Presenilin: a role in neurogenesis via notch?

A different view on Alzheimer's disease pathology

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Abstract

Alzheimer's disease (AD) is a severe neurodegenerative disease characterized by the formation of amyloid plaques and neurofibrillary tangles. Familial Alzheimer's disease (FAD) is an early onset form of AD and can be caused by mutations in three different genes; presenilin 1 (PS1) presenilin 2 (PS2) and amyloid precursor protein (APP). Presenilins are intramembranous proteins that are part of the γ-secretase complex. This proteolytic complex is responsible for the cleavage of several transmembrane proteins such as APP and Notch. Mutations in PS1 and PS2 are known to alter the ratio of two forms of amyloidβ, the soluble form (Aβ40) and the more aggregation prone Aβ42. This is thought to enhance plaque formation and cause neuronal degeneration and cognitive decline. Recently, the amyloid hypothesis is challenged by the fact that there can be neuronal degeneration without the presence of plaques. In addition, immunisation with Aβ42 has beens shown to reduce plaque load, but has no effect on neurodegeneration and stage of dementia. This led to the idea that presenilin mutations could also enhance AD pathology via different mechanisms than increasing the Aβ42/Aβ40 ratio. One possible mechanism could be via altering neurogenesis. Neurogenesis is the formation of new neurons, and is limited to discrete zones in the adult mammalian brain. It could be a compensatory mechanism in response to injury and neurodegeneration. A shift from neurogenesis to gliogenesis could enhance the vulnerability of the brain to AD. The question in this thesis is whether AD presenilin mutations could alter neurogenesis via defective notch signalling. The evidence for this hypothesis shows to be hard to interpret. Data from human and animal studies seems to suggest that neurogenesis is impaired in AD, despite defective notch signalling. However, it is important not to rule out the other functions of presenilins, such as its role in Wnt signalling, apoptosis and synaptic functioning. More knowledge about the fundamental roles of all involved proteins is of crucial importance to be able to unravel all the critical steps in AD pathology.

List of Abbreviations

AD	Alzheimer's disease
APP	Amyloid precursor protein
APh1	anterior pharynx defective 1
BRDU	bromodeoxyuridine
CNS	Central nervous system
DCX	doublecortin
DG	dentate gyrus
FAD	familial Alzheimer's disease
GFAP	glial fibrillary acidic protein
GLAST	glutamate aspartate transporter
GPC's	glial progenitor cells
NCT	nicastrin
NICD	notch intracellular domain
NFT	neurofibrillary tangles
NO	nitric oxide
NSC	neuronal stem cells
Pen-2	presenilin enhancer 2
PS	presenilin
ROS	reactive oxygen species
SCF	stem cell factor
SGZ	subgranular zone
SVZ	subventricular zone

Content

1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease, highly associated with age. At this moment, an estimated 130.000 people suffer from AD in the Netherlands. With the increasing life expectancy, this number will continue to grow. The disease is characterised by the formation of amyloid plaques and neurofibrillary tangles (NFT), which are found in the brains of deceased patients. The exact molecular mechanisms underlying the pathogenesis of the disease are still largely unknown. When several members of a family are affected, it is called familial Alzheimer's disease (FAD). When no other family members are affected and no genetic mutation is identified, it is called sporadic Alzheimer. FAD constitutes about 5-10% of all Alzheimer cases. Although FAD is rare, it can give us a lot of insight in the genetics and molecular mechanisms underlying AD. Mutations in several genes, such as Amyloid Precursor protein (APP) and presenilin (PS) are found to be causative for FAD (Sherrington *et a*l 1995, Levy-Lahad *et al* 1995). Often, FAD patients have an early onset of the symptoms, sometimes even before the age of 40 is reached, dependent on the severity of the mutation. Alzheimer patients suffer from cognitive decline, which is thought to be caused by synaptic dysfunction and the loss of neurons. Neuronal degeneration in AD starts in the enthorinal cortex and hippocampus (Janke *et al* 2001). This degeneration is even visible before the onset of AD symptoms, and is most profound in the anterior hippocampus and amygdala. Starting at the temporal cortices, the wave of neuronal degeneration proceeds to the frontal cortex and then to the sensori-motor cortices. This neuronal loss is highly correlated with cognitive performance (Thompson *et al* 2003).

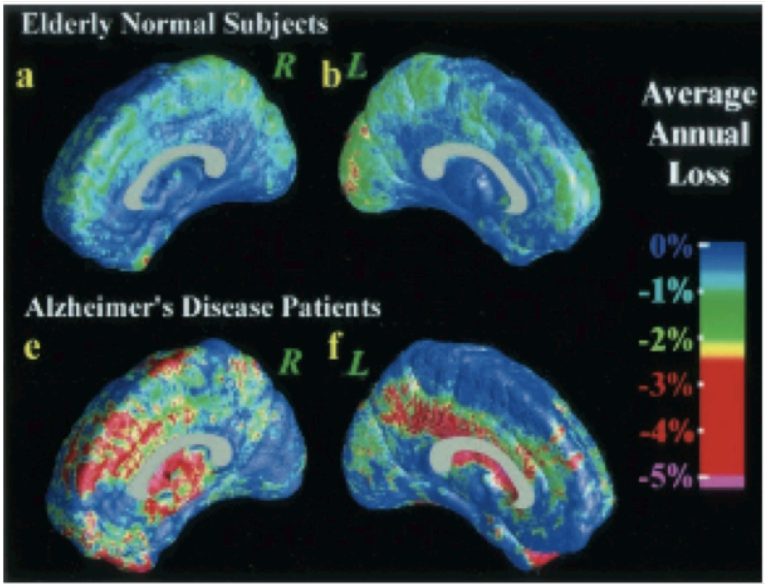

Fig. 1.1: MRI image of AD patients (e, f) compared to normal elderly subjects (a,b). Depicted is the average annual gray matter loss in the right (R) and left (L) hemisphere. In AD patients, the gray matter loss spreads from the temporal to the frontal lobes and is more pronounced in the right hemisphere. Thompson *et al* 2003.

Presenilin mutations are known to alter the ratio of Aβ42/Aβ40. One cleavage product of APP, Aβ42, is less soluble and therefore more prone to aggregation. Via this mechanism, mutations in PS1 and PS2 can contribute to Alzheimer's disease pathology. PS is also known to be involved in neurogenesis. Mutations in the PS genes are recently shown to alter neurogenesis. Neurogenesis is an intrinsic reaction of our brain to injury it is required for efficient learning and memory processes (Wang *et al* 2004), which are known to be compromised in AD patients. Presenilin is therefore hypothesised to play a role in AD pathology. Since presenilin is also essential in proteolytic cleavage of notch,

which functions as an important receptor in stem cell proliferation, a disrupted notch signalling due to defective PS function could lead to a higher sensitivity for Alzheimer via altered neurogenesis processes.
In this thesis, the question 'Can presenilin mutations contribute to AD pathogenesis via a disrupted notch signalling and altered differentiation of neuronal stem cells' will be addressed. This explores a whole new aspect in AD pathogenesis, not focussing on the role of plaques and tangles. The hypothesis is supported by the fact that in AD patients, neuronal degeneration can be observed without severe plaque formation, and that plaque burden and NFT formation is not correlated with both the severity and duration of the disease (Gomez-Isla 1997). In addition, AD patients immunised with Aβ42, show reduced plaque load, but this has no effect on neurodegeneration and the stage of dementia (Holmes et al 2008).
More insight into the underlying processed of AD pathology could lead to more efficient prevention and treatment strategies. This could include therapy to enhance the formation of new neurons to compensate for the severe neuronal loss.

