; mean age=14.2); wild-type–saline ($N=6$; mean age=15.0); wild-type–LiCl ($N=7$; mean age=14.0); experiment 2 (9–17 month old APP alone, PS1 alone or wild-type mice; mean age=13.4): APP–saline ($N=8$; mean age=13.6); APP–LiCl ($N=9$; mean age=13.5); PS1–saline ($N=8$; mean age=13.6); PS1–LiCl ($N=8$; mean age=13.0); experiment 3 (2–5 month old APP/PS1 or wild-type mice; mean age=3.5): APP/PS1–saline ($N=11$; mean age=3.5); APP/PS1–LiCl ($N=11$; mean age=3.6); wild-type–saline ($N=11$; mean age=3.5); wild-type–LiCl ($N=12$; mean age=3.4). The numbers of males and females were roughly equivalent within groups, and the age range of mice was counterbalanced across groups., e.g. the mean ages for the mice in experiment 1 were: APP/PS1–saline=13.6 months; APP/PS1–LiCl=14.2 months; wild-type–saline=15.0 months; wild-type–LiCl=14.0 months.

Histology

At the completion of the behavioral testing, mice were perfused with phosphate-buffered saline followed by paraformaldehyde. The brains were removed and frozen for sectioning. The brain slices were stained with Congo Red solution and counterstained with Cresyl Violet. The hippocampus, amygdala and cortex were visually examined for the presence of congophilic amyloid deposits, but the number of plaques was not quantified.

Data analysis

Planned comparisons were conducted to evaluate saccharin preference after treatment with saline versus LiCl within each genotype. The critical α level was set at 0.05 for all statistical tests. The values in the figures represent the means \pm S.E.M. The data were analyzed using the SPSS statistical program version 11.0.

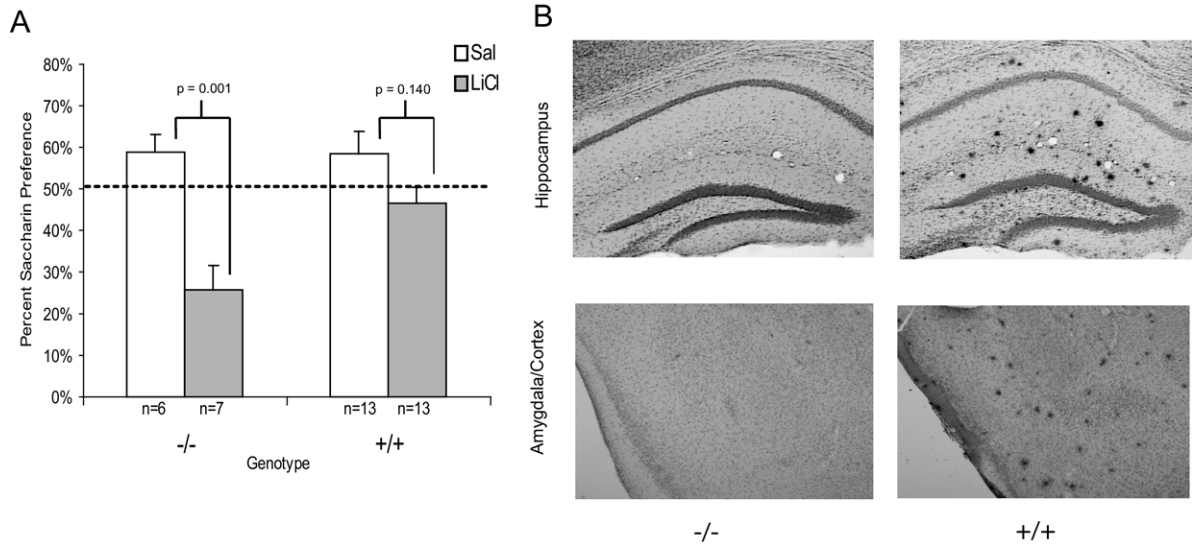


Fig. 1. (A) Mean saccharin preference (± 1 S.E.M.) after LiCl or saline administration in older APP/PS1 and wild-type mice. (B) Images of the hippocampus, amygdala and cortex from representative brains of 10–17 month old APP/PS1 and wild-type mice, stained with Congo Red and counterstained with Cresyl Violet. The images were taken at 5× and then cropped with image editing software. The brains were examined visually and no quantitative analysis was conducted.

