Possible Compensatory Events in Adult Down Syndrome Brain Prior to the Development of Alzheimer Disease Neuropathology: Targets for Nonpharmacological Intervention

E. Head[a,b], I.T. Lott[a,b,c], D. Patterson[d], E. Doran[a] and R.J. Haier[a,c]

[a]Institute for Brain Aging & Dementia, University of California, Irvine, CA, USA
[b]Department of Neurology, University of California, Irvine, CA, USA
[c]Department of Pediatrics, University of California, Irvine, CA, USA
[d]Eleanor Roosevelt Institute and the Department of Biological Sciences, University of Denver, Denver, CO, USA

Abstract. Adults with Down syndrome (DS) develop Alzheimer disease (AD) pathology progressively with age but clinical signs of dementia are delayed by at least 10 years after the first signs of disease. Some individuals with DS do not develop dementia despite extensive AD neuropathology. Given the discordance between clinical decline and AD neuropathology, compensatory events may be of particular relevance for this group. Imaging studies using PET suggest compensatory increases in metabolic rate in vulnerable brain regions in DS prior to the development of dementia. Neurobiological studies of similarly aged DS autopsy cases provide further evidence of activation of plasticity mechanisms. Genes that are overexpressed in DS (APP, DSCAM, MNB/DYRK1A, and RCAN1) produce proteins critical for neuron and synapse growth, development and maintenance. We present the hypothesis that these genes may lead to developmental cognitive deficits but paradoxically with aging, may participate in molecular cascades supporting neuronal compensation. Enhancing or supporting compensatory mechanisms in aging individuals with DS may be beneficial as suggested by intervention studies in animal models. In combination, adults with DS may be a unique group of individuals well-suited for studies involving the manipulation or upregulation of compensatory responses as an approach to promote successful brain aging in the general population.

Introduction

Down syndrome (DS) was initially described by J. Langdon Down in 1866 [43] and identified as a chromosome 21 trisomy by Lejeune in 1959 [104]. DS or trisomy 21 is one of the most common causes of mental retardation and recent national prevalence estimates suggest that 13.65 per 10,000 live births are infants with DS leading to 5,429, on average, annual DS births [26]. DS is associated with characteristic facial features, deficits in the immune and endocrine systems and delayed cognitive development [150]. Improvements in medical care for children and adults with DS have led to significant extensions in lifespan and enhanced quality of life [17,57]. As a consequence, up to age 35 years of age, mortality rates are comparable in adults with DS to individuals with mental retardation from other causes [173]. However, after age 35, mortality rates double every 6.4 years in DS as compared to 9.6 years for people without DS [173] and the life expectancy of a 1-year-old child with DS may be between 43 and 55 years depending on the level of retardation. Although longevity in adults with DS has been

Corresponding author: Elizabeth Head, Ph.D., Institute for Brain Aging & Dementia, Department of Neurology, University of California, 1259 Gillespie Neuroscience Research Facility, Irvine, CA, 92697-4540, USA. Tel.: +949 824 8700; Fax: +949 824 2071; E-mail: ehead@uci.edu.

increasing progressively this has not been equivalent for all races [52,196].

A key challenge to adults with DS as they age is the increasing risk for developing AD. A recent report suggests that 75% of adults with Down syndrome survive to 50 years of age and 25% over 60 years of age [57]. The proportion of these surviving individuals that develop dementia can vary considerably. Between the ages of 20–29, two studies consistently report that no individuals with DS were demented [51,142]. Between the ages of 30 and 39 years, prevalence ranges between 0 to 33% of individuals being demented [51,79, 80,131,142,181]. From 40–49 years of age, 5.7–55% may be demented [51,78,79,131,142,181,186] and between 50–59 years to range from 4–55% [79,80,90, 100,142,181,201]. Although based on smaller sample sizes, the range of individuals affected by dementia over the age of 60 years is between 15–77% [80,100, 142,181,186,201]. Further, estimated ages of onset in those with dementia also appear to range from 48 to 56 years [21,39,48,87,100,130,143,181,186,202] with a subset of individuals showing an earlier age of onset (e.g. 46 years [40]). A consistent observation in all of these studies, however, is that there is a subset of aged DS subjects that do not appear to develop dementia at any age.

