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Age- and sex-dependent profiles of APP fragments and key secretases align with changes in despair-like behavior and cognition in young APPSwe/Ind mice

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ABSTRACT

Biological sex exerts distinct influences on brain levels of the β-amyloid (Aβ) peptide in both clinical depression and Alzheimer disease (AD), yet studies in animal models focus primarily on males. We examined behavioral 'despair'/depression (using the tail-suspension test) and memory (using the novel object recognition task) in J20 ($hAPP_{Swe/Ind}$) mice. Three month-old male (but not female) J20 mice exhibited less despair-like behavior, but more evidence of cognitive deficits. In young J20 mice, only soluble Aβ peptides −primarily Aβ(1−40)− were detected. There was no evidence of an effect on despair-like behavior in the six month-old J20 mice, although cognitive deficits were now evident in both sexes, and coincided with a greater proportion of the neurotoxic Aβ(1−42) species (in soluble as well as insoluble fractions). This age-dependent shift in Aβ peptide profile coincided with reduced expression of glycosylated species of ADAM-10 (α-secretase) and BACE1 (β-secretase), and an increased co-immunoprecipitation of presenilin-1 with nicastrin (components of the γ-secretase complex). Sex-dependent changes in depression-related monoaminergic, *e.g.* serotonin and dopamine (but not noradrenaline), systems were evident already in young J20 mice.

It is critical to acknowledge that sex-dependent APP-related phenotypes might differentially influence modifiable depression-related monoaminergic signalling at some of the earliest pathological stages of clinical AD.

1. Introduction

The β-amyloid (Aβ) peptide aggregates in the form of plaque, which is used for the neurohistological confirmation of a diagnosis of Alzheimer disease (AD) and has been promoted as a causative factor in AD [1]. Yet, a 'one size fits all' *anti*-Aβ strategy, while ideal, is highly unlikely as unsuccessful clinical trials highlight the complexity of the disease process as well as the need to consider nonamyloidogenic targets, particularly in earlier stages of the disease [2].

AD-related substitutions in the gene encoding for the Amyloid Protein Precursor (APP) have contributed important insight into the role of Aβ in cognition. APP can be cleaved by β-secretase/BACE1, after which it is cleaved by the γ-secretase complex to yield Aβ. Alternatively APP can be cleaved by α-secretase/ADAM-10, which targets the Aβ sequence and precludes an intact Aβ fragment. AD is associated with more amyloidogenic processing of APP as well as with a shift from generation of the shorter physiological Aβ(1−40) peptide to the hydrophobic and neurotoxic Aβ(1−42) peptide that eventually aggregates into plaques.

Symptoms of depression (*e.g.*, altered sleep, cognitive & memory deficits) can often be mistaken as signs of dementia/early stage AD [3] and Aβ might factor into the progression of both diseases. Indeed, a low plasma ratio of Aβ(1−42)/Aβ(1−40) −believed to reflect the progressive retention and aggregation of Aβ(1−42) into plaque in brain [4]− is observed in depressed patients and might

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predispose to dementia [5,6], and amyloid plaques are detectable in the brains of middle-aged, mildly depressed [but not demented] patients [7]. However, discrepancies do exist; for instance, CSF levels of Aβs have been reported to be similar in depressed patients and in AD patients [8,9], yet elderly women with depression appear to have higher CSF Aβ(1–42) levels than women with AD [10]. The Framingham study found an increased incidence of AD in individuals who were depressed at baseline [11], which supports other evidence that depression might increase risk for AD-related cognitive dysfunction [12–15]. Our own work reveals sex-dependent differences in Aβ(1–42)/Aβ(1–40) profiles and related secretases [16] as well as in the expression of depression-related proteins –*e.g.* the serotonin transporter [17] and monoamine oxidases [18]– in autopsied AD brain samples.

Any overlap in pathological mechanisms between depression and AD support sex-dependent differences, yet preclinical studies invariably focus on males, as the estrous cycle is often viewed as a confound in any phenotypic screening [19]. We investigated how sex might influence APP processing in a mouse model of AD and whether any differences align with cognitive and/or depressed-like phenotypes.