RESULTS

CTA in 10–17 month old APP/PS1 mice

Results of *t*-tests indicated 10–17 month old wild-type (-/-) mice administered LiCl exhibited significant avoidance of the saccharin solution during the choice test ($t_{(11)}=4.82$, $P=0.001$) compared with mice given saline (see Fig. 1A). However, for the 10–17 month old APP/PS1 (+/+) mice, there was no significant difference between the saline- and LiCl-injected mice for saccharin preference ($t_{(25)}=1.53$, $P=0.140$), indicating a failure of the 10–17 month old APP/PS1 mice to acquire a CTA. An ANOVA indicated no signif-

icant interaction or main effects for saccharin consumption on the initial conditioning day suggesting no initial group biases for saccharin preference. Histological examination revealed extensive A β deposition in the hippocampus, amygdala and cortex of the 11–17 month old APP/PS1, but not wild-type mice of the same age (see Fig. 1B).

CTA in 9–17 month old heterozygous mice

The results from this study indicated the mice with the APP (+/-) ($t_{(15)}=2.89$, $P=0.01$) or the PS1 (-/+) ($t_{(14)}=3.083$, $P=0.008$) mutation alone administered LiCl exhibited

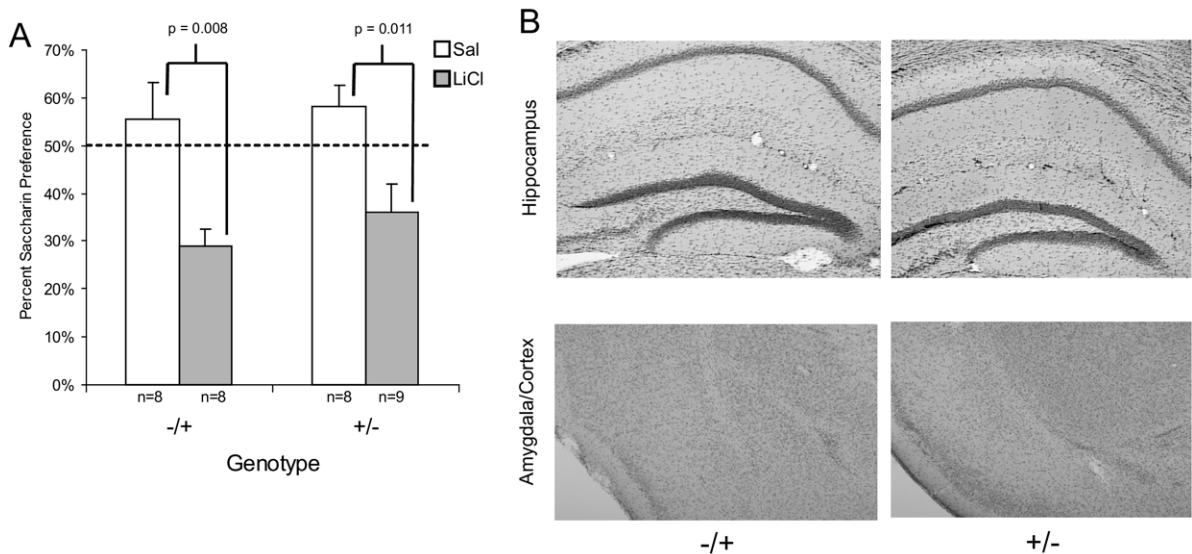


Fig. 2. (A) Mean saccharin preference (± 1 S.E.M.) after LiCl or saline administration in mice with either the mutation in APP (+/-) or PS1 (-/+). (B) Images of the hippocampus, amygdala and cortex from representative brains of 9–17 month old APP (+/-) and PS1 (-/+), stained with Congo Red and counterstained with Cresyl Violet. The images were taken at 5× and then cropped with image editing software.

