Brief Communications

Memory Deficits of British Dementia Knock-In Mice Are Prevented by Aβ-Precursor Protein Haploinsufficiency

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Familial British Dementia (FBD) is caused by an autosomal dominant mutation in the *BRI2/ITM2B* gene (Vidal et al., 1999). FBD_{KI} mice are a model of FBD that is genetically congruous to the human disease, because they carry one mutant and one wild-type *Bri2/Itm2b* allele. Analysis of these mice has shown that the British mutation causes memory impairments due to loss of Bri2 function (Tamayev et al., 2010b). BRI2 is a physiologic inhibitor of processing of the Aβ-precursor protein (*APP*; Matsuda et al., 2008), a gene associated with Alzheimer's disease (Bertram et al., 2010). Here we show that *APP* haploinsufficiency prevents memory dysfunctions seen in FBD_{KI} mice. This genetic suppression is consistent with a role for APP in the pathogenesis of memory deficits. Moreover, it provides compelling evidence that the memory dysfunctions caused by the British BRI2 mutant are dependent on endogenous APP and that BRI2 and APP functionally interact. This evidence establishes a mechanistic connection between Familial British and Alzheimer's dementias.

Introduction

Familial British Dementia (FBD) is an autosomal dominant neurodegenerative disease characterized by the early onset of personality changes, memory and cognitive deficits, spastic rigidity, and ataxia, which is caused by a mutation in the *BRI2/ITM2B* gene (Vidal et al., 1999). BRI2 is a type II membrane protein of 266 aa that is cleaved at the C terminus into a peptide of 23 aa (Bri23) plus a membrane-bound mature BRI2 product (Kim et al., 2002; Choi et al., 2004). In FBD patients, a point mutation at the stop codon of *BRI2* results in a read-through of the 3′-untranslated region and the synthesis of a BRI2 molecule containing 11 extra amino acids at the COOH terminus. Cleavage by convertases generates a longer peptide, the ABri peptide, which is deposited as amyloid fibrils. FBD and Alzheimer's patients share common neuropathology including neurodegeneration, amyloid, and neurofibrillary tangles (Vidal et al., 2000; Holton et al., 2001, 2002; Rostagno et al., 2002).

To study the pathogenesis of FBD, we have generated FBD_{KI} mice (Tamayev et al., 2010b). In these knock-in mice, the pathogenic human mutation is inserted in the mouse allele. Thus, this knock-in model is genetically faithful to the human disease. FBD_{KI} mice present severe memory impairments, which are evident at 9 months of age. Interestingly, these mice never develop measurable amyloid lesion or tauopathy (Tamayev et al., 2010b). These memory deficits are instead associated with depletion of mature Bri2 protein levels in FBD_{KI} mice. Of note, a similar decrease in mature BRI2 has also been observed in brain samples from FBD patients (Tamayev et al., 2010b). These data suggested to us that loss of BRI2 function, rather than amyloidosis, plays a prominent role in the pathogenesis of memory loss in FBD. The evidence that *Bri2/Itmb2* haploinsufficient mice present memory deficits similar to FBD_{KI} mice (Tamayev et al., 2010a,b) supports this hypothesis.

BRI2 is a physiological interactor of APP and regulates APP metabolism (Fotinopoulou et al., 2005; Matsuda et al., 2005, 2008, 2011b; Kim et al., 2008; Kilger et al., 2011). Since APP plays a central role in Alzheimer's disease (AD) pathogenesis and mutations in *APP* cause familial forms of AD (Bertram et al., 2010) we postulated that APP mediates memory impairments caused by loss of BRI2 function in FBD. Here we have investigated this hypothesis.

Materials and Methods

Mouse handling

Mice were handled according to the Ethical Guidelines for Treatment of Laboratory Animals of Albert Einstein College of Medicine. The procedures were described and approved in animal protocol number 200404.

Behavior

The animals used for these studies were backcrossed to C57BL/6J mice for at least 14 generations. Only male mice were used to avoid variations due to hormonal fluctuations during the female estrous cycle, which influence severely behavioral and electrophysiological tests.