The age of onset of dementia, and whether or not dementia is present may depend on several factors as thoroughly reviewed by Bush & Beail [22] and by Schupf [161]. Some of these factors are experimental and dementia prevalence estimates vary based upon the sample assessed, the sample size, and the criteria used to diagnose dementia [21]. The diagnosis of dementia in DS is itself challenging because of a background intellectual impairment and the inappropriateness of tools used to detect dementia in the general population. Standardized criteria for the diagnosis of dementia in DS may include both informant-based and direct measures [13,20,37,140]. Other factors influencing the development of dementia in DS may be endogenous including variations in ApoE genotype, gender, estrogen levels [161] education level [177]. For example, the severity of preexisting cognitive impairment may be a predictor of the rate of cognitive deterioration in DS and a higher level of cognitive functioning (indirectly related to education level and other environmental factors) is associated with fewer cases with dementia [177]. Males develop dementia at a younger age overall than females [159]). In females, menopause and post menopausal estrogen levels may confer an additional vulnerability to developing dementia [160,

162]. Genetic factors such as the presence or absence of the apolipoprotein E4 allele and risk of developing dementia in DS is still somewhat controversial with some studies reporting an earlier age of onset, increased mortality or no effect on the development of dementia (reviewed in [161]). For example, Prasher et al. [141] performed a meta-analysis of APOE in 100 adults with DS and 346 normal controls. There was no association between the APOE epsilon 4 allele and the frequency of AD but DS subjects with the allele tended to have a younger age of onset of dementia. A similar finding was reported by Mann et al. [109].

Decline in function in specific cognitive domains, in contrast, may be more sensitive to early decline and occurs at an earlier age than a diagnosis of dementia. The profile and sequence of cognitive impairments, distinct from a diagnosis of dementia, in adults with DS exhibit characteristics similar to AD in the general population [34,101,130,132,179,189]. Memory processes are affected early in the course of DS dementia [98]. Severe cognitive deterioration, such as acquired apraxia and agnosia, has been reported in 28% of individuals with DS at age 30 years with a higher prevalence of these impairments in subsequent years [101,130]. The earliest manifestations of dementia in DS appear to involve changes in personality and behavior [13,28,78]. Pragnosia or socially deficient communication may be an early sign of frontal lobe dysfunction in DS and may represent a striking change from previous well developed social capacities in the disorder [127]. Throughout the aging process, individuals with DS show less of a decline in verbal ability with more deterioration in performance skills in comparison to individuals with intellectual disability who do not have DS [25].

In parallel with the age-dependent increased risk for developing dementia, virtually all adults over the age of 40 years have sufficient neuropathology for a diagnosis of AD [111,190,191], which includes the accumulation of senile plaques (amyloid- protein) and neurofibrillary tangles (hyperphosphorylated tau protein). Senile plaques contain the amyloid- (A) peptide that is derived from a longer precursor protein, amyloid- protein precursor (A PP), the gene for which is on chromosome 21. The most common form of DS trisomy 21 leads to the overexpression of A PP [153]. Thus, a primary focus of neurobiological studies in aged DS cases has been on A PP processing and the temporal events in A pathogenesis [75] reflecting the general hypothesis that A is thought to be the a causative factor in AD pathogenesis and that overexpression of A PP may lead to the elevated levels of A in DS [71, 152,180].

However, despite life-long overexpression of AβPP in the DS brain and in other tissues [133,153], Aβ accumulation in plaques does not typically begin until after the age of 30 years [111]. Between the ages of 30 and 40 years, neuropathology rapidly accumulates until it reaches levels sufficient for a diagnosis of AD by 40 years [191]. There are reports of younger individuals with AD pathology although typically, not of sufficient extent for a neuropathology diagnosis of the disease [105,106]. Nevertheless, dementia is more commonly observed in individuals with DS with an age of onset between 48 and 56 years [22,100,142,181]. Thus, there is a prodromal or asymptomatic phase in DS when AD pathology progressively accumulates (30–40 years) but clinical signs of dementia may be delayed by up to a decade if not longer (>10 years) [100], similar to estimates of 10–20 years for AD in the general population [9,45,124,166].