2 Astrocytes and Alzheimer's disease

Astrocytes are known as the housekeeping cells of our brain. They support healthy brain functioning via a wide range of mechanisms, with exciting new functions being explored (for a review see: Wang and Bordey 2008). In summary they provide housekeeping functions, they support and shape synaptic transmission and, a recent striking finding, in the adult neurogenic zones they function as neural stem cells. The production of new astrocytes, commonly referred to as gliogenesis, takes place both during embryonic development and in the adult stages in the subventricular zone (SVZ) (Goldman *et al* 1991). A marker thought to be specific for astrocytes in the CNS is GFAP (glial fibrillary acidic protein).

Astrocytes are implicated in a lot of pathological conditions in the brain. This is summarized in the "neuro-neglect hypothesis" (Fuller *et al* 2009). Instead of protecting the brain against neural damage, astrocytes become inflammatory mediators by becoming reactive. This leads to glial scar formation, which isolates the injured site. They thereby 'neglect' their neuroprotective role. Reactive gliosis is implicated in a lot of pathological conditions such as stroke and AD. An increased expression of inflammatory mediators has been shown in affected areas in AD patients including reactive astrocytes and activated microglia (mcGeer and mcGeer 1995). This inflammation is triggered by amongst other things Aβ plaques.
Different kind of glial cells are involved in the inflammatory response in AD. Human microglia treated with Aβ increase transcription of pro-inflammatory cytokines and chemokines (Walker *et al* 2006). In a mouse model for AD expressing mutant tau protein, activated microglia were shown to correlate with synaptic dysfunction (Yoshijama *et al* 2007). In the physiological condition, microglia clear the neural environment of neuro-toxic substances such as plaques (Swab and mcGeer 2008). A chronic inflammation could compromise this capacity leading to an increase of plaque burden. In healthy aging individuals, microglia become senescent, thereby decreasing their phagocytic function (Streit *et al* 2006). It has to be noted though that microglial activation is also required for their phagocytic function (Akiyama *et al* 2004).

Recently it has become clear that astrocytes themselves can also contribute to the inflammatory response. Besides microglia, astrocytes are also able to phagocytose Aβ (Pihlaja *et al* 2007, Nagele *et al* 2004). Astrocytes have distinct spatial reactions to

plaques. The ones surrounding the plaques undergo gliosis, while the ones further away from the affected site undergo atrophy (Rodriguez *et al* 2009). Reactive astrocytes and activated microglia produce pro-inflammatory cytokines and chemokines that in turn lead to the production of more cytokines and chemokines. This provides a positive feedback loop that leads to exacerbated inflammation that is not beneficial and neuroprotective anymore. Reactive astrocytes also produce proteins of the complement system, known to attract factors of the membrane attack complex (Bradt *et al* 1998), and prostaglandins, inflammatory factors that might contribute to AD pathology by enhancing APP expression (Satoh *et al* 2000).

Microglia and astrocytes are able to produce reactive oxygen species in response to injury (ROS). These substances give oxidative stress, which is thought to lead to more neuronal damage in AD (Simonian and Coyle 1996). ROS can oxidise proteins lipids and DNA, thereby greatly compromising healthy functioning of neurons. Oxidised DNA, proteins and lipids can be found in the cortex of patients suffering from AD (Christen 2000). Astrocytes and microglia can also release reactive nitrogen species such as Nitric oxide (NO). This leads to the nitration of tyrosine residues, leading to compromised protein function. The amount of nitrated tyrosine is greatly increased in neurons bearing NFT compared to healthy controls, indicating a pathological role for NO in AD (Bolanos *et a*l 1997). ROS might also contribute to AD pathology by enhancing the formation Aβ42, which has a higher propensity to aggregate then Aβ40, thereby increasing the plaque burden (Simonian and Coyle 1996).

It is not only the 'acquired' function of glial cells that contribute to AD pathology, but also the loss of the supporting role that compromises neuronal functioning and could eventually lead to cell death. One example is the decrease of glucose uptake in the brain resulting from astrocytic dysfunction (Freemantle *et al* 2006). Astrocytes dysfunction could also lead to disturbances in glutamate recycling. AD pathology has been shown to be inversely related to expression of EAAT (glutamate transporter) (Simpson *et al* 2008). Increasing extracellular glutamate is in turn excitotoxic, and could contribute to neuronal damage.

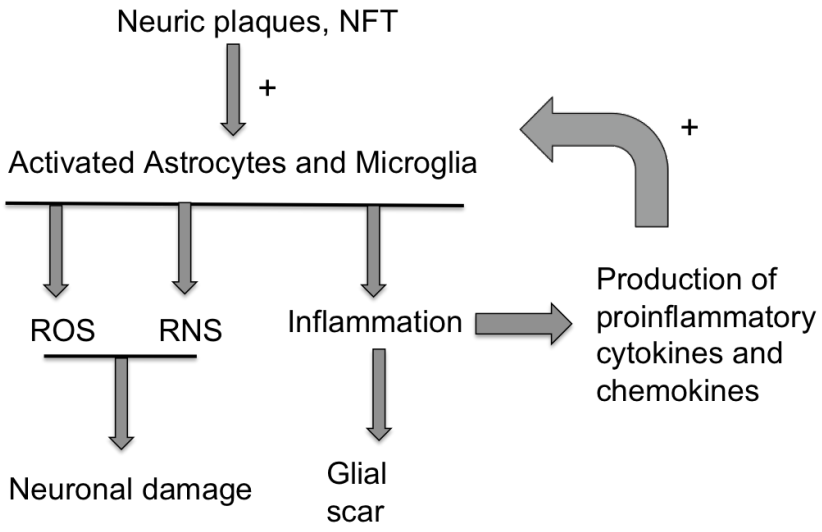

Fig 2.1: diagram of the various ways in which glial cells can enhance AD pathology. Activation of glial cells leads to an exacerbated inflammatory response, glial scar formation and to the production on ROS that can damage neurons.

The above-mentioned evidence makes it clear that the initial neuroprotective role of glial cells is completely lost in the progressive inflammation observed in AD. Treatment strategies aiming at returning glial cells from their activated state to their neuroprotective state might greatly reduce the amount of neuronal damage (Fuller et al 2009). Furthermore, it makes clear that the shift from neurogenesis to gliogenesis that is proposed in this hypothesis could enhance AD pathology.

3. Neurogenesis and Alzheimer

3.1 Neurogenesis in physiological conditions

Neurogenesis was long thought to only occur in the formation of the CNS during embryonic development. Recently researchers have shown that there are also discrete sites in the adult brain where new neurons are formed (Alvarez-Buylla and Lim 2004), although this might change under pathological conditions. It is now known that newly formed neurons are added to the olfactory bulb, and to the dentate gyrus of the hippocampus (Ming *et al* 2005). Neuronal stem cells (NSC) in de adult brain are located in the subventricular zone (SVZ) of the lateral ventricle and in the subgranular zone (SGZ, see figure 3.1) in the dentate gyrus (DG) of the hippocampus (Lois and Alvarez-Buylla 1994; Gould and Cameron 1996). The SVZ is the most robust neurogenic zone, producing 30.000 new neuroblasts each day in adult rats (Alvarez-Buylla *et a*l 2000). These NSC's are derived from radial glial cells and are also know as B-cells (see figure 3.2). B-cells will via several steps produce neuroblasts that will migrate to the olfactory bulb to form interneurons (Kriegstein *et al* 2009). The radial astrocytes in the SGZ of the hippocampus are also likely to derive from radial glial cells and are also known as type I progenitor cells (Fukuda *et al* 2003). The neurogenic niche of the SGZ lies in close proximity to blood vessels, suggesting that circulating factors are able to influence NSC behaviour (Palmer *et al* 2000). NSCs in both neurogenic niches have characteristics of astrocytes, including the expression of GFAP, GLAST and other astrocytic markers (Doetsch *et al* 1997). The local environment is essential for the determination of the fate of those NSC (Shihabuddin *et al* 2000). It is postulated that this neurogenic niche is provided by specialized astrocytes (Ninkovic and Gotz 2007). Several signalling pathways are implicated in the regulation of adult neurogenesis, including the Wnt/beta-catenin and the notch-signalling pathway, which will be discussed in the following chapters. Adult neurogenesis is known to be reduced during aging (Kuhn *et a*l 1996; Bizon *et al* 2003). Hippocampal neurogenesis is shown to be necessary for certain forms of learning (Shors *et al* 2002) and processes in hippocampal neurons during learning and memory formation are able to enhance the formation and survival of newly formed neurons in the SGZ (Gould *et al* 1999; Trouche *et al* 2009). This evidence points