2. Materials and methods

2.1. Antibodies and reagents

The 6E10 antibody [targets Aβ(1–16): cat# SIG-39320] and the 4G8 antibody [targets Aβ(17–24): cat# SIG-39220] were obtained from Cedarlane Laboratories Ltd. The IgG-HRP conjugates were obtained from Bio-Rad Laboratories Ltd. The 22C11 antibody [recognizes residues 66–81 of APP: cat# MAB348], the anti-ADAM-10 antibody [cat# AB19026], and antibodies raised against components of the γ-secretase complex, *i.e.* presenilin-1 [loop region: cat# MAB5232] and Nicastrin [cat# MAB5556], were obtained from Millipore. The anti-BACE1 (cat# D10E5) antibody was obtained from Cell Signalling Technology and the antibody raised against the C-terminal region of human APP695 (amino acids 676–695: cat# A8717) was obtained from Sigma-Aldrich. Protein-A/G sepharose and the enhanced chemiluminescence kit were obtained from GE Healthcare Bio-Sciences Inc. Buffer constituents were obtained from commercial sources.

2.2. The APP mouse

The B6.Cg-Tg(PDGFB-APPSwInd)20Lms/2Mmjax (J20) mouse strain (#006293: Jackson Laboratory) carries a human APP_{695} transgene harboring the aggressive Swedish and Indiana substitutions. Animal work –based on heterozygous J20 mice and their wildtype (WT) littermates– was approved by the University of Saskatchewan's Animal Research Ethics Board (protocols 20040068 & 20060070) and adhered to the Canadian Council on Animal Care guidelines for humane animal use.

2.3. Assessment of depression-like and cognitive phenotypes

Behavioral 'despair' (depression-like behavior) was assessed using the tail-suspension test (TST) [20], which relies on the premise that rodents, if placed in an 'inescapable' situation, will eventually develop an immobile posture that has been likened to 'despair'. Briefly, mice were suspended by the tail 15 cm from a surface and following a 2-min acclimation period, immobility was monitored for a 4-min test period.

Mice were also subjected to the novel object recognition (NOR) memory task. Briefly, mice were left to explore two identical test objects for a period of 10 min daily over three consecutive days (habituation period). One day after the last habituation, the mice were presented with two objects, one familiar and one novel. Memory of the familiar object should result in the mice spending more time exploring the novel object.

In both tests, trials were videotaped and scored by 2–3 observers (blinded to the mouse's genotype) for the time mice spent immobile (TST) or the relative time mice spent exploring each object (NOR).

2.4. High performance liquid chromatography

Mouse brains were regionally dissected, snap-frozen, and stored at −70 °C until processed for either immunodetection (see below) or monoaminergic transmitters based on our reported protocol using reverse phase high performance liquid chromatography (HPLC) with electrochemical detection [18]. Amino acid levels were determined using precolumn derivatization with *ortho*-phthaladehyde and *N*-isobutyl-L-cysteine followed by HPLC with fluorimetric detection [21]. Peak height ratios of a set of authentic standards processed in parallel were used to quantify tissue concentrations of analytes in all runs.

2.5. Immunodetection and immunoprecipitation

Brain samples (20–30 mg wet weight) were homogenized in 20 vol of ice-cold RIPA buffer containing a protease inhibitor cocktail (Sigma-Aldrich) and centrifuged at 12,000×*g* (10 min; 4 °C). An aliquot of the supernatant was used for protein determination. This RIPA-*soluble* fraction was used for immunodetection of full length-APP (FL-APP) and the major secretases involved in APP processing, *i.e.* BACE1/β-secretase, ADAM-10/α-secretase, and PS-1 (and nicastrin)/γ-secretase. Proteins (15–20 μg/lane) were resolved on 10% or 12% SDS-PAGE systems [16]. This fraction was also used to isolate various soluble APP fragments. First, the fraction was immunodepleted of FL-APP by immunoprecipitation with a C-terminally-directed antibody and then immunoprecipitated using the 6E10 antibody; the 6E10-immunocomplex was resolved either on a 10% SDS-PAGE for detection of the sAPPα fragment [using the 22C11 antibody] or on a discontinuous 8 M urea gel system [16] for detection of Aβ peptides [using the 6E10 antibody]. The 6E10-immunodepleted supernatant was resolved on a 10% SDS-PAGE system and probed with the 22C11 antibody for detection of the sAPPβ fragment.