The lack of concordance between the typical age of onset for dementia in adults with DS and the observation that virtually all over the age of 40 years have significant neuropathology has been emphasized by a number of researchers in the field [35,151,179]. Several explanations (initially summarized in [35]) to account for this discrepancy have evolved over the years including the suggestion that the distribution of AD pathology may differ in sporadic AD as compared to DS [108], a higher threshold for dementia in adults with DS [188], a "pathological threshold" as suggested by Mann [110] or a long preincubation period before clinical signs appear [100]. ApoE genotype may also influence the extent of AD pathology in DS and cases with the APOE4 genotype exhibit twice the accumulation of Aβ, especially in entorhinal cortex [86]. We hypothesize that the brains of DS individuals with AD pathology upregulate compensatory responses, which is consistent with the concept of a higher pathological threshold for function decline that allows neurons to function relatively normally despite significant AD pathology. These same compensatory events, in a different age epoch (i.e. during development), may be detrimental. Indeed, a similar scenario in the general aging population occurs where individuals function normally despite significant AD pathology – called "high pathology controls" [32,83,94]. In vivo imaging studies in adults with DS provide support for the hypothesis that compensatory responses may exist in the brain prior to the development of dementia.

Neuroimaging in DS

Only a few functional brain imaging studies of DS have been reported. These are characterized by small samples and a variety of scanning conditions so the results are sometimes inconsistent. For example, early reports on a small number of people with DS studied with PET and FDG showed higher cerebral glucose metabolic rate (GMR) than in non-trisomic individuals [33,163]. This was consistent with reports of cases of DS where higher than normal rates of synaptic density (and therefore more presumed neuronal activity) were found at autopsy [31,84]. Although these findings could be interpreted as consistent with some compensatory response, a larger PET study [156] failed to find any global or regional cerebral glucose metabolic rate differences (lower or higher) between Down's (N = 14) and non-trisomic controls (N = 13). The earlier result of higher GMR was thought to be an artifact of an older method of image processing (i.e. calculated attenuation correction instead of a measured correction). However, the larger PET study was done with subjects at rest–no cognitive task activation was used. At rest is a poor condition for functional imaging studies because subjects are free to engage any mental activity rather than having all subjects perform a standard mental task. We reported [67] on 7 young adult cases of DS without dementia who completed PET with FDG while performing the Continuous Performance Test (CPT) of attention. We found that individuals with DS had higher glucose metabolic rate throughout the brain (i.e. not specific to temporal lobe) compared to matched non-trisomic controls [67,68]. Other PET studies of DS showed inconsistent results [36,138,156, 157].

Subsequently, we studied a new group of middle-aged people with DS (N = 17) who showed no clinical signs of dementia. Each subject completed PET FDG imaging, as did comparison groups of people with mild AD and matched non-trisomic controls. The DS group showed higher GMR than their matched controls in exactly the same brain areas where the AD group showed lower GMR than their matched controls [66]. These areas of increased GMR in the DS group were mostly in the temporal/entorhinal cortex and included parts of the fusiform gyrus and inferior temporal lobe (Brodmann areas (BA) 19, 20, 37, 28) and the parahippocampal gyrus. The DS group also showed lower GMR along with the AD group in several areas including parts of the cingulate gyrus and parts of the temporal and parietal lobes (BAs 37, 39, 40) (see [66] for a complete

list). We proposed that the areas of increased GMR in the DS group may reflect early compensatory neural responses in the dementing process and that regional GMR increases would predict subsequent signs of dementia.

Although we have followed these DS subjects for 5 years, to-date, only one shows clear clinical evidence of dementia. This has limited our ability at this time to evaluate the prospective prediction of conversion to dementia based on increased GMR. However, each DS subject also completed a cognitive evaluation when entered into the study using the Dementia Questionnaire for Persons with Mental Retardation (DMR) [49]. Although none of the DS subjects showed evidence of clinical dementia at the time, there was a range of DMR scores, suggesting subjects may be at different stages of pre-clinical dementia. In a recent analysis, we found brain areas where increased GMR correlated to increased DMR scores, consistent with a compensatory hypothesis (Haier et al., unpublished observations). Moreover, each DS subject also had completed a structural MRI at the baseline evaluation along with the PET and the DMR. Using voxel-based morphometry, we determined gray matter (GM) volumes throughout the brain; there were areas where decreased GM correlated to DMR score. We reasoned that the combination of increased GMR and decreased GM in the same brain areas would be consistent with a compensatory hypothesis (i.e. more activity in brain areas showing less gray matter). Therefore, we identified brain areas where this combination correlated to the DMR ratings ($p < 0.05$, corrected for multiple comparisons). These areas were in the temporal cortex, including the parahippocampus/hippocampus, in the thalamus, caudate, and in the frontal lobe (BA 47). We are continuing the clinical follow-up of these DS subjects so we can complete the prospective, longitudinal analyses of conversion to clinical dementia; no other such studies are known to us. At this stage, we believe our neuroimaging results are consistent with the existence of compensatory processes at both the neuronal and the network levels.