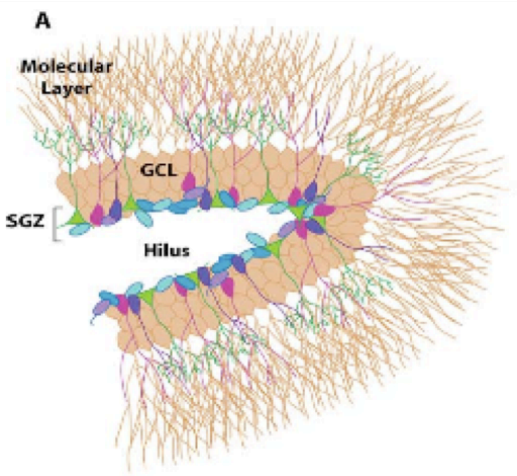

Fig. 3.1: localization of the subgranular zone in the hippocampus. Rodriquez *et al* 2009a

out a possible role for neurogenesis in neurodegenerative diseases with learning and memory deficits such as AD. In injury such as stroke or ischemia (Gould & Tanapat 1997), neurogenesis is enhanced. This suggest that this might be a way of the CNS to self regenerate lost neurons, but it is unknown if the same mechanisms are capable to successfully regenerate lost neurons in AD. In the following paragraphs, current knowledge about neurogenesis in AD will be discussed.

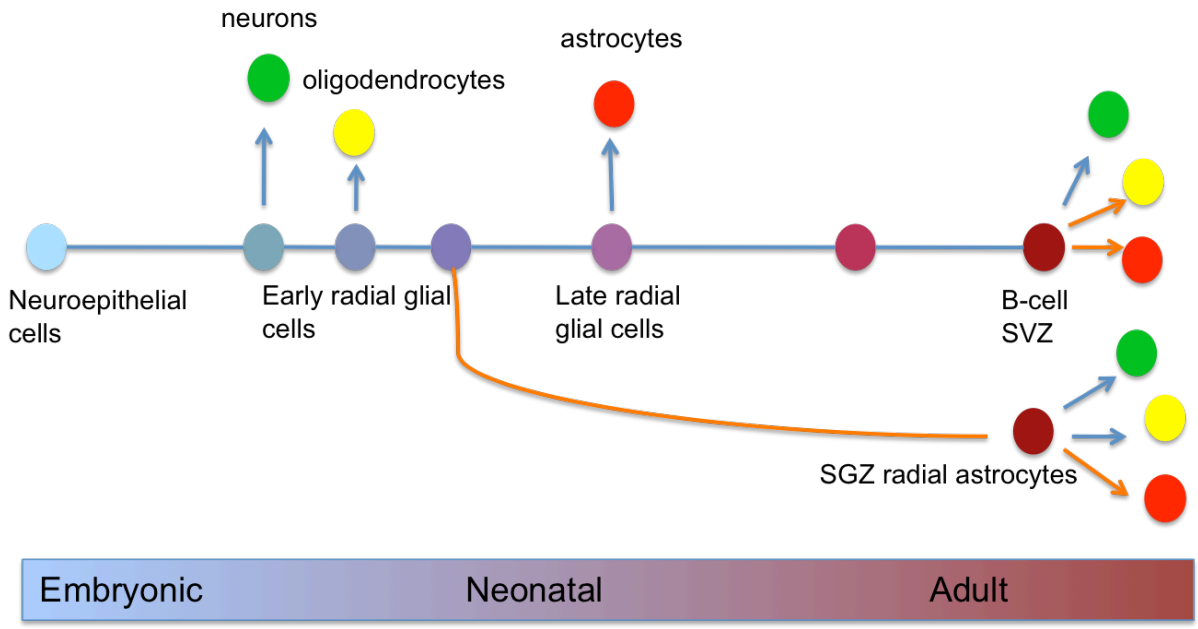

Fig. 3.2: NSC lineage tree. The blue and purple dots depict the development of the NSC from neuroepithelial cells to B-cells in the SVZ, and SGZ radial progenitors in the hippocampus. The blue lines and arrows represent lines for with experimental evidence is available, the orange lines and arrows are hypothetical. Neurons are depicted in green, oligodendrocytes in yellow and astrocytes in red. Figure based on Kriegstein *et al* 2009.

3.2 Neurogenesis in AD patients

Studying neurogenesis in AD patients comes with a few important drawbacks. Specific staining methods that require pre-mortem injection of a substance, such as bromodeoxyuridine (BRDU), a detectable substitute that is build into newly synthesised DNA instead of thymidine, cannot be performed. Of most patients used in human studies it is not known if they bear a presenilin mutation, and if so, which one. Statistically, more patients suffering from sporadic AD will be included in these studies, since only 1-2% of all AD patients have presenilin mutations. Furthermore, although most of the presenilin mutants contain missense mutations, it is unlikely that all have the same functional consequences.

An increased neurogenesis was observed in post mortem studies of patients diagnosed with AD (Jin *et al* 2004). In this study an increase in doublecortin (DCX) expression, which is a marker for newly formed and migrating neuroblasts, was found in a cohort of senile patients. Li *et al* 2008 reported that despite an increased proliferation in AD patients, these neurons did not fully mature (Li *et al* 2008). This could be because the microenvironment does not favour survival of newly formed neuron (Li *et al* 2008). These results are challenged by Boekhoorn *et al* 2006, who investigated neurogenesis in

a presenile younger group of AD patients, using the proliferation marker Ki-67. They found that the increased proliferation was due to glial proliferation and vasculature associated changes. The differences between these studies could very likely represent the different pathological conditions the patients were in, and this again pinpoints the complexity of the situation. Another study, carried out by Laske *et al* 2008, reports a decrease in stem cell factor, a growth factor that supports neurogenesis SCF ,in plasma of AD patients compared to healthy controls. This was inversely correlated with the severity of dementia, indicating a high clinical relevance (Laske *et al* 2008). When glial progenitor cells obtained from deceased AD subjects and controls without neurological pathology were compared, GPC's from AD patients showed to have less self-renewal capacity and less neurogenesis occurred (He *et al* 2009). The authors contribute this to reduced β-catenin/Wnt signalling due to disruption by Aβ plaques.
A lot of studies use doublecortin (DCX) as a marker for neurogenesis. The reliability and the selectivity of this marker are not confirmed, so data about this marker have to be carefully interpreted (Verwer *et al* 2007). They found that DCX was also present in differentiated astrocytes, and that there was no strong correlation between AD pathology and alterations in DCX expression. Ziabreva *et al* studied brain tissue of deceased AD patients using the markers musashi-1 (to label neural progenitors), GFAP and nestin. In the SVZ of AD patients, a nine-fold reduction was found in musashi-1 expression, which is interpreted as a decrease in the neural progenitor cell pool. They also found a significant increase in nestin expression, but this was hard to interpret (Ziabreva *et al* 2006).

