Neuronal Migration and Neurodegeneration: 2 Sides of the Same Coin

The human genome contains only about double the number of genes in comparison to the fruit fly. This necessitates efficient recurrent usage of the same molecular components to participate in different processes. When the same proteins are used for different signaling pathways, it may be conceivable that if they go awry the phenotypic consequences may vary to a great extent. The involvement of amyloid β precursor protein, Presenilin-1, and Tau in the pathogenesis of Alzheimer’s disease is well established. Here we are highlighting a second facet of their function, their participation in developmental and adult neuronal migration. We propose that the prevalent and early Anosmia found in Alzheimer’s patients may be due in part to malfunctioning of the above-mentioned proteins.

Keywords: Alzheimer’s disease, APP, neuronal migration, PSEN1, Tau

Introduction

Alzheimer’s disease has been extensively studied for more than a century (reviewed by Goedert and Spillantini 2006; Hardy 2006; Small and Cappai 2006). This intensive research has uncovered the identity of proteins involved in the pathogenesis of this devastating and common neuronal degeneration. The hallmarks of the disease include progressive memory loss with the accumulation of typical neuritic plaques and neurofibrillary tangles. The plaques contain deposits of amyloid β-protein (Aβ), which is the proteolytic product of amyloid β precursor protein (APP; reviewed by Selkoe 2001; Wolfe and Guenette 2007). The protein products of 2 similar genes Presenilin-1, -2 (PSEN1 and PSEN2) are part of the γ-secretase complex involved in APP intramembranous cleavage. The neurofibrillary tangles are composed of filaments of hyperphosphorylated tau (reviewed by Avila et al. 2004; Mandelkow et al. 2007). Despite extensive research in this field, our current understanding of the molecular mechanisms underlying disease pathogenesis is incomplete. We suggest that implementation of our knowledge on the functions of the same protein products studied in other processes will contribute to our understanding of their pathological related roles. In particular, we want to emphasize the functions of these gene products during neuronal migration processes occurring in the developing embryo and in the adult brain. Finally, we propose that malfunctioning neuronal migration processes may be relevant to one early aspect of Alzheimer’s disease, which is loss of olfaction.

Neuronal migration is key to proper brain formation because most neurons are born in a position different from which they will reside in. The 6 layers of the cerebral cortex are composed from neurons that are born in different areas but are subsequently organized according to their birthdating. Neurons reach their target destination using different modes of migration. Neurons born in the germinal zones of the dorsal telencephalon migrate toward the pial surface of the cortex in a radial path. These neurons are the pyramidal or the excitatory neurons of the cerebral cortex. Neurons migrating along this route attach to radial glia, which provide the primary pathways for directed migration (Hatten 2002; Kriegstein and Noctor 2004; Ayala et al. 2007). Live cell imaging and in utero electroporation experiments have revealed that these neurons change their morphology during migration. During most of their migratory route, they exhibit a bipolar structure with a leading edge directed toward the pial surface and a trailing process pointed below. Within the subventricular zone (SVZ) and lower intermediate zone, an additional transient multipolar stage has been detected. This transient multipolar stage has been detected in several types of neurons and for neocortical neurons is a step preceding the migration along radial glia (Loturco and Bai 2006).

A different mode of migration, known as tangential migration, is employed by a subpopulation of neurons, which migrate tangentially across the plane of the glial fiber system (Marin and Rubenstein 2001; Kriegstein and Noctor 2004; Ayala et al. 2007). In rodents, the main source of cortical inhibitory neurons is from the proliferative zones of the ganglionic eminences in the ventral telencephalon. These neurons migrate along a tangential route to the cerebral cortex.

One tangential migration route is maintained in the adult brain. Active neurogenesis and migration are necessary to replace neurons in the olfactory bulb (reviewed by Lledo et al. 2006). These inhibitory neurons are born in the SVZ and migrate along the rostral migratory route in a chain migration stream to the olfactory bulb (Marin and Rubenstein 2001).