It must be noted, that the majority of similar neuroimaging studies of patients with early AD, MCI, and persons at risk for AD (e.g. APOE4 positive) do not show brain activity increases [122,146–148,167,168], although some do [18,58]. However, by the time clinical symptoms appear, any transitory compensatory response may be over in early AD and in MCI. Also, dementia in DS may prove to have a different origin and sequence than in people at genetic risk for dementia, although the dementia in both cases may be indistinguishable clinically.

Neuroanatomical evidence for compensatory responses in DS brain

Increased metabolism observed in PET studies in nondemented adults with DS, prior to significant AD pathology, may reflect the engagement of molecular cascades that support sprouting and/or maintenance of synapses. Further, given an accelerated aging process in DS [134] and earlier age of onset of AD in parallel with an apparently similar prodromal phase, compensatory events may be particularly protective for DS. The concept of compensatory/sprouting responses or neural reserve in aging or in early AD in the general population has been suggested by several researchers [30,94,115]. For example, normal aging is associated with neuron loss in the entorhinal cortex, a region vulnerable to AD pathology, but a compensatory maintenance of the synapse associated protein synapsin is observed [107]. In the locus ceruleus of AD patients, profound neuron loss is typically observed but also compensatory sprouting of dendrites and axons [174]. Other brain regions show widespread proliferation of nitric oxide synthase III-immunoreactive neurites [172]. Increased levels of growth-associated proteins such as pro-nerve growth factor [136] or GAP-43 [114,115] also suggests compensatory increases in response to the development of pathology in the AD brain.

Similar events also may occur in the aging DS brain. DS brains show a developmental recapitulation of fetal proteins with age [192]. As in AD, NOS positive sprouting neurities in the hippocampus are seen [172]. Further, small pyramidal neurons in the frontal cortex can have a sprouting morphology as described in a case study of a 52 year old individual [129]. RNA levels for the synaptic protein, SNAP-25, is also increased in the adult DS brain [61].

Recently, we described an immunohistochemistry and confocal microscopy study of the hippocampus from 15 individuals with DS ranging in age from 5 months to 67 years and compared markers of normal and abnormal tau accumulation and A with the extent and location of neuronal growth markers (BDNF, GAP-43, MAP-2), that in combination represented measures of both a pathological and compensatory response [76]. The hippocampus exhibits significant plasticity and can mount a sprouting response as a consequence of entorhinal cortex dysfunction or damage in rodents and in human AD brain [53,56]. In middle-age (30–40 yrs) adults with DS, prior to entorhinal neuron loss but after significant A pathology in the entorhinal cortex, we observed tau accumulation in the dentate granule out-

er molecular layer (OML) of the hippocampus, which was consistent with compensatory fetal tau expression. At later ages, however, tau protein accumulates into neurofibrillary tangles suggesting that an initial growth response to AD neuropathology may subsequently become abnormal. These events were followed at a later age, associated with entorhinal neuron loss, by an increase in the growth protein, GAP-43. Hilar neurons exhibiting a sprouting morphology were also noted. Thus, these and other findings suggest that compensatory growth responses may occur in DS prior to or in parallel with the development of AD pathology. However, these compensatory events may ultimately become pathological or fail to adequately counter progressive degeneration [120,126]. For example, increased tau protein levels we have described previously in DS can lead to the accumulation of more phosphorylated tau, which in turn, contributes to neurofibrillary tangle formation during AD pathogenesis [120]. In addition, the production or maintenance of synapse or growth proteins necessary for maintaining neuron function in the presence of AD pathology most likely diminishes over time leading to neuron death. At this time, the clinical signs of dementia are most likely to be evident and severe.