Pellets from the initial RIPA lysate centrifugation above were dissolved in 5 M guanidine.HCl (1:20, wt:vol; RT, 2hr). This *insoluble* fraction was diluted with TBS (1:1, vol:vol) and, as above, Aβ peptides were separated by sequential immunodepletion and immunoprecipitation based on 300 μg of input protein.

2.6. Statistical analyses

Data ($n = 6–15$/group) were analyzed using ANOVA and $P < 0.05$ as the criterion for significance. *Post hoc* analysis relied on Tukey's Multiple Comparisons test.

3. Results

3.1. Assessment of depression-like and cognitive phenotypes

The TST revealed an unanticipated *decrease* in time spent immobile (suggesting a *reduction* in 'despair') in young male J20 mice *versus* their WT littermates, which was not observed in the older male J20 mice (*e.g.* at 6 months of age) (Fig. 1). A similar trend in female J20 mice just barely reached significance. Cognitive deficits were observed in young male (but not female) J20 mice, while

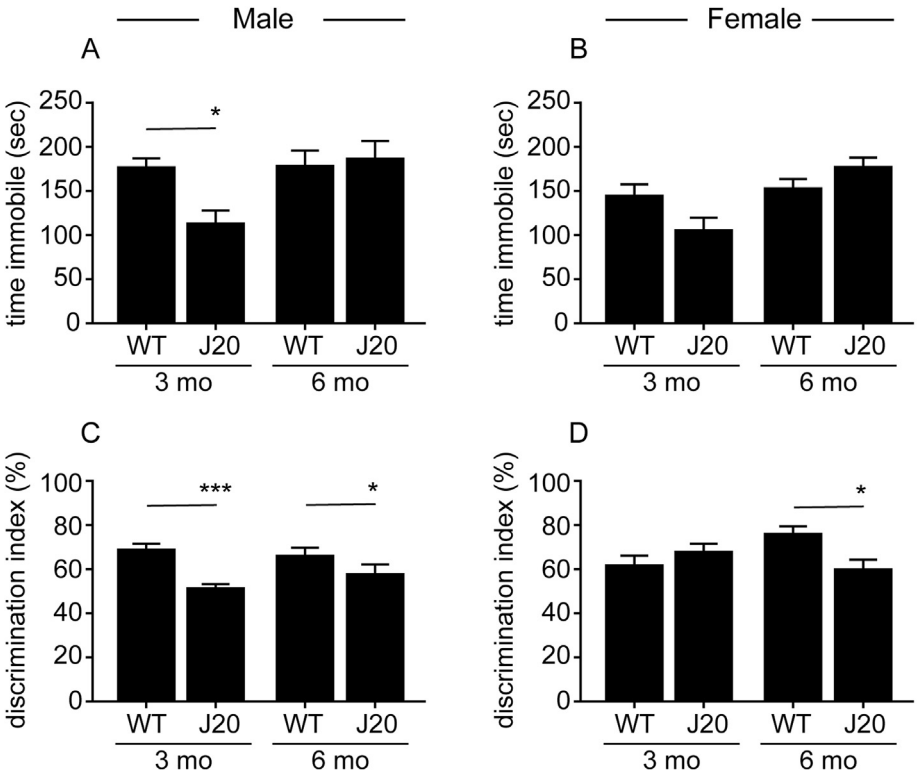

Fig. 1. Behavioral and cognitive phenotypes in young and old J20 mice.
Despair (depression-like) behavior was assessed using the tail-suspension test in (A) male [$F(3,45) = 4.502$, $P = 0.0076$] and (B) female [$F(3,33) = 2.833$, $P = 0.0533$] three month-old (3mo) and six month-old (6mo) wildtype (WT) and APP heterozygous (J20) mice. Memory was assessed in the same (C) male [$F(3,37) = 6.655$, $P = 0.0010$] and (D) female [$F(3,18) = 6.279$, $P = 0.0042$] mice using the novel object recognition paradigm. *: $P < 0.05$; ***: $P < 0.001$.

cognitive deficits were observed in the older J20, regardless of sex (Fig. 1).