Taken together, these findings are not all in concurrence with each other, and cannot be linked to a clear AD-related genotype. Studies in animal models of AD could give more information about the different component that play a role in AD pathology, and their role in neurogenesis.

3.3 Neurogenesis in AD mouse models

A wide range of animal models for AD are investigated and phenotyped. The results on altered neurogenesis are inconclusive. These results are also very hard to interpret, since a lot of different models and experimental setups are used. A comprehensive review on neurogenesis in AD models is the review of Lazarov and Marr, 2009.
A lot of mouse models contain multiple mutated proteins known to be associated with AD pathology, and therefore effects of those mutations on itself are hard to differentiate. During embryonic development, mice with a known clinical mutation of PS1 were found to have a decrease in neurogenesis. Despite a higher proliferation rate, less newly formed neurons were found in these mice, which could be due to a decrease in neuronal survival and an increase in gliogenesis (Eder-Colli *et al* 2009). These results are consistent with the findings of Handler *et al* 2000. They report a reduction in the neural progenitor population during embryonic neurodevelopment, which is caused by premature differentiation. In a triple AD model, carrying mutated APP, PS1 and tau, neuronal proliferation was impaired in both the SVZ and the DG, indicating a role for PS1 not only in the embryonic brain, but also in the adult brain (Rodriguez *et al* 2008, Rodriguez *et a*l 2009b). A lot of research has been done regarding the influence of amyloid plaques on neurogenesis. Aβ42 has been shown to both enhance or compromise neuronal survival and differentiation (reviewed in Lazarov and Marr 2009). This controversy will not be discussed here, since the focus will be on the direct role of presenilins on neurogenesis, and not via altered amyloid beta processing. In the following chapter the effects of PS mutations on neurogenesis will be discussed further.

4. Presenilin

4.1 Physiological role

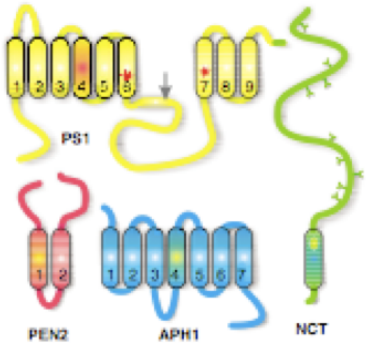

Fig. 4.1: The γ-secretase complex is formed by PS1/PS2, pen-2, Aph1 and nicastrin. Red asteriks indicate the aspartyl residues that ere the catalytic site of the complex. Spasic and Annaert 2008.

Presenilins (PS) are 9-transmembrane cleaving proteases (Doan *et al* 1996;Li and Greenwald 1996), responsible for the cleavage of more then 30 transmembrane proteins, including APP and notch. PS is located in the membranes of the golgi and endoplasmatic reticulum and in the plasmamembrane (Kovacs *et al* 1996). The mammalian presenilin family constitutes of 2 presenilins, PS1 and PS2, which are highly homologous. Presenilins were discovered to be involved in familial Alzheimers disease in 1995 (Levy-lahad *et al* 1995; Sherrington *et al* 1995; Rogaev *et al* 1995), on to date more than 150 mutations in these gene are known to be associated with FAD (http://www.molgen.ua.ac.be/ADmutations). PS constitutes the catalytic domain of the γ-secretase complex, which is formed together with the co-factors nicastrin (NCT), anterior pharynx defective 1 (APH1) and PS enhancer 2 (PEN2)(figure 4.1). Two aspartyl residues in the core of PS contain the catalytic activity (Wolfe *et al* 1999).

Presenilin has several substrates that are known to be involved in AD pathology. The most acknowledged role is via APP cleavage (figure 4.2). APP is first cleaved by β-secretase or BACE, a member of the ADAM family. This results in the formation of soluble APP, and a membrane bound C-terminal fragment, which in turn is cleaved by γ-secretase. This results in the release of Aβ-fragments at the γ-cleavage site and a released C-terminal residue (AICD) at the ε-cleavage site that is suggested to be able to translocate to the nucleus and might be able to function as a transcriptional activator (de Strooper *et a*l 1998). Another substrate of presenilin is Notch, a protein that is implicated in cell differentiation and survival. Notch is cleaved via essentially the same mechanism as APP and is discussed in the following chapter.

Presenilin is known to play an important role in the development of the central nervous system. It is widely expressed during embryogenesis, with the highest expression present in the ventrical zone (Moreno-Flores *et al* 1999). $PS1^{-/-}$ mice die shortly after birth and have severe CNS defects including impaired neurogenesis and neuronal survival (Shen *et al* 1997). This is thought to be due to defective notch signalling (Wong *et al* 1997). Besides its γ-secretase dependent functions, PS also has other functions. PS is physiologically involved in the regulation of the threshold for excitotoxicity. Neurons obtained from mice expressing an FAD-linked PS1 mutant showed to be more vulnerable to excitotoxicity, while neurons from $PS1^{-/-}$ mice showed a decrease in sensitivity (Grilli *et al* 2000). It is not known via which pathway PS exert this effect, whether this is γ-secretase dependent or independent, but this could be via involvement in the apoptosis pathway

Presenilin also functions as a scaffold for degradation of β-catenin, by facilitating phosphorylation of PS by PKA and GSK-3β (Kang *et al* 2002). An absence of PS1 leads to decreased degradation and nuclear accumulation of β-catenin, which can potentiate the β-catenin/Wnt pathway (Soriano *et al* 2001).

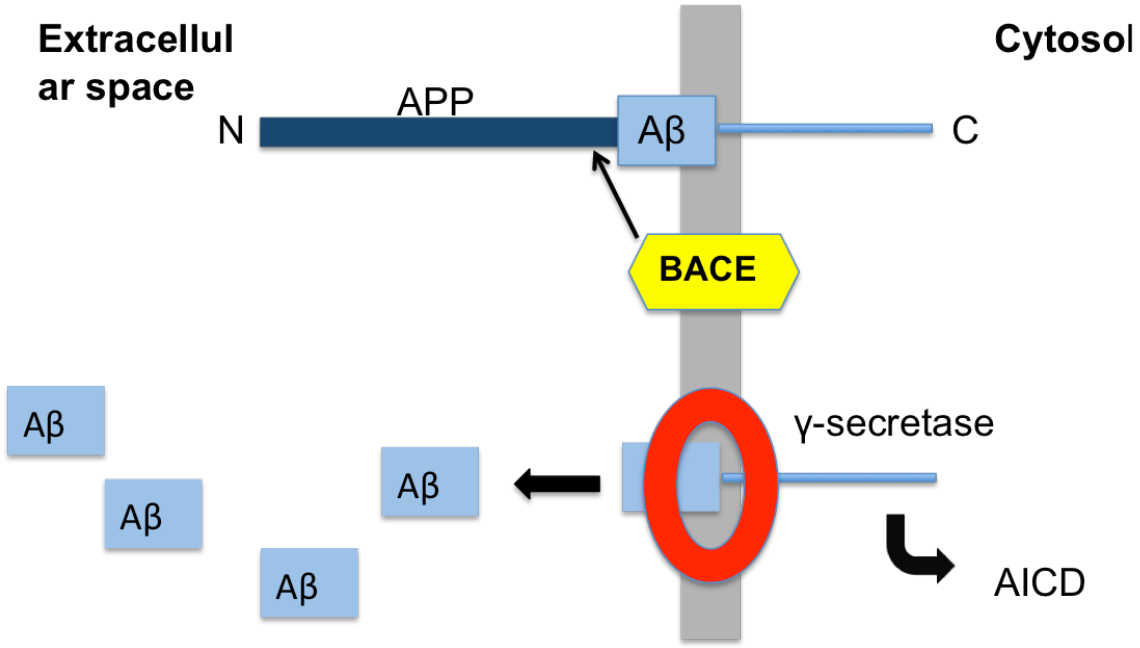

Fig. 4.2: cleavage of APP. APP is cleaved during several sequential steps. First, it is cleaved by a β-secretase (BACE) which results in release of a soluble N-terminal fragment. The membrane-bound C-terminal fragment is then cleaved at the γ-site by γ-secretase to release Aβ peptides and at the ε-site to release the intracellular cleavage domain (AICD) which is thought to be able to translocate to the nucleus and has been reported to function as a transcriptional activator.