Chromosome 21 genes that may support compensatory responses

In addition to AβPP, other possible compensatory events, paradoxically, may be linked to genes and protein products that during development cause cognitive deficits (i.e. are detrimental) but may be protective with age. For the purposes of this discussion, we use the term compensatory (i.e. in response to the development of disease) to indicate genes or gene products that may be protective in older adults with DS but in younger individuals may be associated with impaired brain function or organization. Possible genes and gene products we provide as examples in support of the concept of compensatory events is derived from the recent publication of the sequence of genes on chromosome 21 [73], studies reported in DS transgenic mouse models (e.g. [54, 128,145], and other models of DS (e.g. drosophila). Several genes on chromosome 21 in addition to AβPP have received attention over the last 10 years because they may play a role in synaptic plasticity in DS and contribute to developmental cognitive deficits but we hypothesize may be candidates in addition to others, for playing a role in prodromal AD compensatory respons-

es. Some examples will be discussed in more detail, three genes in addition to AβPP, DSCAM, DYRK1A and RCAN1 and their protein products may lead to aberrant dendritic growth, synapse development, and cognitive deficits in younger individuals with DS. However, these same proteins may also be protective in middle age as AD pathology begins to accumulate.

AβPP (amyloid-β protein precursor) is a single transmembrane protein that is produced as 3 isoforms varying in length from 695 to 770 residues long [164]. The normal function of AβPP and its cleavage products has not been clearly established but are thought to play a role in plasticity. For example, secreted forms of AβPP (alpha) can function as neuroprotective and neurotiotrophic factors [116], or as possible cell adhesion molecules [144,158]. More recent evidence suggests that AβPP and in particular the C-terminal fragment derived from secretase processing may also play a role in cell signaling [154] by interacting with cytosolic phosphotyrosine binding domains (PTB) or Src homology 2 (SH2) domains through the YENPTY motif. In particular, AβPP or CTFs can interact with growth factor receptor-bound protein 2 (Grb2) [199], which is involved with the MAPK pathways and can also anchor to dynamin and synapsin [119,197]. The possible downstream consequences of AβPP anchoring to complex protein networks may be to modulate tau phosphorylation, neuronal migration, axonal elongation and dendritic arborization and thus, potentially compensatory responses. In transgenic mouse models of DS involving the overexpression of AβPP, learning and memory impairments are consistently observed [23,54]. These behavioral impairments become progressively worse with age [60,85]. Further, AβPP overexpression in these mouse models has been linked to synaptic abnormalities [99] and changes in synaptic plasticity [16,38,81, 165,171]. Mice without the AβPP gene are viable but develop gliosis and locomotor deficits with age [198]. However, neuronal cultures derived from young animals are less viable, show reduced axonogenesis and arborization [137]. In combination these results suggest that AβPP plays an important role in synaptic function and plasticity and thus may contribute to compensatory responses in DS.

DSCAM (Down syndrome cell adhesion molecule) is a member of the immunoglobulin superfamily present on chromosome 21 (21q22.2–q22.3) and functions as a cell adhesion molecule [194]. DSCAM is expressed in the brain and is thought to play a role in the observed abnormalities in the central nervous system in DS [194]. Different transcripts of the DSCAM

gene are expressed in the human brain with regions including the substantia nigra, amygdala and hippocampus highly expressing the 9.7 kb transcript. DSCAM is expressed during periods of neurite outgrowth in the brain but is further expressed in differentiated neurons in the cortex suggesting a role in the formation or possible maintenance of neural circuits [2,3,194]. In *Drosophila*, overexpression of Dscam, the homolog of DSCAM in humans, leads to more diffuse dendrites, that are less organized and shifted to more ventral positions than normal in the projection neurons innervating glomeruli [200]. Although primarily thought to be involved with neuronal growth and development there is also the possibility that DSCAM could be involved with compensatory responses in the adult DS brain during the development of AD pathology. Levels of DSCAM are increased by more than 20% in DS brain [14] and Saito and colleagues (2000) used immunohistochemistry and Western blotting to detect DSCAM in individuals with DS ranging in age between 34 gestational weeks to 60 years of age ($n = 21$) [155]. In normal controls, DSCAM immunolabeling was consistent with myelinated white matter and labeled nerve fibers. Further, neuronal labeling for DSCAM decreases with age in normal cases but remained in DS cases. In DS with AD, DSCAM was localized to the cores and peripheral fibers associated with senile plaque formation. The presence of DSCAM in association with neurons and plaques in DS cases with AD may suggest that this protein can function as a possible compensatory response to increasing AD pathology.