Spatial working memory

The task studied with the radial arm water maze (RAWM) test has been described previously (Trinchese et al., 2004). The scores for each mouse

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L.D. is an inventor of a patent on the FBD_{KI} mice. The assign is the Albert Einstein College of Medicine. The Albert Einstein College of Medicine has licensed the patent to a Biotech company (Remegenix) of which L.D. is a cofounder.

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on the last 3 d of testing were averaged and used for statistical analysis. Briefly, a six-armed maze was placed into a white tank filled with water (24–25°C) and made opaque by the addition of nontoxic white paint. Spatial cues were presented on the walls of the testing room. At the end of one of the arms was positioned a clear 10 cm submerged platform that remained in the same location for every trial in 1 d but was moved approximately randomly from day to day. On each trial, the mouse started the task from a different randomly chosen arm. Each trial lasted 1 min, and errors were counted each time the mouse entered the wrong arm or needed >10 s to reach the platform. After each error, the mouse was pulled back to its starting position. After four consecutive acquisition trials, the mouse was placed in its home cage for 30 min, then returned to the maze and administered a fifth retention trial.

Visible platform. Visible platform training to test visual and motor deficits was performed in the same pool as in the RAWM; however, the arms of the maze were removed. The platform was marked with a black flag and positioned randomly from trial to trial. Time to reach the platform and speed were recorded with a video tracking system (HVS 2020; HVS Image).

Open field and novel object recognition. After 30 min to acclimate to the testing room, each mouse was placed into a 40 × 40 cm open field chamber with 2-foot-high opaque walls. Each mouse was allowed to habituate to the normal open field box for 10 min, and repeated again 24 h later, in which the video tracking system (HVS 2020; HVS Image) quantifies the number of entries into and time spent in the center of the locomotor arena. Novel object recognition was performed as previously described (Bevins and Besheer, 2006). Results were recorded as an object discrimination ratio, which is calculated by dividing the time the mice spent exploring the novel object, divided by the total amount of time exploring the two objects.