4.2 Presenilin and neurogenesis

The fact that presenilin is of crucial importance in notch signalling, made it interesting to investigate the effect of presenilin and presenilin mutations on neurogenesis (for a summary of literature, see the appendix).

Researchers showed that in a model of c. elegans lacking the PS1 homologue sel-12, wild type human PS1 was able to rescue the egg laying deficient phenotype, while a specific mutated form of PS1 showed reduced rescue activity. However, both wild type PS1 and the FAD-linked mutant PS1-A264E were able to rescue the developmental deficits in $PS1^{-/-}$ mice, indicating that this mutation does not cause abnormalities during embryonic development (Davis *et al* 1998). These findings are replicated in $PS^{-/-}$ mice embryos. They show thinning of the ventricular zone, due to a reduction of the neuronal population. They also show a decrease in the neural progenitor pool, which is caused by a premature differentiation of progenitor cells (Handler *et al* 2000).

Because PS deficient mice are not viable, conditional knockouts are created in order to investigate the role of PS1 in the adult mammalian brain. Conditional knock out mice, where PS1 expression is silenced from 6 months postnatally show severe neuronal loss independently of Aβ deposition, which is absent in this model (Chen *et al* 2008). However, in the early stages of neurodegeneration they found increased neurogenesis in the same mouse model, while this neurogenesis is decreased or almost absent in late stages of neurodegeneration. This leads to the suggestion that the neurogenesis in this model is not due to the deficiency of presenilin per se, but that it could also be a direct effect of neurodegeneration. This could also explain the inconsistencies with studies

were decreased neurogenesis was found, in the absence of neurodegeneration (Chen *et al* 2007).

A more relevant model for AD is the use of transgenic animals, expressing FAD linked mutants of PS1 or PS2. Often, these mice also express mutant APP, which makes is sometimes difficult to interpret the result as a consequence of solely the PS1 mutation. Most of the studies report a decrease in neurogenesis, although there is a lot of contradictory data, especially about the mechanisms behind the observed phenotype. Taniuchi *et al* report decreased proliferation of hippocampal progenitor cells in 9 months old mice expressing the Swedish APP mutant and the PS1ΔE9 mutant. In this model, no neuronal degeneration is observed, which is generally considered as a hallmark of AD. They state that the decreased proliferation is due to Aβ plaques (Taniuchi *et al* 2007). In the same model Niidome *et al* report no differences in proliferation in the DG of the hippocampus, but a decreased survival of newly formed neurons. In the other neurogenic zone in the adult, the subventricular zone, no impairments in neurogenesis were observed. This might be due to the localization of Aβ plaques in the hippocampal area (Niidome *et al* 2008). In another model expressing mutant APP and two different FAD-linked presenilin mutations, a decrease in neurogenesis in the hippocampus is observed due to less proliferation and differentiation of neural progenitor cells. This is accompanied by amyloid deposition and neuronal loss (Faure *et al* 2009). This data is somewhat unexpected since in a mice model expressing only APP mutants, neuronal proliferation is often shown to be increased (Ermini *et a*l 2008). Ermini *et al* compared a mice model with only mutant APP with a model expressing both mutant APP and mutant PS1. In the APPmutant model, neurogenesis was increased in 23 months old mice, while in 8 months old APPPS1 mutant mice neurogenesis was decreased. Both animal strains showed plaque load, although there were some differences in distribution.

To investigate the effect of solely FAD-linked PS1 mutations, transgenic animals can be used. $PS1^{-/-}$ mice expressing the P117L mutant show impairments in neurogenesis due to decreased survival and differentiation of newly formed neurons (Wen *et al* 2002, Wen *et al* 2004). This deficiency in neuronal survival is also observed in NPC's derived from transgenic animals expression the P117L mutant, although this was accompanied by an increased proliferation (Eder colli *et al* 2009). The effect of presenilin is also linked to environmental enrichment, since FAD-linked presenilin mutations only impaired neurogenesis by decreased proliferation and decreased survival in an enriched environment (Choi *et al* 2008). They also found that this decreased neurogenesis was influenced by activated microglia, secreting neurogenesis-suppressing substances.

In an adult mouse model, several FAD-linked PS1 mutants showed an increased proliferation in the dentate gyrus of $PS^{-/-}$ animals. These mutants were not able to promote the survival of the newly formed neurons, no difference was observed in the amount of differentiated neurons. This effect is thought to be due to alterations in β-catenin/Wnt signalling that promote proliferation of neuronal stem cells (Chevallier *et al* 2005). Knock-in mice expressing a mutant form of PS1 are shown to enhance nuclear accumulation of β-catenin (Chevallier *et al* 2005). This will lead to enhanced cell proliferation but suppressed neuronal differentiation via complex formation between β-catenin and NICD (Shimizu *et al* 2008).

The exact role of presenilins in neurogenesis remains unclear. It seems that in the physiological situation, presenilins promote the survival of newly formed neurons (Wen *et al* 2002, Wen *et al* 2004). This is consistent with the notion that neurons that express

high levels of PS1 are more resistant to neuronal degeneration in patients with AD (Giannakopoulos *et al* 1997). From the above-mentioned results no clear conclusion can be drawn. The differences in used animal models, presenilin mutants, experimental setups and staining methods make it hard to compare the results. It seems that presenilin mutations sometimes increase proliferation, but that in general the differentiation and survival of the newly formed neurons is impaired, leading to impaired neurogenesis.

5. Notch

5.1 Physiological roles

Notch proteins are a family of transmembrane receptors that exert important functions in cell fate determination and development. The first implications that presenilin was important in Notch signalling came from a study done by Levitan and greenwald in1995. The homologue in c. elegans of presenilin sel-12 was shown to be important for the signalling of lin-12, the c. elegans homologue of the mammalian Notch receptor. Physical interaction of Presenilin and Notch also provided evidence for a role of presenilin in Notch signalling (Ray *et al* 1999). Furthermore, mice deficient for $PS1^{-/-}$ showed to have severe developmental CNS defects, resembling the loss of Notch function (Wong *et al* 1997; Shen *et a*l 1997). These findings are replicated in drosophila harbouring mutant presenilin. These animals have a phenotype that cause lethal Notch-like deficiencies, implicating that presenilin is required for the normal proteolytic cleavage and nuclear entry of Notch (Ye *et al* 1999; Struhl and Greenwald 1999).