3.2. Detection of APP, Aβ peptides, and related secretases

Extracts from frontocortical samples representing each age, sex, and genotype were examined for expression of selected proteins. There was an age-dependent loss of a high-molecular weight (~107 kDa) species of ADAM-10 (α-secretase) in both males and females, regardless of genotype (Fig. 2). Similarly, an age-dependent loss of a higher molecular weight (~110 kDa) species of BACE1 was observed, regardless of sex or genotype. Although the expression of nicastrin was also weaker with age (again, regardless of sex or genotype) and expression of presenilin-1 was unchanged with age, the co-immunoprecipitation of nicastrin and presenilin-1 was far more evident in the older mice, particularly the male mice (Fig. 2).

The levels of expression of FL-APP were not uniform across J20 mice (Fig. 3). Levels of the α-secretase-mediated, soluble N-terminal sAPPα fragment were generally higher in the young mice, and surprisingly did not always adhere to genotype. In older mice, sAPPα tended to be detected more specifically in the J20 mouse extracts (Fig. 3). Levels of the β-secretase-mediated, soluble N-terminal sAPPβ fragment were unaltered by age and this fragment was more evident in the J20 mouse extracts.

RIPA-soluble Aβ peptides were detected in both young and older J20 mice, with a stronger representation by the physiological Aβ(1–40) species in young J20 mice (Fig. 3) and a proportionally greater representation by the neurotoxic Aβ(1–42) species in older J20 mice. In some of the extracts from older J20 mice, Aβ peptides were also detected in the guanidium/insoluble fraction. These patterns were more evident in the corresponding hippocampal extracts (Fig. 3).

The β-secretase-mediated C99 and the α-secretase C83 C-terminal fragments were both detectable in male cortical and hippocampal samples, but the C99 fragment could not be detected in female samples, regardless of age or brain region (Fig. 4).

Cortical samples were also assayed for levels of monoamines. The ratio of 5-hydroxyindoleacetic acid (5-HIAA) to 5-HT, an index of serotonin (*i.e.* 5-HT) turnover, was lower in the 6-month old male mice, regardless of genotype [$F(3,41) = 3.285$, $P = 0.0301$] (*data not shown*). In contrast, the 5-HIAA/5-HT ratio was no different between young and older female WT mice, but was significantly increased in the young J20 mice compared to their wildtype littermates [$F(3,28) = 3.425$, $P = 0.0303$]. Dihydroxyphenylacetic acid (DOPAC), a product of dopamine oxidation *via* monoamine oxidase, and homovanillic acid (HVA), a product of dopamine metabolism *via* catechol-*O*-methyltransferase and monoamine oxidase, were also measured. The DOPAC/HVA ratio was near unity in male cortical samples, regardless of age or genotype [$F(3,41) = 0.1160$, $P = 0.9503$]. In contrast, the DOPAC/HVA ratio was 0.31 in young female WT mice and increased to 0.78 in female J20 littermates, whereas the ratio was 1.11 in older female WT mice and increased to 1.53 in the corresponding female J20 mice [$F(3,29) = 5.800$, $P = 0.0031$] (*data not shown*). The levels of noradrenaline remained unchanged in both males [$F(3,42) = 0.5379$, $P = 0.6596$] and females [$F(3,29) = 0.9432$, $P = 0.4325$], regardless of age and/or genotype (*data not shown*). Levels of D-serine or glutamate were unaffected by sex, age, or genotype, whereas there was an age-dependent increase in levels of GABA in female WT mice, which was exaggerated in female J20 mice [$F(3,22) = 4.395$, $P = 0.0144$] (*data not shown*).