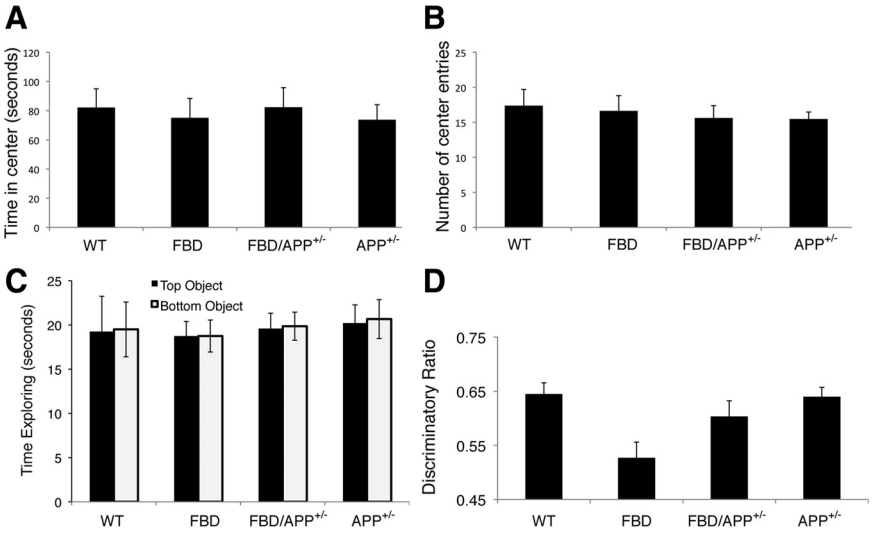

Figure 1. APP haploinsufficiency prevents the Novel object recognition deficit of FBD_{KI} mice. Open field is a sensorimotor test for locomotor, habituation, exploratory, and emotional behavior, including risk assessment and anxiety-like behavior, in novel environments. The time spent in the center (***A***) and the number of entries into the center (***B***) are indicators of anxiety levels. The more the mouse enters the center and explores it, the lower the level of anxiety-like behavior. Since the $APP^{+/-}$, FBD_{KI}, and $FBD_{KI}/APP^{+/-}$ mice are similar to the WT mice, there is no deficit or excess of anxiety. ***C***, All four genotypes (WT, $APP^{+/-}$, FBD_{KI}, and $FBD_{KI}/APP^{+/-}$) mice spent similar amounts of time exploring the two identical objects on day 1. ***D***, WT, $APP^{+/-}$, and $FBD_{KI}/APP^{+/-}$ mice performed similarly in NOR tests (WT vs $APP^{+/-}$, $p = 0.85$; WT vs $FBD_{KI}/APP^{+/-}$, $p = 0.29$; $APP^{+/-}$ vs $FBD_{KI}/APP^{+/-}$, $p = 0.36$), showing that APP haploinsufficiency prevented the novel object recognition deficit of FBD_{KI} mice (FBD_{KI} vs WT, $p = 0.0037$).

Statistical analysis

All data are shown as mean ± SEM. Experiments were performed in blind. Statistical tests included using the *t* test when appropriate.

Homogenates and synaptic membranes preparation

Hippocampal samples from FBD_{KI} mice and WT littermates were prepared by homogenizing the hippocampus (w/v = 10 mg tissue/100 ml buffer) in HEPES-sucrose buffer (20 mM HEPES/NaOH pH 7.4, 1 mM EDTA, 1 mM EGTA, and 0.25 M sucrose) supplemented with protease and phosphatase inhibitors. Homogenates were centrifuged at 800 × *g* for 10 min. The supernatant (S1) was separated into supernatant (S2) and pellet (P2) by spinning at 9200 × *g* for 15 min. P2 was lysed on ice for 30 min in HEPES buffer (20 mM HEPES/NaOH pH 7.4, 1 mM EDTA, and 1 mM EGTA) containing 35.6 mM sucrose. The lysed P2 was separated into supernatant (LS1) and pellet (LP1) by spinning at 25,000 × *g* for 20 min.

Antibodies

The following antibodies were used: α-APP (22C11, Millipore MAB348); α-APP C-terminal fragments (CTF; Invitrogen/Zymed 36–6900); anti-α-tubulin (Sigma 111DM1A); α-BRI2 (Santa Cruz Biotechnology).

Results

APP mediates the recognition memory deficit of FBD_{KI} mice

FBD_{KI} mice develop severe memory deficits that are evident at ~9 months of age (Tamayev et al., 2010b). These deficits are attributable to loss of mature BRI2 protein caused by the FBD mutation in BRI2 (Tamayev et al., 2010b). Because the best-characterized function of BRI2 is to bind to and regulate the processing of APP, and because APP plays a central role in the pathogenesis of AD, we tested whether APP mediates the memory deficits of FBD_{KI} mice. To do this, we used a genetic approach in which we tested whether reducing APP load would prevent memory loss in FBD_{KI} mice. Nine-month-old WT, $APP^{+/-}$, FBD_{KI}, $FBD_{KI}/APP^{+/-}$ mice were first subjected to the standard Open Field test, which is commonly used to assess locomotor, exploratory, and anxiety-like behavior in laboratory animals (rats/mice). The Open Field area consists of an empty and bright square arena, surrounded by walls to prevent the animal from escaping. The animal is placed in the center of the arena and its behavior recorded over a chosen period of 10 min. The Open Field task approaches the conflict between the innate fear that rodents have of the central area of a novel or brightly lit open field versus their desire to explore new environments. When anxious, the natural tendency of rodents is to prefer staying close to the walls (thigmotaxis). In this context, anxiety-related behavior is measured by the degree to which mice avoid the center of the Open Field test. The results showed that the four genotypes spent similar amounts of time in the center (WT vs FBD_{KI}, $p = 0.59$; WT vs $FBD_{KI}/APP^{+/-}$, $p = 0.99$; WT vs $APP^{+/-}$, $p = 0.47$; FBD_{KI} vs $FBD_{KI}/APP^{+/-}$, $p = 0.60$; FBD vs $APP^{+/-}$, $p = 0.91$; $FBD_{KI}/APP^{+/-}$ vs $APP^{+/-}$, $p = 0.51$, Fig. 1*A*) and that they entered the center the same number of times (WT vs FBD_{KI}, $p = 0.74$; WT vs $FBD_{KI}/APP^{+/-}$, $p = 0.36$; WT vs $APP^{+/-}$, $p = 0.28$; FBD_{KI} vs $FBD_{KI}/APP^{+/-}$, $p = 0.60$; FBD vs $APP^{+/-}$, $p = 0.49$; $FBD_{KI}/APP^{+/-}$ vs $APP^{+/-}$, $p = 0.92$, Fig. 1*B*). Moreover, WT and FBD_{KI} mice showed similar total track lengths ($p = 0.94$) and vertical activity ($p = 0.76$).