In vertebrates there are 4 known notch proteins (notch 1-4) and 5 ligands for the notch receptor (jagged 1 and 2, delta 1-3) (reviewed by Weinmaster 1997). Most research has been done regarding Notch1. Notch1 is a type 1 integral transmembrane protein just as APP. During trafficking of Notch to the cell surface it is cleaved in the Golgi by a furin-like convertase at cleavage site 1 (S1) (Blaumueller *et al* 1997; Logaet *et al* 1998). The two cleavage fragments that remain associated form the functional receptor. Upon ligand binding Notch sheds its ectodomain upon cleavage (S2) by TACE, a member of the ADAM protein family and is further cleaved by the γ-secretase complex (S3 and S4) to release the Notch intracellular domain (NICD) and the Aβ-like peptide Nβ (de Strooper *et al* 1999). Hence, the active NICD is only released after appropriate synthesis, trafficking and activation by an appropriate ligand. PS1 deficiency decreased the amount of released NICD, thereby indicating a proteolytic cleavage by presenilin as an essential step in notch pathway (de Strooper *et al* 1999). The NICD can translocate to the nucleus where it binds members of the CSL DNA-binding protein family, CBF1 and RBPjk and the transcriptional co-activator mastermind (Wu *et al* 2000). This complex can recruit general transcription factors and increased the expression of Notch target genes such as the Hes family (Fryer *et al* 2002) to antagonize proneural genes and inhibit neuronal differentiation (Gaiano *et al* 2000). Fast degradation of the NICD is important to prevent inappropriate signalling and is therefore tightly regulated. It involves ubiquitination and degradation by the proteasome (Fryer *et al* 2004). Not only the Notch receptor, but also the ligands delta and jagged are shown to be cleaved by presenilin (Six *et al* 2003; Lavoie *et al* 2003) but the significance of this is not yet fully understood.

Notch activation is mediated by cell-cell contact between cells expressing a Notch receptor ligand, and cells expressing Notch. This enables cells to direct neighbouring

cells via a mechanism called lateral inhibition. This mechanism is generally assumed to be the cornerstone of notch signalling. Early studies showed that in a neuronal

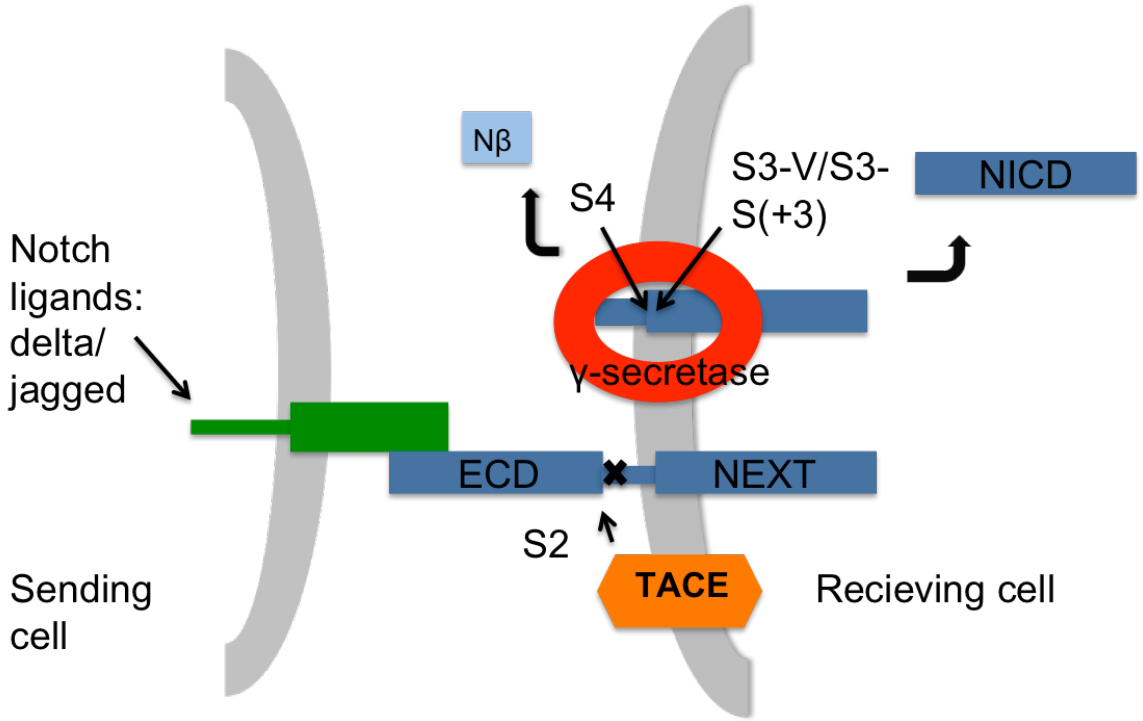

Fig. 5.1: Notch cleavage. Upon ligand binding S2 cleavage takes place to shed the ectodomain (ECD) of notch. This cleavage step is mediated by a member of the ADAM family, TACE. The notch extracellular truncation (NEXT) is cleaved at 2 sites by γ-secretase. The S3 step produces the notch intracellular domain which can translocate to the nucleus and function as a transcriptional activator. The S4 step produces the Aβ-like version of notch: Nβ.

lineage of a grasshopper embryo, developing neuroblasts direct their neighbours into a supporting fate. Once a developing neuroblast is ablated, an adjacent neighbour takes over its place and develops into a neuroblast (Doe and Goodman 1985). The same holds true for Notch signalling. Initially neighbouring cells express the same amounts of Notch and Notch ligands, but subtle stochastic changes direct the cells into overexpress the one and inhibit expression of the other. This in turn results into cell fate specification via lateral inhibition (reviewed in Fortini 2009).

Notch has several roles in the regulation of stem cell proliferation and differentiation both during embryonic neurogenesis, and in the adult stages. Neurospheres derived from embryonic stem cells that are deficient for Delta like gene-1 (notch ligand) show an increased formation of new neurons, at the expense of the formation of glial cells (Grandbarbe *et al* 2003). They state that Notch is involved in step like process, first it is important for the decision between neuronal and glial fate, and then it supports the survival of newly formed glial cells. This inhibition of neuronal differentiation is also shown widely both in vivo and in vitro (Fortini *et al* 1993; Struhl *et al* 1993). There are strong implications that once the glial switch has been made, the progenitor cell irreversibly loses its neuronal potential (Morrison *et al* 2000). These glial promoting properties of Notch are confirmed by other authors (Tanigaki *et al*

2001). Recent evidence shows that Notch-activated neuronal stem cells acquire the astrocytic potential by induction of astrocyte-specific genes (Nahimira *et al* 2009).
Another hypothesized function of Notch is the maintenance of the NSC pool. Grandbarbe *et al* report that they were unable to obtain neurospheres from homozygous Delta like gene-1 knock out mice. This is consistent with the finding that in $PS1^{-/-}$ mice, the stem cell pool is depleted (Hitoshi et al 2001). Mice deficient for presenilin or other factors in the Notch signalling pathway die shortly after birth, making it impossible to investigate them in adult states. In the embryo, notch promotes symmetric stem cell divisions, in order to expand the NSC pool. In the adult stages Notch functions as a regulator of NSC divisions, to prevent depletion of the pool. This might be due to alterations in cell cycle time (Alexson *et al* 2006). This knowledge about the function of notch in neurogenesis lead to the hypothesis that presenilin could influence neurogenesis via altered Notch signalling.