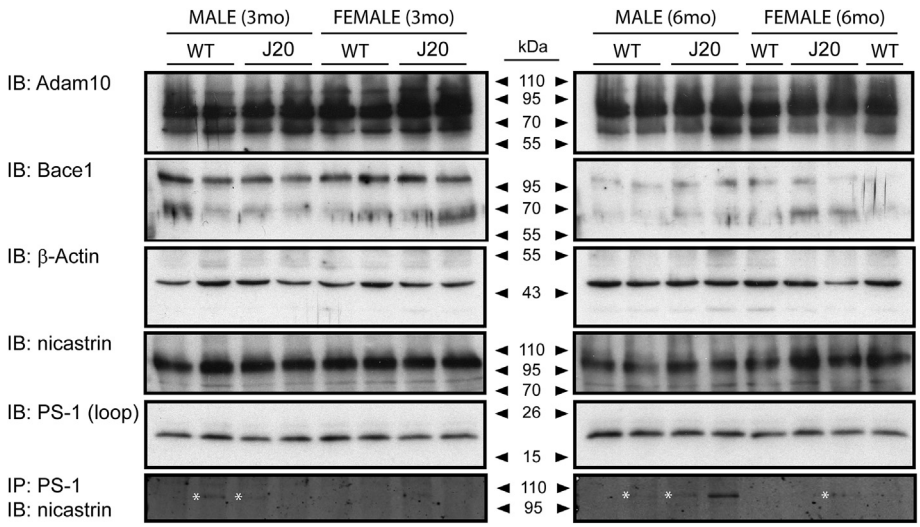

Fig. 2. Expression of APP-relevant secretases.
Cortical protein extracts were immunoblotted for α-secretase (ADAM-10), β-secretase (BACE1) and γ-secretase (Presenilin-1 (PS1) and nicastrin) (labels as in Fig. 1). White asterisks identify weaker signals in the PS-1:nicastrin co-immunoprecipitation (IP) blot. kDa: molecular weights (ladder) in kiloDalton.

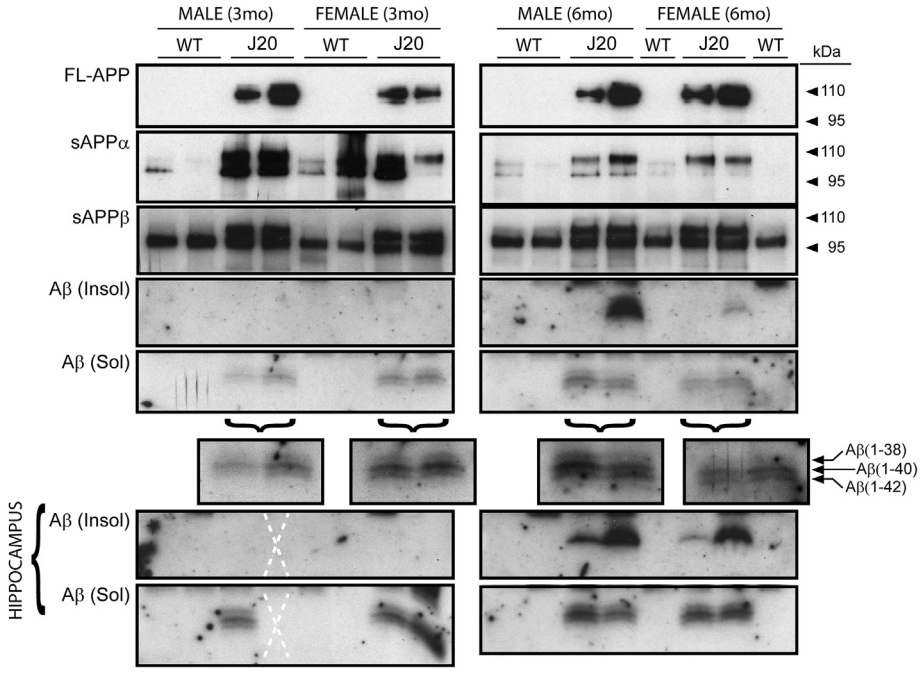

Fig. 3. APP fragments in young and old J20 mice.
Cortical protein extracts were assayed for FL-APP (Full Length-APP), sAPPα, sAPPβ, and Aβ peptides (in the soluble and insoluble fractions). Aβ peptides extracted from corresponding hippocampal fractions ('X' indicates sample lost in initial step) included for comparison. Labels as in Fig. 2.