After the open field studies showed that $APP^{+/-}$, FBD_{KI}, $FBD_{KI}/APP^{+/-}$ mice have no defects in habituation and locomotor behavior, and anxiety-like behavior in novel environments,

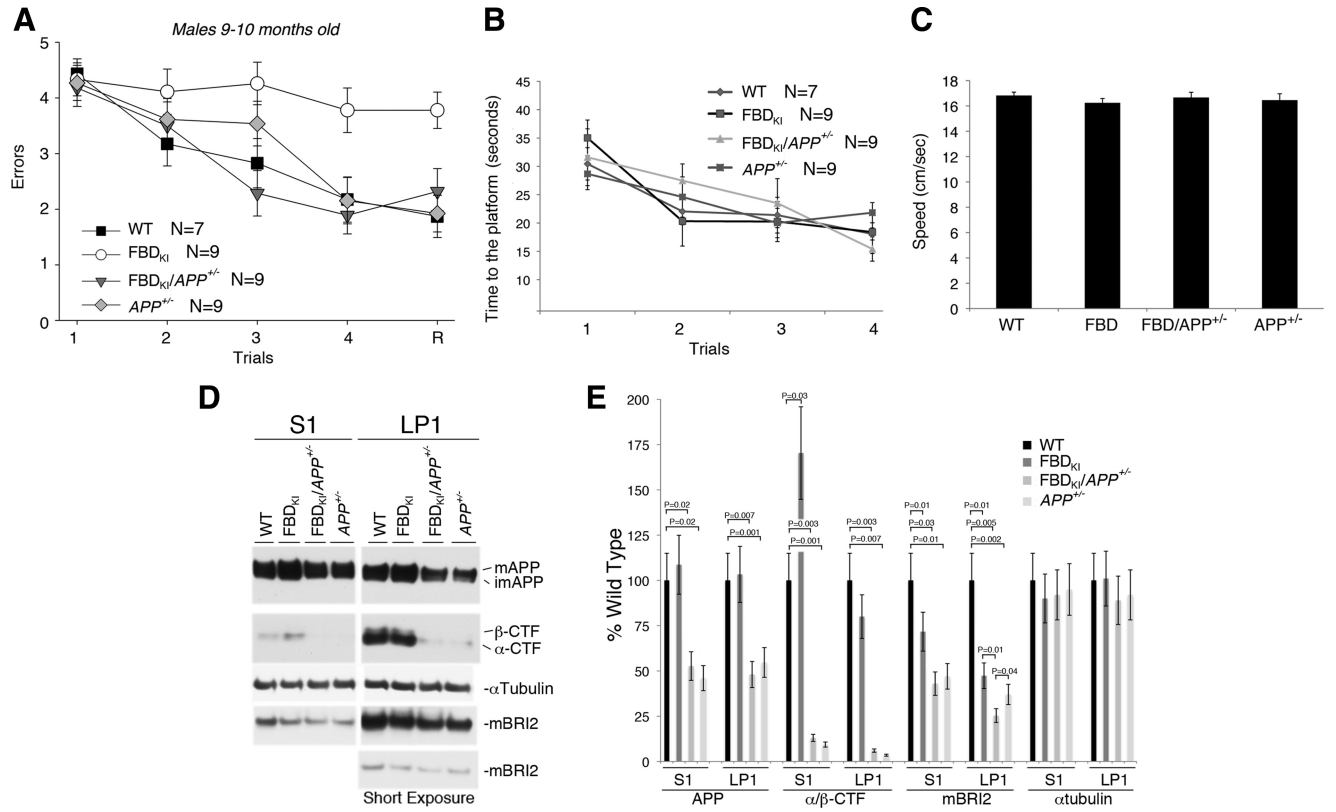

Figure 2. APP haploinsufficiency prevents the working-memory deficits of FBD_{KI} mice. ***A***, In RAWM testing, $APP^{+/-}$ and $FBD_{KI}/APP^{+/-}$ mice made the same number of errors as WT mice. FBD_{KI} mice made significantly more errors at A3 (vs $FBD_{KI}/APP^{+/-}$ $p = 0.0008$; vs WT $p = 0.018$), A4 (vs $APP^{+/-}$ $p = 0.0075$; vs $FBD_{KI}/APP^{+/-}$ $p = 0.0006$; vs WT, $p = 0.0074$) and R (vs $APP^{+/-}$ $p = 0.0002$; vs $FBD_{KI}/APP^{+/-}$ $p = 0.0071$; vs WT, $p = 0.0004$). ***B***, $APP^{+/-}$, FBD_{KI}, and $FBD_{KI}/APP^{+/-}$ mice have similar swimming speeds as the WT mice. ***C***, $APP^{+/-}$, FBD_{KI}, and $FBD_{KI}/APP^{+/-}$ mice needed similar time to reach a visible platform. Overall, the data show that *APP* haploinsufficiency prevents the insurgence of working memory deficits in FBD_{KI} mice. ***D***, APP, β-CTF, and α-CTF levels are reduced in both S1 and LP1 fractions of $FBD_{KI}/APP^{+/-}$ and $APP^{+/-}$ mice. Mature