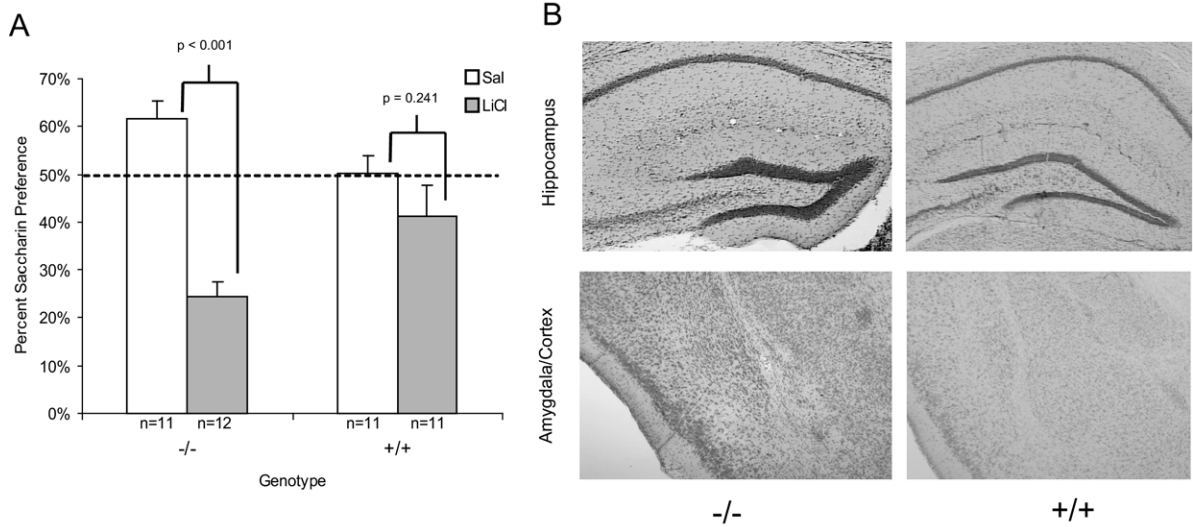


Fig. 3. (A) Mean saccharin preference (± 1 S.E.M.) after LiCl administration in 2–5 month old APP/PS1 and wild-type mice. (B) Images of the hippocampus, amygdala and cortex from representative brains of 2–5 month old APP/PS1 and wild-type mice, stained with Congo Red and counterstained with Cresyl Violet. The images were taken at 5 \times and then cropped with image editing software. The brains were examined visually and no quantitative analysis was conducted.

avoidance of the saccharin solution compared with saline-treated mice (see Fig. 2A). An ANOVA for saccharin consumption on conditioning day suggested no baseline differences in saccharin preference between the groups. Histology showed the lack of A β deposition in the hippocampus, amygdala and cortex of both groups of mice (see Fig. 2B).

CTA in 2–5 month old APP/PS1 mice

Similar to the first experiment with older mice, the 2–5 month old APP/PS1 (+/+) mice treated with LiCl exhibited saccharin preference similar to those treated with saline

($t_{(20)}=1.21$, $P=0.24$) indicating a failure to acquire CTA to the saccharin solution (see Fig. 3A). The wild-type mice of the same age treated with LiCl were able to acquire CTA to the saccharin solution ($t_{(21)}=7.06$, $P<0.001$). Further analysis of the data from this experiment revealed a potential gender difference in the onset of memory deficits in the young APP/PS1 mice. While the 2–5 month old female +/+ mice administered LiCl ($n=5$) exhibited saccharin preference similar to 2–5 month old female +/+ mice administered saline ($n=6$) ($t_{(10)}=0.315$, $P=0.76$), indicating a failure to acquire CTA, the 2–5 month old male +/+