4. Discussion

Studies of the neurobiology (and potential interventions) in hAPP mice are often biased towards older animals, wherein any amyloidogenic phenotype is stronger. This bias tends to extend to many studies attempting to associate any depression-related risk phenotype with progression of neuropathology in these models [22].

We confirm the early-onset, and sustained, deficits in the NOR memory task previously reported for young male J20 mice [23], but we did not observe any cognitive deficits in young female J20 mice. Cognitive deficits were evident in older J20 mice (regardless of sex). Harris' study also found an increase in anxiety-like behavior in young J20 mice, which was still evident in older mice, although the effect size had diminished [23]. We observed that young J20 mice (males and, to a lesser extent, females) exhibited a decrease in 'despair'/depression, which also diminished (was lost) in older mice. This is in contrast to previous reports wherein young (2–4 months) TgCRND8 $APP_{Swe/Ind}$ mice did not exhibit any despair phenotype [24], although despair was evident in older (6–7 months) TgCRND8 [24] and (10 months) 3xTg-AD [25] mice. In all three of these reports [23–25], there was a dissociation between aggregated Aβ burden and any behavioral phenotype. We could only detect Aβ peptides in the soluble fraction of young J20 mice

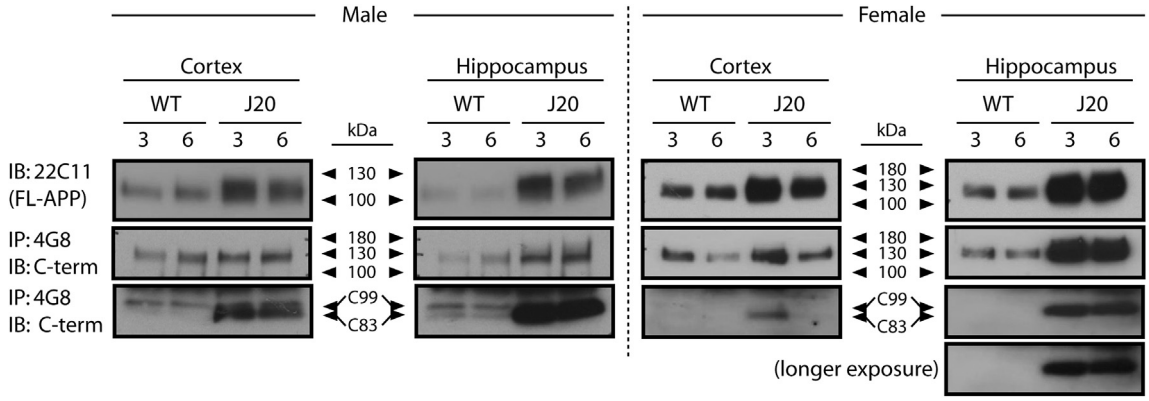

Fig. 4. C99 and C83 fragments in young and old J20 mice.
Cortical extracts were immunoblotted for FL-APP (using either 22C11 or the 4G8/C-term combination), and for C99 (~11.2 kDa) and C83 (~9.2 kDa) fragments. Labels as in Fig. 2.

(represented more so by the Aβ(1–40) peptide), whereas in older J20 mice, when cognitive deficits were more evident, the Aβ peptides were evident in both soluble and insoluble fractions, and there was increased evidence of the hydrophobic, AD-related Aβ(1–42) variant.