BRI2 levels are reduced in FBD_{KI} mice, as previously reported. Surprisingly mBRI2 expression in halved in $APP^{+/-}$ mice and further reduced in synaptic membranes of $FBD_{KI}/APP^{+/-}$ animals. ***E***, Quantization of triplicates. The expression of each protein in the WT sample has been set to an arbitrary value of 100. Expression of the same protein in the same fraction of the other genotypes has been expressed as a percentage of the WT levels.

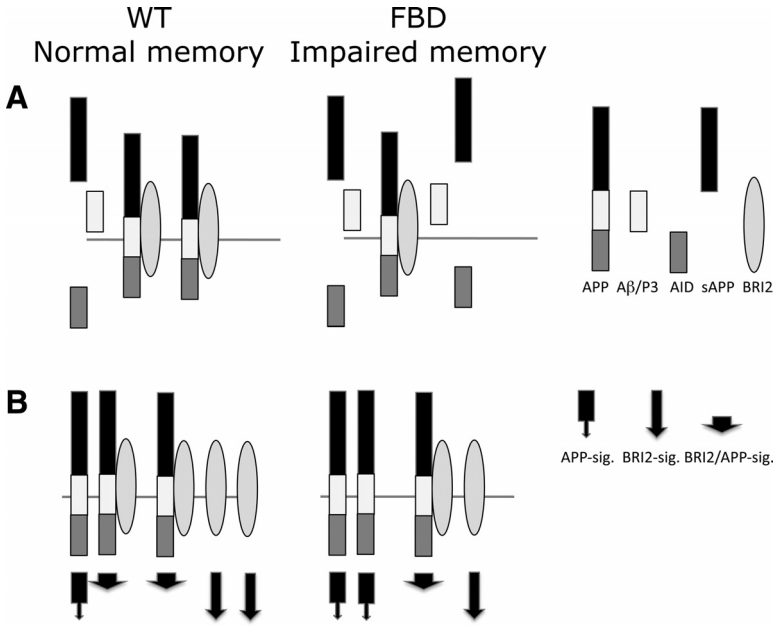

Figure 3. Models depicting the mechanisms by which APP leads to memory deficits in FBD. ***A***, In this model, memory deficits in FBD are caused by the increased production of toxic APP-derived metabolites due to loss of inhibitory function of APP processing by BRI2. Bri2, APP, and the APP derived metabolites [soluble APP (sAPP), Aβ, P3, and the APP intracellular domain (AID)] are schematically represented. ***B***, Alternatively, membrane bound BRI2, APP, and APP/BRI2 complexes could regulate distinct signaling pathways (indicated as APP-sig., BRI2-sig., and BRI2/APP-sig.). In FBD, the reduction of BRI2 levels result in a "signaling unbalance" leading to synaptic and memory dysfunction.