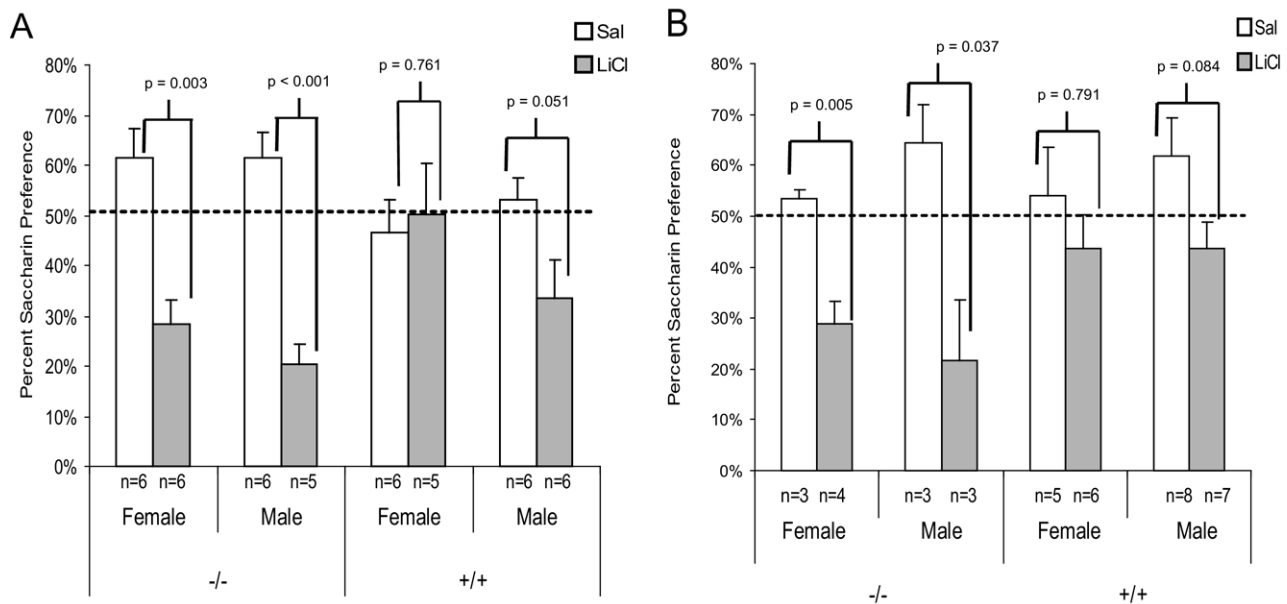


Fig. 4. (A) Mean saccharin preference (± 1 S.E.M.) in 2–5 month old APP/PS1 and wild-type mice from experiment 3 broken into groups by gender and genotype. (B) Mean saccharin preference (± 1 S.E.M.) in 10–17 month old APP/PS1 and wild-type mice from experiment 1 broken down into groups by gender and genotype.

mice administered LiCl ($n=6$), approached, but did not exhibit, significantly different preference from 2–5 month old male $+/+$ mice administered saline ($n=6$) ($t_{(10)}=2.22$, $P=0.051$) suggesting a trend to acquire CTA (see Fig. 4A). This raises the possibility the presence of a gender difference in the age of onset for memory deficits in the APP/PS1 mice. Based on this finding, the data from experiment 1 were further analyzed to evaluate potential gender differences. As shown in Fig. 4B, by 10 months of age (1st experiment) any gender differences appear to have disappeared, since both 10–17 month old male ($t_{(13)}=1.88$, $P=0.08$) and female ($t_{(10)}=0.27$, $P=0.79$) $+/+$ mice failed

to acquire CTA to the saccharin solution. However, it must be noted that the group numbers, when broken down by gender, were rather small making it difficult to reach a substantial conclusion about any potential gender differences. This may be an area warranting future research.

Examination of $A\beta$ deposition in the brains of a subset of the young male and female $+/+$ mice suggested there might be some gender differences in plaque deposition. In general, the 2–5 month old female mice exhibited intermittent $A\beta$ deposition in the hippocampus, amygdala and cortex, while the male 2–5 month old mice had few or no deposits in the same regions (see Fig. 5). This observation might suggest