Activated BACE1 favours generation of Aβ(1–40), whereas changes in PS-1/γ-secretase function favour the generation of the Aβ(1–42) species [26]. Therefore, the loss of a 110 kDa BACE1 species (representing a possible glycosylated/dimeric and activated form of the enzyme, [27,28]), concurrent with an increased co-immunoprecipitation of PS-1 and nicastrin (suggestive of an activated γ-secretase complex, [29]) could underpin this shift towards more Aβ(1–42) in the older J20 mouse brain. We also observed a loss of a potentially glycosylated (and active) ADAM-10 species [30], concurrent with lower expression of sAPPα, in the older mice. We were unable to detect the α-secretase/γ-secretase-mediated p3 fragment (*data not shown*) in the J20 mice, which corroborates a report [31] that the APP_{Swe} variant preferentially generates the Aβ peptide rather than the p3 fragment; this would align with the lower levels of sAPPα we observed, at least in the older J20 mice.

Changes in 5-HT signalling have been associated with depression as well as some of the earliest stages in AD/dementia [32] and with ADAM-10-mediated production of the sAPPα fragment [33]; however, any changes in 5-HT turnover (an index of 5-HT activity) that we observed in J20 mice do not align with changes in the expression of ADAM-10 or any other secretase (or Aβ peptides), nor do they align with outcomes in our despair/TST paradigm. While despair in the TgCRND8 mouse model aligned with a loss of noradrenergic signalling [24], the J20 mice did not show any deficit in noradrenaline brain levels. A decrease in 5-HT turnover in young male J20 mice could explain their lowered 'despair', yet we did not observe a similar change in 5-HT turnover in females. Furthermore, while an Aβ(1–42)-mediated disruption of dopamine function (reflected by the increase in dopamine turnover that we observed) in older J20 female mice could underpin memory deficits explained by the increase in Aβ(1–42) [34], this cannot explain the phenotype in male J20 mice (memory deficits, but no change in dopaminergic turnover). It is interesting that we were only able to detect the C99 fragment in male samples (regardless of genotype), which, according to a report, could be predisposing (prior to Aβ) to phenotypes in mouse models of AD [35]. Clearly, the $APP_{Swe/Ind}$ transgene influences sex-dependent monoaminergic phenotypes with potential contributions to distinct behavioral phenotypes. It remains to be determined which fragments, *e.g.* Aβ(1–40), Aβ(1–42), C99, or sAPPα/β, contribute, if at all, to these behaviors.

Our analyses did not reveal any evident changes in the levels of D-Serine or Glutamate, two amino acids thought to play a role in depression and/or AD/cognition [36,37], yet we could speculate that the significant increases in GABA levels could be influencing (at least in the female J20 mice) changes in sAPPα levels [38], which could, in turn, be regulating the expression of transthyretin [39], a protein associated with depressive-like phenotypes [40] and with the clearance of Aβ peptides [41]. This warrants further investigation.

As stated above, our own work –based on autopsied human brain samples– reveals different Aβ profiles in the male and female AD brain [16] as well as sex-dependent patterns in the glycosylation of synaptic markers of the 5-HT neuron, including the 5-HT transporter [17] and in the function of monoamine oxidase (which degrades monoamines such as 5-HT) [18]. This sexual dimorphism in depression- and AD-related protein expression in brain strongly suggests that AD might follow distinct pathological processes in men and women.

We acknowledge that the present observations remain correlational, but they do corroborate published reports of monoaminergic deficits emerging well before the appearance of the overt amyloidogenic phenotypes traditionally studied in models of AD. Our observations reveal age- and sex-dependent changes in α-/β-secretase glycosylation and in γ-secretase functionality (*e.g.* increased co-immunoprecipitation of PS-1 and nicastrin) that could certainly impact APP fragment and Aβ peptide profiles. This could be influenced by –or could be contributing to– monoaminergic and GABA-ergic neurochemistry, all of which could be influencing complex behavioral phenotypes. Yet we remain intrigued as to why monoaminergic systems are so vulnerable in the context of AD. As we continue to acknowledge that mood disorders, including depression and anxiety, could be critical markers of AD progression in certain vulnerable individuals, we will likely identify earlier and modifiable stages of the disease when intervention will still be able to provide benefit to clinical outcomes.

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