we tested memory using novel object recognition (NOR), a nonaversive task that relies on the mouse's natural exploratory behavior. During the training session, mice of all genotypes spent the same amount of time exploring the two identical objects (Fig. 1*C*). The following day, when a novel object was introduced, FBD_{KI} spent the same amount of time exploring the two objects as if they were both novel to them, while the WT and $APP^{+/-}$ mice still spent more time exploring the novel object (Fig. 1*D*). Notably, $FBD_{KI}/APP^{+/-}$ mice behaved like the WT mice and explored preferentially the novel object (Fig. 1*D*). These data confirm that memory is impaired in FBD_{KI} mice upon aging in an ethologically relevant, nonaversive behavioral context; remarkably, development of this deficit is fully prevented by *APP* haploinsufficiency.

The short-term memory deficit of FBD_{KI} mice is mediated by APP

Next, we performed a spatial working memory test such as the RAWM, which depends upon hippocampal function (Di-

amond et al., 1999) and tests short-term memory, a type of memory that is affected at early stages of AD. Mice were required to learn and memorize the location of a hidden platform in one of the arms of a maze with respect to spatial cues. WT and $APP^{+/-}$ mice were able to acquire (A) and retain (R) memory of the task. FBD_{KI} mice showed severe abnormalities during both acquisition and retention of the task (Fig. 2*A*), confirming that FBD_{KI} mice have severe impairment in short-term spatial memory for platform location during both acquisition and retention of the task. Once again, halving APP expression prevented the development of short-term spatial memory in FBD_{KI} mice (Fig. 2). Importantly, none of the four genotypes showed an anxiety phenotype and the absence of search behavior such as floating or thigmotaxis (swimming constantly along the perimeter of the pool).

A visible platform test was performed to determine whether genotypic manipulations resulted in crude alterations in visual acuity and/or locomotory activity that might confound the analyses of data that depend on the use of distal visual cues and swimming ability for task performance. Testing with the visible platform showed no difference in the time needed to find the platform (WT vs FBD_{KI}, $p = 0.89$; WT vs $FBD_{KI}/APP^{+/-}$, $p = 0.36$; WT vs $APP^{+/-}$, $p = 0.38$; FBD_{KI} vs $FBD_{KI}/APP^{+/-}$, $p = 0.37$; FBD vs $APP^{+/-}$, $p = 0.48$; $FBD_{KI}/APP^{+/-}$ vs $APP^{+/-}$, $p = 0.91$; Fig. 2*B*), and swimming speed (WT vs FBD_{KI}, $p = 0.20$; WT vs $FBD_{KI}/APP^{+/-}$, $p = 0.77$; WT vs $APP^{+/-}$, $p = 0.53$; FBD_{KI} vs $FBD_{KI}/APP^{+/-}$, $p = 0.48$; FBD vs $APP^{+/-}$, $p = 0.74$; $FBD_{KI}/APP^{+/-}$ vs $APP^{+/-}$, $p = 0.73$; Fig. 2*C*), among the four genotypes. Thus, the RAWM deficits of FBD_{KI} are a deficit in memory *per se* and are not due to deficits in vision, motor coordination, or motivation. Together, these findings provide compelling genetic evidence that APP and BRI2 functionally interact, and that the synaptic and memory deficiencies due to loss of Bri2 function in FBD_{KI} mice only occur when sufficient levels of APP are supplied.