MNB/DYRK1A (homolog of drosphilia minibrain gene/dual-specificity Tyrosine (Y) regulated kinase 1A) is a protein kinase thought to be involved with neurogenesis [176] and is present on the DSCR of chromosome 21 [65]. Thus, a potential role for DYRK1A in cognitive dysfunction and neurobiological differences relative to non-DS individuals has been proposed [70]. In fetal DS tissue, DYRK1A or MNB is overexpressed relative to control brains [64]. DYRK1A activates the transcriptional factor cAMP response element-binding protein (CREB) and directly phosphorylates CREB, stimulating CRE-mediated gene transcription, particularly during neuronal differentiation [195]. CREB is critically involved with the formation of contextual memories [12], conditioned taste aversion [15] and spatial learning [123]. CREB can further increase the transcription of BDNF, which promotes the maintenance and survival of neurons and synapses [19]. Further DRYK1A may also be involved with the regulation of dendritic trees of neurons late in a "second wave" of development [69]. A major substrate of DYRK1A is dynamin-1 [82], which is essential for synaptic vesicle recycling and affects synaptic activity required for learning in drosphila [44,118].

Mice overexpressing 21q22.2 containing the DYRK1A gene show increased neuronal density in the cerebral cortex and learning deficits [169], which may be consistent with MRI volumetric studies in DS [96,187]. More specific DRYK1A overexpression in transgenic mice leads to motor and behavioral deficits in association with LTP impairments [6]. Deficits in spatial learning and cognitive flexibility indicate dysfunction in hippocampal and prefrontal cortical circuits. Recently, DYRK1A BAC mice were generated that show increased long term potentiation and decreased long term depression in addition to spatial learning and memory deficits [4]. In combination, overexpression of the DYRK1A gene in DS may be a significant contributor to increased regional brain volume, impaired synaptic function and cognitive deficits. In addition, DYRK1A is not the only gene that codes for a mediator of gene transcription but others are also present on chromosome 21 suggesting a drive towards the production of other proteins [55].

RCAN1 (Regulator of Calcineurin 1; also known as calcipressin, ADAPT78, or DSCR [Down Syndrome Critical Region]1) has recently been shown to act synergistically with DYRK1A to cause dysregulation of NFAT (Nuclear factor of activated T-cells) transcription factors that are regulators of vertebrate development [11]. Interestingly, expression of RCAN1 appears to be dependent upon NFATc1 during cardiac valve formation [102]. The RCAN1 gene is located on chromosome 21 and was discovered by two laboratories (36). It is transiently induced during cellular adaptation to oxidative stress [47]. RCAN1 has been shown to stimulate expression of GSK-3β, which phosphorylates tau, an important step in the neuropathology of AD in DS [46]. Although RCAN1 expression protects cells from oxidative stress when induced transiently, its constitutive overexpression has been associated with DS, AD, and cardiac hypertrophy and may attenuate angiogenesis and cancer [72]. RCAN1 is highly expressed in neurons and overexpressed in DS brain [95]. In Drosphila, both over- and underexpression of the RCAN1 orthologue, *nebula*, cause serious learning defects. Possible additional roles for RCAN1 include modulation of the chromosome 21 gene SOD1 [46] and playing a critical role in mitochondrial function [27].

Transgenic mice engineered to express RCAN1 in heart tissue are viable, and the gene is trisomic in

Ts65Dn mice [185]. Expression of RCAN1 is elevated in Ts65Dn mouse brain compared to euploid controls [7]. The Ts65Dn mouse is the most widely used mouse model of Down syndrome and is trisomic for a region of mouse chromosome 16 that is homologous to about half of human chromosome 21. It is trisomic for about 130, or about half, of the genes present on human chromosome 21 and has many phenotypic features of Down syndrome, including learning and memory deficits, abnormalities in brain structure, and abnormal synaptic function. In general, genes trisomic in the Ts65Dn mice show elevated levels of expression consistent with trisomy (see Patterson and Costa, 2005 [135] for a discussion of the features and origin of the Ts65Dn mouse [93]).