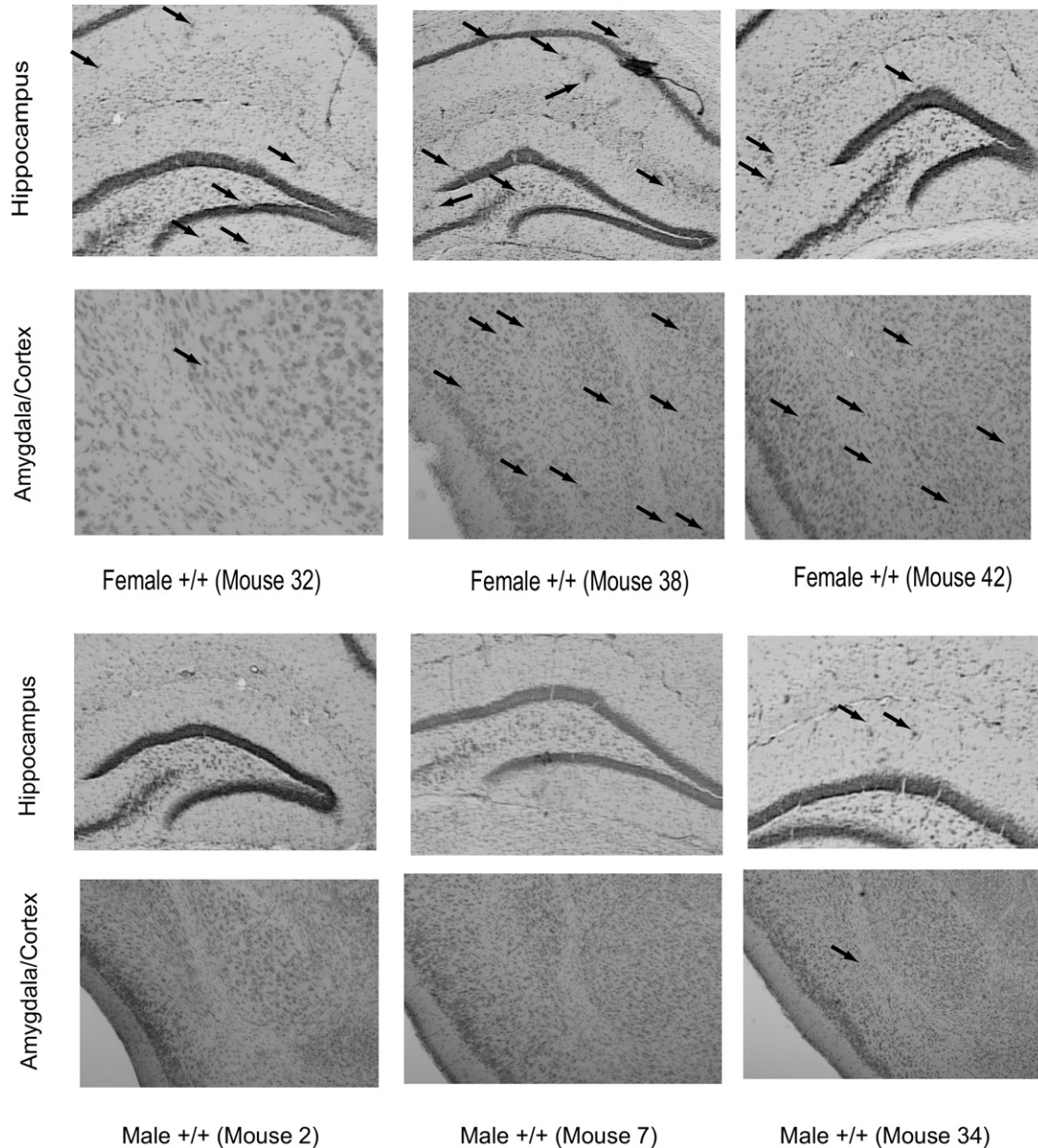


Fig. 5. Images of the hippocampus, amygdala and cortex from representative brains of 2–5 month old male and female APP/PS1 mice, stained with Congo Red and counterstained with Cresyl Violet, showing the sporadic $A\beta$ deposition present in some of the brains. The images were taken at $5\times$ and then cropped with image editing software. The brains were examined visually and no quantitative analysis was conducted. Because the plaques were more difficult to visualize in black and white, for the younger mice, arrows indicate the presence and location of plaques.

that the failure to acquire CTA was correlated with A β deposition. However, examination of CTA in individual animals, and A β deposition in their brains, did not indicate such a correlation. Evaluation of individual brains from 2–5 month old female mice showed that despite the presence of sporadic plaque deposition mouse 42 did acquire CTA, while both mouse 32 and 38 failed to acquire CTA. Within the group of 2–5 month old male brains, both mice without detectable A β deposition (2 and 7) acquired CTA while mouse 34 with sporadic A β deposition failed to acquire CTA. So while among the 2–5 month old male mice, the presence of A β was consistent with the behavioral results, the results were not so clear in the 2–5 month old female mice.