To verify that *APP* hemizygosity results in halving APP expression, we prepared hippocampal total lysates (S1) and purified synaptic membrane fractions (LP1) from WT, $APP^{+/-}$, FBD_{KI}, and $FBD_{KI}/APP^{+/-}$ mice. As shown in Figure 2, *D* and *E*, APP levels were reduced by ~50% in $APP^{+/-}$ and $FBD_{KI}/APP^{+/-}$ mice compared with WT littermates, both in S1 and synaptic membrane fractions. As expected, WT and FBD_{KI} expressed similar levels of APP. We also tested the expression levels of β-CTF and α-CTF, the two C-terminal fragments derived from cleavage of APP by β- and α-secretases, respectively. First, we noticed that α/β-CTFs are significantly enriched in synaptic membrane fractions compared with total lysates. Moreover, we found a ~90% and ~95% reduction in α/β-CTFs in S1 and LP1 preparations from $APP^{+/-}$ and $FBD_{KI}/APP^{+/-}$ mice (Fig. 2*D*,*E*). Why this reduction is larger that what would be expected by halving expression of the precursor of these fragments is unclear. However, this observation is interesting given the recent finding that β-CTF plays a pathogenic role in the Danish dementia (Tamayev et al., 2011a).

Next we tested whether reduced APP expression could rescue the behavioral deficits in FBD_{KI} mice by restoring normal levels of mBRI2 expression. Interestingly, APP hemizygosity reduces mBRI2 expression both in mice WT for *Bri2/Itm2b* and FBD_{KI} mice (Fig. 2*D*,*E*). These results further underline the close functional and biochemical relationship between APP and BRI2 and suggest that APP can stabilize BRI2. Regardless, they exclude that halving APP can restore normal mBRI2 functions.

Discussion

Here, we have investigated whether APP plays a role in the pathogenesis of memory impairments in FBD_{KI} mice. The evidence of genetic suppression of cognitive deficits by *APP* haploinsufficiency shows that FBD pathogenesis is attributable to APP. Because BRI2 is a physiological inhibitor of APP processing, and given the loss of mature Bri2 in FBD_{KI} mice, a possible interpretation of our data is that deregulation of APP processing causes memory loss in FBD (Fig. 3*A*). This model is supported by the analysis of a knock-in mouse model for the other familial dementia (Familial Danish dementia, FDD_{KI} mice; Giliberto et al., 2009) caused by mutation of the *BRI2/ITM2b* gene (Vidal et al., 2000). FDD_{KI} mice present reduction in mature Bri2 levels in synaptic compartments (Tamayev et al., 2010a) and an increase in APP processing in the CNS (Matsuda et al., 2011a; Tamayev et al., 2011b). These animals develop progressive hippocampal memory deficits that are dependent on APP (Tamayev et al., 2011b) and, more specifically, on APP processing by β-secretase (Tamayev et al., 2011a). However, analysis of the whole brains of FBD_{KI} mice did not reveal obvious signs of APP processing alterations (data not shown). It should be noted that the Danish mutation causes a more dramatic reduction in mature Bri2 levels in synaptic preparation; synaptic mature Bri2 is reduced by ~80% in FDD_{KI} mice and ~25% in FBD_{KI} animals (Tamayev et al., 2010a,b). Therefore, it is possible that APP processing is altered less dramatically in FBD, and that this reduction cannot be detected when analyzing the steady-state levels on endogenous APP metabolites in the CNS. The recent finding that memory deficits of FDD_{KI} mice can be rescued by inhibiting β-secretase cleavage of APP (Tamayev et al., 2011a) supports this hypothesis. Alternatively, it could be postulated that APP, BRI2, and APP/BRI2 complexes deliver distinct signals. In FBD, an augmentation of APP-signaling and a reduction of BRI2-signaling and APP/BRI2-signaling could lead to memory deficits (Fig. 3*B*). In both models, reducing APP load would reconstitute normal signaling.

In conclusion, here we show that endogenous APP is implicated in the pathogenesis of FBD. This evidence underlies strong analogies between FBD and Familial Alzheimer disease pathogenesis, where *APP* itself or genes that regulate APP processing (i.e., *PSEN1/2*) are mutated. These data suggest that the FBD_{KI} mice could prove useful to study the pathogenic mechanisms of APP and/or proteolytic APP products. Additionally, this mouse model could help in testing disease-modifying therapeutic intervention strategies for resulting dementias.

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