A recent report describes attempts to produce RCAN1 transgenic mice using a BAC clone containing the gene under the control of its endogenous control regions [97]. These investigators report that RCAN1 injection was not toxic in eggs and that the presence of the RCAN1 gene could be detected in 14 of 57 embryos and resorbed sites. Moreover, expression of transgene mRNA was detected in early embryos. Nonetheless, no transgenic mice expressing RCAN1 could be obtained. These investigators specifically propose that overexpression of RCAN1 by itself is an embryonic lethal event, but that overexpression of other genes trisomic in the Ts65Dn mice compensates for the overexpression of RCAN1 alone [97]. This hypothesis is consistent with the observed overexpression of RCAN1 in Ts65Dn mice. Given the complexity of the effects of RCAN1, the maintenance of appropriate stoichiometry of RCAN1 and other genes may well be essential. Thus, RCAN1 may be transiently expressed in response to increasing oxidative damage, typically associated with aging and with the development of AD [8], and serve as a compensatory response. Further although RCAN1 mediated upregulation of GSK-3β and tau phosphorylation may be involved with the development of AD pathology not all tau phosphorylation is pathological. GSK-3β-mediated tau phosphorylation may also serve to enhance neuronal remodeling [91]. However, as with other synaptic plasticity gene products, continued overexpression may ultimately lead to AD pathology and neuronal dysfunction.

Although we have focused only on a few protein products of genes overexpressed in DS it is more than likely that others behave similarly and may interact with each other [92] leading to learning and memory deficits during development but that may subsequently be protective with increasing age.

Therapeutics targeting compensatory responses

There has been significant effort in the AD field to reduce Aβ in the brain as a therapeutic approach to slowing or halting disease progression, but we suggest that the combination of reducing Aβ pathology with nonpharmacological treatments that may help to restore neuron function or support plasticity mechanisms may be more effective. Particularly with respect to DS, because Aβ begins to accumulate after the age of 30 years, and in some cases younger, reducing or eliminating AD pathology in older individuals may be insufficient, if neuronal damage has already occurred. Thus interventions that promote synaptic plasticity or compensatory responses in combination with reducing Aβ pathology may be particularly critical for slowing pathological aging in DS. Based upon work in rodent models and in a canine model of human brain aging, we suggest that the use of behavioral enrichment (including physical exercise) may have a significant impact on healthy brain aging in DS. These same interventions may promote pathways and molecular cascades involving genes overexpressed in DS that may enhance compensatory mechanisms.

In rodent models, physical exercise and/or environmental enrichment can lead to a rapid and sustained increase in growth molecules in regions of the brain demonstrating plasticity. For example, voluntary wheel running in rats leads to the induction of BDNF in the hippocampus both at the gene expression level and in protein levels [29,125]. Further, wheel running can lead to increased neurogenesis and synpatogenesis [182–184]. In mouse models of AD, wheel running [1] and environmental enrichment [103] leads to reduced Aβ deposition. However, other studies find either increased Aβ or no change in Aβ in environmentally enriched transgenic mice despite behavioral improvements [10,88,89]. Thus, physical exercise either alone or in the context of environmental enrichment can have a significant impact on brain function by mechanisms that may not necessarily critically involve reducing AD pathology.

We further tested the potential for behavioral enrichment (physical exercise, environmental enrichment, etc) to improve cognition and reduce neuropathology in the canine model of human brain aging that naturally and in an age-dependent manner develops Aβ and cognitive decline (reviewed in [77,175]). A group of 24 aged beagle dogs (9–11 years at the start of the study) was provided with a program of behavioral enrichment, which included physical exercise, social

enrichment, environmental enrichment and cognitive training. At this age, beagles typically show diffuse Aβ plaques, with a morphology and distribution that is similar to that seen in DS brain between the ages of 30–40 years [77]. We observed significant improvements in complex learning ability and maintenance of cognitive function over a treatment period of 2.8 years and these effects could be further enhanced by the addition of a diet rich in a broad spectrum of antioxidants and mitochondrial co-factors [121]. In contrast to some reports in transgenic mice, we found that Aβ pathology in the brains of these treated animals remained unaffected [139].

However, in the Ts65Dn mouse model of DS, only a few studies of the effects of environmental enrichment on learning and memory have been reported with relatively disappointing results. Spatial learning was improved by environmental enrichment in female Ts65Dn mice but not males [112]. Further examination of male Ts65Dn mice exposed to enrichment suggested that excess social or physical stimulation led to impairments in emotional components associated with tasks used to assess learning [113]. Morphologically, neocortical pyramidal cells in Ts65Dn mice that show fewer spines on dendrites compared to wild type controls also show little change in response to environmental enrichment (3% more spines) as compared to wild type controls (increased 32%) [41]. We were unable to find any studies with older mice. When the impact of environmental enrichment and/or physical exercise in different animal models are considered in combination they suggest that environmental manipulations can have a significant impact on AD progression and cognitive decline but are less supportive with respect to reducing developmental cognitive delays. Translating the results of animal models into the clinic may lead to new interventions but it can also be problematic as will be discussed next.