5.2 Presenilin mutations: effects on Notch cleavage

Presenilin mutations were shown to neither influence composition and expression nor brain distribution of the γ-secretase complex (Siman and Salidas 2004). Therefore, PS1/PS2 mutations are hypothesized to alter the enzymatic activity of the γ-secretase complex. The question if presenilin mutations in FAD are pathologic via a gain or a loss of normal function is one of ongoing debate. Bentahir *et al* investigated clinical mutations of presenilin, and the effects on γ-secretase activity. They found that all mutations caused impairment in APP and Notch processing. Some mutations caused an increase in Aβ42 fragments, but most caused a decrease in Aβ40 fragments. Overall this increased the Aβ42/ Aβ40 ratio, increasing the risk of plaque formation. These results are in concurrence with other studies, where 9 clinical mutations in presenilin were tested on APP processing. All of the studied mutations decreased Aβ40, which correlated with the disease onset, while only a few increased Aβ42 production (Kumar-Singh et al). This also raises the possibility that Aβ40 might be a protective molecule. With the current knowledge, it might be more appropriate to speak about a shift in function, instead of only a loss or a gain. Besides this, it has to be taken into account that presenilin has other functions, independent of γ-secretase activity. To fully understand the role of presenilin mutations on AD pathology, possible changes in these functions due to mutations have to be investigated.

Besides alterations in APP cleavage, altered Notch cleavage is assessed in several FAD-linked PS1 mutants and some artificial mutants and are summarized in table 5.1. Most of the studies investigated notch cleavage by measuring the amount of formed NICD, and the amount of uncleaved notch substrate. Several FAD-linked mutations were found to greatly impair notch cleavage with almost no detectable levels of NICD. This included the PS1-L166P, PS2-N141L, PS1-C410Y, G209V and PS1Δ9 mutations (Bentahir et al 1006; Song et al 1999; Nakajima *et al* 2000; Moehlmann *et al* 2002), while other mutations only partially reduced NICD formation. The PS1-A246E mutation was found not to inhibit Notch cleavage (Nakajima *et al* 2000; Bentahir *et al* 2006). Several researchers observed that mutations that would decrease NICD production increased the amount of Aβ42 formed suggesting that the cleavage of APP and Notch might not be regulated in the same way (Moehlmann *et al* 2002; Kulic *et al* 2000). In summary, most investigated FAD-linked mutations in PS1 and PS2 are shown to inhibit notch cleavage and NICD formation, although the severity of this defect varies greatly.

Mutation	Author	Effect on NICD
PS1 ΔE9	Bentahir *et al* 2006 Nakajima *et al* 2000	reduced Almost not detectable
PS1 L166P	Bentahir *et al* 2006 Moehlmann *et al* 2002	No detectable NICD Reduced
PS1 L166R	Moehlmann *et al* 2002	Reduced
PS1 G384A	Bentahir *et al* 2006 Song *et al* 1999	Reduced Reduced
PS1 A246E	Bentahir *et al* 2006 Nakajima *et al* 2000	No effect No effect
PS1 C410Y	Song *et al* 1999	Greatly reduced
PS1 G209V	Song *et al* 1999	Greatly reduced
PS1 M146V	Song *et al* 1999 Nakajima *et al* 2000 Carter *et al* 2008	Reduced No effect No effect
PS1 I143T	Song *et al* 1999	Reduced
PS1 Y115H	Song *et al* 1999	Reduced
PS1 L286V	Kulic *et al* 2000	No effect
PS2 N141L	Bentahir *et al* 2006	No detectable NICD
PS2 D366A	Steiner *et al* 1999	Reduced

Table 5.1: The effect of presenilin mutations on notch cleavage.

5.3 Notch signalling in AD patients

Contradictory to the abovementioned inhibition of the notch signalling pathway in presenilin mutants, the expression of notch is shown to be increased almost 2-fold in sporadic Alzheimer patients (Berezovska *et al* 1998). Again, the question here is whether or not these patients have mutated PS, but for general AD pathology, as far as this exists, these findings could be very relevant. The findings of Berezovska were confirmed by Nagarsheth *et al* 2006. They hypothesize that the increased notch expression might be a way to compensate for the neurodegeneration in AD (Nagarsheth *et al* 2006; Costa *et al* 2003). It is also known that notch signalling is increased in a model of neuronal injury, and that this is associated with reactive astrogliosis (Givogri *et al* 2006). Potentiation of notch signalling is also found in Down syndrome patients (Fischer *et al* 2005). They found significant upregulation of Notch1 and Notch2 and of the Notch downstream target gene Hes1. Notch was shown to directly interact with APP, so this might have nothing to do with altered presenilin function.

6. Discussion

The literature concerning this topic contains a great variety in data. Could presenilin mutations affect neurogenesis via altered Notch signalling? The reasoning could begin at two sides.

Altered neurogenesis, due to presenilin mutations?
The first one is the observed alterations in neurogenesis in both human studies and animal studies. Since in human studies, most of the cases suffered from sporadic AD, and it is not known if they bear a presenilin mutation, animal studies on presenilin mutations bearing transgenic animals seem to be more relevant. The results of these studies are not all in concurrence with each other, but most of the studies show a decrease in neurogenesis, which is due to a decrease in neuronal differentiation and survival (see the appendix for a summary). From what is known about the role of Notch in neurogenesis, this would be most in agreement with an increase of Notch signalling. This would inhibit neuronal differentiation, and would enhance gliogenesis as observed by Handler et al 2000. In this respect, the findings in human studies kind of match with the animal studies: they have found an increase in proliferation (Jin *et al* 2004), but a decrease in neuronal differentiation and survival (Li *et al* 2008), an increase in gliogenesis (Boekhoorn *et a*l 2006) and a reduction in the neural progenitor pool (Ziabreva *et al* 2006). However, this is not in line with the findings on the effect of presenilin mutations on Notch cleavage. When the reasoning starts there, the decreased amount of NICD due to PS mutations would lead to less inhibition of neuronal differentiation hence an increased neurogenesis. A few studies show an upregulation of Notch receptor and downstream targets of Notch (Berezovska *et al* 1998; Fischer *et a*l 2005). However, an increase in Notch expression could be a way to try to compensate for the decreased Notch cleavage thus Notch signalling. The activation of Notch downstream targets is observed in a study in Down Syndrome patients, that are known to have a very similar pathology. An interesting observation is that the study in which increased proliferation/neurogenesis was observed was in a mouse model containing the A246E mutation (Chevallier *et a*l 2005), which was shown to have no effect at all on NICD production (Bentahir *et a*l 2006; Nakajima *et al* 2000). This probably explains the difference, and also suggests that Notch has at least some role in this play.
A mechanism that could enhance the sensitivity for AD is that Notch is important during embryonic development to maintain the neuronal stem cell pool. $PS^{-/-}$ mice, and mice that are deficient of Notch have no neuronal stem cell pool. One mutated allele could lead to a partial depletion, which could influence the ability of the brain to respond to neuronal degeneration during AD pathogenesis. But this does not explain any of the above-mentioned problems in contradictory findings during adult stages.

How can presenilin mutations affect Notch?
How can Notch signalling be affected differently then a change in the amount of NICD production? Recent evidence suggests that, as with the process of APP cleavage, during notch cleavage a notch-1 Aβ-like peptide is formed also known as Nβ. This S4 cleavage corresponds to the γ-cleavage of APP, releasing Aβ peptides (Okochi *et al* 2002). Some FAD-linked PS1 mutants are shown to increase the formation of the aggregation prone Aβ42 form, are now also shown to increase the relative amount of the similar Nβ25 species instead of the Nβ21 species which are comparable to Aβ40 (Okochi *et al* 2006). Although there is nothing known about the function of these Nβ species and about the

consequences of altered Nβ21/Nβ25 ratio, this could be a very interesting topic to investigate further.
Another recent paper reports a shift in S3 cleavage specificity of Notch (see figure 5.1). In cultured cells, Notch is cleaved at different sites. S3-V cleavage leads to formation of NICD-V which is very stable and produces robust notch signalling. S3-V cleavage is shown to be primarily present at the plasma membrane. S3-S(+3) cleavage leads to formation of unstable NICD-S(+3) and primarily occurs in endosomes. They show that in a pathological condition, FAD-linked PS1 mutations shift the ratio stable/unstable Notch towards an increase in unstable Notch (Tagami *et al* 2008). They present this as a novel way in which Notch signalling is regulated, but concomitantly this could also have major consequences in the light of AD pathology.