DISCUSSION

Results from the current study indicate CTA is a suitable paradigm to evaluate learning and memory deficits in AD transgenic mice. Similar to results reported by Janus et al. (2004) in TgCRND8 mice, both old (10–17 month) and young (2–5 month) APP/PS1 mice exhibited deficits in CTA. In the case of the old APP/PS1 mice, this deficit only appeared when both the APP and PS1 mutation were present, as mice carrying only the APP or PS1 mutation were capable of acquiring CTA. Importantly, these results, along with others (Janus et al., 2004; Madani et al., 2006), indicate that CTA acquisition deficits are not limited to one transgenic model of AD suggesting that the paradigm is generalizable to a variety of AD models. One interesting discovery was the potential gender difference observed in the 2–5 month old APP/PS1 mice. However, the group numbers for gender comparison were not large enough to reach any conclusions, therefore making it mostly speculative at this point in time.

Another important aspect of the results from the current study, in conjunction with those of Janus et al. (2004), is the ability to study forms of non-spatial learning and memory. CTA is a relatively non-invasive means to evaluate learning and memory using a task where the learning is rapidly acquired (in a single conditioning trial). CTA provides a rapid form of learning that is quickly assessed and does not require a significant training regimen. CTA is also not as sensitive to potential declines in motor function and visual perception, two potential confounds when evaluating behavior in aged mice with paradigms such as the water maze.

One surprising finding from this study was the gender difference that was observed in the young 2–5 month old APP/PS1 +/+ mice. Although based on the examination of the data, it is not possible to prescribe the differences to the presence of A β deposition, there is evidence for gender-based differences in AD pathology in these mice. Wang et al. (2003) evaluated levels of A β 40, A β 42 and A β deposition in hippocampus of 2-, 12- and 17-month old male and female APP/PS1 mice. They found that at each age the female mice had higher levels for all measures. While this still does not provide an explanation of the underlying mechanism involved in the learning deficits, it

does suggest that there may be an accelerated pathology in the female mice that may reflect the earlier onset of CTA deficits and might be one of the reasons that the 2–5 month old female mice, as a group, failed to acquire CTA. While there is an increased risk in women for developing AD, that may be linked to decreases in estrogen levels associated with menopause (Zheng et al., 2002; Yue et al., 2005), the age of the mice where the gender differences occurred suggests a decline in estrogen from menopause is unlikely in this case, making it difficult to easily link a decline in estrogen to the observed behavioral deficit. However, because this study was not designed to evaluate gender differences, and the group sizes when split by gender were too small for adequate assessment, a more directed study would need to be conducted in order to verify the current results.

One debate in research utilizing AD transgenic mice has centered on the relationship between A β deposition and memory deficits. While AD is associated with various amounts of A β deposition, neurofibrillary tangles, changes in synaptic function and neuronal loss, the factors that lead to the onset of these pathological functions remain unclear. In more recent years evidence indicates that prior to A β deposition increased levels of soluble oligomer forms of A β may be toxic to neuronal function and highly correlated with the extent of cognitive dysfunction (Cherny et al., 1999; Lue et al., 1999; Naslund et al., 2000). Electrophysiological studies indicate synthetic or cell-produced forms of soluble A β can inhibit long-term potentiation *in vitro* and *in vivo* (Lambert et al., 1998; Kim et al., 2003), and in various mouse models of AD, cognitive deficits appear before plaque deposition is evident (Ashe, 2005). Although soluble forms of A β were not measured in the current studies, it may be an explanation for the CTA acquisition failure in the young 3–5 month old mice where there was lack of extensive plaque deposition.

Overall it appears that CTA is potentially a reliable paradigm for evaluating non-spatial learning and memory in various mouse models of AD. Along with the current study, deficits in the acquisition or extinction of CTA have been found to be present in more than one AD mouse model (Janus et al., 2004; Pennanen et al., 2004; Madani et al., 2006). Therefore, it may offer a rapidly acquired form of learning that can be used to evaluate potential therapeutic interventions. Based on the gender differences observed in the current study it may be worthwhile to further investigate the mechanisms underlying them. CTA appears to offer an additional viable avenue for investigating AD-induced learning and memory deficits in areas of the brain outside of the hippocampus, but further support would be provided by investigation of CTA in additional mouse models of AD.

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