Translating animal studies to the DS clinic

Work in animals suggests that even in the presence of significant Aβ pathology, neuronal function can be improved and maintained by modifying environmental factors. However there are two caveats in considering the translation of these interventions into strategies for promoting healthy aging or slowing AD progression in adults with DS. Many individuals with AD (both with and without DS) most likely have significant AD pathology by the time of diagnosis; can these interventions restore neuronal function? Further, what would be

the impact of such interventions on the DS brain, which essentially has been exposed to abnormally high levels of AβPP throughout life? Even in DS individuals that overexpress the AβPP protein, environmental enrichment may be beneficial given that studies in transgenic mice with a far higher fold overexpression of the gene show improved cognition with intervention regardless of changes in Aβ. Evidence from canines also suggests that reducing Aβ pathology may not be critically involved when considered against a background of improved neuronal health, allowing neurons to tolerate extensive pathology.

Studies in animals suggest that environmental enrichment alone may be of limited benefit in reducing developmental cognitive impairments in DS, as suggested by studies in Ts65Dn mice. However, animal models of normal human brain aging (canine) and AD (transgenic mice) strongly suggest that environmental enrichment and/or physical exercise can slow AD progression. How well might these animal studies predict intervention efficacy in adults with DS? Overall, people with DS show lower levels of physical activity, which may leave them vulnerable to type 2 diabetes, cardiovascular disease, osteoporosis and obesity [149,178]. These health problems in turn may lead to reduced employment and opportunities to engage in social or recreational activities [50]. Further, as adults with DS aged over a period of 13 years, they showed a more rapid decline in physical fitness than the general non disabled population [59]. Thus, physical exercise and environmental enrichment, associated with increased social engagement or employment may improve brain function and be protective against dementia.

Physical exercise can have multiple benefits throughout the lifespan in DS from improving overall cardiovascular health, increasing social engagement, improving activities of daily living even in elderly individuals [24,42,149]. There are also observational studies of adults with DS suggesting that additional environmental factors can influence pathological aging. Temple and colleagues show that lower pre-morbid cognitive function influences the development of dementia, with a higher level of cognitive function being associated with fewer cases of dementia [177]. Further, although educational level, years in an institution and employment was not directly associated with cognitive decline, overall level of cognition was associated with these environmental variables. People with DS with a lower level of cognitive function prior to dementia also show a faster rate of decline if they develop the disease [130]. Thus, an enriched environment (social and recreational activities) in addition to physical fitness may have a significant impact on healthy aging in DS.

Summary

The current review focused on a small number of genes or gene products associated with synaptic plasticity and compensation that may play a role in the aging process in DS. However, other genes on chromosome 21 can affect multiple tissues in the body, which in turn may also have a significant impact on the development of AD. For example, immune system deficits in DS may also be intimately involved with pathological brain aging as observed in non-DS populations [117, 193]. The brains of AD patients in the general population [5] and those of DS adults with AD show extensive brain inflammation [5,62,63,74]. Endocrine system dysfunction in DS may also promote neuropathology and dysfunction as suggested for aging in the non-DS population (reviewed by [170]). Thus, there are a number of other physiological consequences to trisomy 21 affecting multiple systems, both peripheral and central, that may influence the age of onset, whether or not a DS adult becomes demented, or the rate of disease progression. However a number of these may also be amenable to environmental manipulation or modifications to lifestyle that engage compensatory responses that may be healthy for the brain and other tissues.

Studying longitudinal changes in cognition, in vivo brain imaging and autopsy studies of adults under the age of 40 years with DS will provide unique insights into compensatory responses that may occur in the brain prior to the development of AD. In vivo imaging using structural or functional approaches can provide very useful outcome measures representing the development of AD and possible manipulation by interventions. As more genes are identified and a possible protective role for brain aging examined, these cognitive, structural and molecular pathways may be manipulated to promote healthy brain aging in DS and be directly translatable to AD in the general population. We also suggest that pharmacological interventions may be one strategy for preventing or treating AD in DS but that modifying lifestyle including diet and physical or cognitive enrichment may be complementary approaches that when provided with other treatments may have significant benefits to this special, at risk population.

Acknowledgements

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