Other pathways
A lot of evidence points to presenilin as being important in the survival of new neurons. Observations in presenilin mutants support this, since a decrease in neuronal survival is reported. An interesting finding links presenilin, neuronal survival and learning and memory. Several molecules known to be involved in learning and memory processes such as LTP are also found to be important in neuronal survival (Mantamadiotis *et al* 2002). These include CREB and BDNF. In PS1 conditional knock out mice, transcription of CREB/CBP target genes is shown to be reduced (Saura *et al* 2004). They suggest that this reduction is caused by impaired Notch signalling which feels counterintuitive since Notch signalling itself is known to inhibit neuronal differentiation. Another interesting finding in this perspective is that reduced Notch signalling is shown to impair spatial learning and memory processes, and could also directly be involved in learning and memory defecits (Costa *et al* 2003).

Presenilin also has an effect on neurogenesis via β-catenin. As described above, presenilin functions as a scaffold for degradation of β-catenin. Mutations in PS1/PS2 could then lead to accumulation of β-catenin, which can influence neurogenesis via the Wnt pathway. Recent research however provides evidence that in a physiological condition, stabilized β-catenin can promote proliferation and suppress differentiation of neural precursor cells by interacting with the notch pathway (Shimizu *et al* 2008). This could also play a role in the pathological condition where mutated presenilin would give an inappropriate stabilization of β-catenin, which leads to enhancement of Notch signalling. Even though the amount of NICD is reduced, there is probably enough to give proper Notch signalling. This is also how Chevallier *et al* 2005 explain the increase in proliferation that is observed in PS1 transgenic animals. They report an increase in active β-catenin in the cytosol of fibroblasts expressing the transgene that gave the phenotype in a mouse model.

No effect presenilin mutations on neurogenesis via Notch?
It could be considered that the role in Notch signalling of presenilin mutants is overrated (see Azheimer disease forum discussion). FAD patients have no clear developmental deficits associated with disrupted Notch signalling, so the assumption that notch signalling is disrupted during adulthood might be one made to soon. Presenilin mutations are also almost predominantly shown to only partially decrease Notch cleavage, and this defect is maybe compensated for by the remaining 3 healthy presenilin alleles (one PS1, and two PS2 alleles). However, presenilin mutations are thought to have dominant-negative activity, which could impair the activity of the other healthy alleles (Schroeter *et al* 2003)

The broad diversity of functions of presenilin has to definitely be taken into account when trying to find a model for the role of presenilin in AD pathology. Presenilin is known to have a very important role in synaptic functioning (Zhang *et al* 2009). A loss of this function could lead to dysfunctional synapses and ultimately to neuronal degeneration. Furthermore, presenilins are known to be involved in apoptosis (Guo *et al* 1997) although its precise role is highly controversial. FAD-linked PS1 mutants are shown to alter this activity leading to less apoptosis (Ye and Fortini 1999). This is suggested to be due to impaired Notch signalling which is shown to trigger apoptosis (Jehn *et al* 1999). However, others report an increase in apoptosis that is mediated by FAD-linked PS mutants (Guo *et a*l 1997). This confusing evidence shows how complex the role of Notch is in developmental processes, and that is hard to concile all the known functions into one model.
Maybe it is more relevant to talk about presenilin and AD pathology as a two-hit model (Saura *et al* 2004). In this paper, it is stated that Aβ plaques do not become a burden to neurons until there is additional stress. This stress could be provided by the disrupted processes in the cell as a consequence of PS mutations. For example, FAD-linked PS mutants are shown to enhance the vulnerability of neurons to excitotoxicity (Grilli *et al* 2000). This might also be the case for the vulnerability for Aβ plaques.

The Alzheimer puzzle
In order to be able to come to one unified model of AD pathology, there has to be more research done into the basal functions of all the players involved. For Notch, a lot is known about its role during embryonic development, but the role of Notch in the adult brain, and in postmitotic neurons is not yet fully understood. Notch expression levels and regulation of downstream targets in fully matured neurons should be examined, and the effect of several FAD-linked PS mutations on Notch components. Furthermore, it would be very interesting to investigate neuronal proliferation and differentiation in a cohort of patients known to have PS mutations. This might be difficult due to the relative rareness of FAD and to all kind off other limitations, but the obtained data can be very valuable. Given the complexity and heterogeneity of the disease, it is hard to find an appropriate animal model. Still, efforts should be put into the development of relevant animal models for AD. Step by step, small pieces can be put together into the big puzzle of AD pathology.

General conclusion
From all the above-mentioned literature it can be concluded that neurogenesis processes in AD pathogenesis are a very interesting topic to investigate further. Evidence from both animal and human studies show that neurogenesis is altered in AD. It seems that this is due to a decrease in neuronal differentiation and survival. There is also some evidence that there is an increase in gliogenesis, which can be harmful through various ways including an excessive inflammatory response. It is sure that presenilin is essential in notch signalling, and that mutations in PS can affect the amount of cleaved notch substrate. How exactly notch signalling is altered due to these mutations and how this can affect neurogenesis is not exactly known. It could well be that the altered neurogenesis is a consequence of altered notch signalling, but taking the wide variety of other functions of presenilins into consideration, it is very unlikely that notch is the only affected pathway by PS mutations. Mutations might render neurons more vulnerable to toxic substances such as Aβ42 via disruption of a variety of

pathways. This adds to the complexity of the pathogenesis of AD, and highlights some of the keypoints that have to be investigated in the future.

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Appendix

	Mutation	age	observed phenotype
PS k.o			
Handler et al 2000	$PS^{-/-}$ mice	embryo's	no difference in proliferation but severe neuronal loss due to less differentiation
Chen et al 2008	conditional PS1 k.o.	adult	enhanced proliferation , but in late neurodegenerative stages, less survival.
Feng et al 2001	conditional PS1 k.o.	adult	reduced neurogenesis in respons to EE
PS + APP transgenic			
Faure et al 2009	PS1-M233T and PS1-L235P, APPswe	6 months	less proliferation and differentiation
Taniuchi et al 2007	APPswe, PS1deltaE9	5 + 9 months	5m: no effect in proliferation, 9m: decreased proliferation
Niidome et al 2008	APPswe, PS1deltaE9	9 months	DG: no decreased proliferation but decreased survival
Ermini et al 2008	APPswe and PS1-L166P mutation	8 months	decreased neurogenesis, despite plaques.
3x Transgenic			
Rodriguez et al 2009	PS1-M146V, APPswe, tau-P301L	3 - 12 months	decreased proliferation in SVZ
Rodriguez et al 2008	PS1-M146V, APPswe, tau-P301L	6 - 12 months	decreased proliferation in DG
PS Transgenic			
Chevallier et al 2005	PS1-A246E in $PS^{-/-}$ mice	3 - 4 months	increased proliferation, no difference in differentiation
Wen et al 2002	PS1-P117L in $PS^{-/-}$ mice	3 - 4 months	decreased survival and differentiation
Eder colli et al 2009	PS1-P117L in $PS^{-/-}$mice	NPC's from embryo's	more proliration but less neurogenesis due to less differentiation
Wen et al 2004	PS1-P117L in $PS^{-/-}$ mice	3 - 4 months	impaired neurogenesis, impaired survival and differentiation
Choi et al 2008	PS1deltaE9 and PS1M146L	NPC's from 1-2 month old mice	only in EE: impaired neurogenesis (proliferation and differentiation)