One of the early features of Alzheimer’s and of additional neuronal degenerative diseases such as Parkinson involves reduction in perception of odors (Doty et al. 1987; Ohm and Braak 1987; Talamo et al. 1989; Hawkes 2006; Albers et al. 2006). Therefore, we propose that impairment in the neuronal migration pathway to the olfactory bulb may be one of the first signs of Alzheimer’s and review the involvement of the above-mentioned proteins in regulation of neuronal migration.

Amyloid β Precursor Protein

The proteolytic product of APP is the main component of the neuritic plaques; however, its importance in Alzheimer’s was underscored by the detection of mutations in the APP gene in patients (Chartier-Harlin et al. 1991; Goate et al. 1991; Murrell et al. 1991). More than 20 point mutations were detected (http://www.molgen.ua.ac.be/ADMutations). However, not only point mutations trigger this devastating disease but also

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duplications of the APP gene were detected in early-onset Alzheimer’s patients (Rovelet-Lecrux et al. 2006; Sleeegers et al. 2006). Thus, strongly suggesting dosage sensitivity for this locus. This finding also explains the high occurrence of Alzheimer’s in Down syndrome patients that have an extra copy of the APP gene (reviewed by Menendez 2005). It appears that a common denominator to many familial Alzheimer’s mutations is an increase in the amyloid forming Aβ42 proteolytic product of APP (Tanzi et al. 2004; Shen and Kelleher 2007). This statement relates not only to mutations in APP but also to mutations in PSEN1 and PSEN2 (discussed below). In summary, it is most likely to categorize APP mutations in Alzheimer’s as gain of function mutations. APP is a single transmembrane protein (Wolfe and Guenette 2007), which is still not fully characterized. APP is a member of a gene family in mammals that includes 2 additional amyloid precursor-like proteins APLP1 and APLP2 (reviewed by (Walsh et al. 2007). Both APLPs are processed by secretases and subject to ectodomain shedding. The in vivo role of the APP proteins during development was studied in compound mutant mice (Heber et al. 2000; Herms et al. 2004). The brains of the triple mutants displayed a phenotype resembling human type II cobblestone lissencephaly (a condition which is characterized by overmigration of neurons into the subarachnoid space) with ectopic clusters of neuroblasts that migrated through the basal lamina and pial membrane. In addition, a reduced survival of Cajal--Retzius cells was noted. The observed phenotype may be related to the known interaction of APP family proteins with the adapter disabled homolog 1 (Dab1; Trommsdorff et al. 1998; Homayouni et al. 1999), which is a mediator of the reelin signaling pathway (Rice and Curran 2001). The “basic” reelin pathway includes the large extracellular ligand, reelin (D’Arcangelo et al. 1995; Hirotsune et al. 1995; Ogawa et al. 1995), 2 receptors belonging to the family of lipoprotein receptors (very low density lipoprotein receptor [VLDLR] and apolipoprotein e receptor [ApoER2]) (D’Arcangelo et al. 1999; Hiesberger et al. 1999; Trommsdorff et al. 1999), and an intracellular adapter molecule, Dab1 (Hong et al. 2000; Howell et al. 1997; Sheldon et al. 1997; Ware et al. 1997). Dab1 needs to be phosphorylated and eventually degraded (Howell et al. 1999, 2000; Feng et al. 2007) in order to properly propagate the reelin signal (Rice and Curran 2001; Reiner and Sapiro 2005). Mutations in the ligand, receptors, or the intracellular adapter protein result in an indistinguishable phenotype known as the mouse “reeler” phenotype. Reeler mice have multiple abnormal cell positioning in different areas of the central nervous system (CNS; reviews: Rice and Curran 2001; Gupta et al. 2002). In the cerebral cortex, the typical layered organization is disrupted, and neurons born relatively late during corticogenesis reside in deep layers beneath the older neurons, thus inverted in comparison with the normal organization (Caviness and Sidman 1973a, 1973b). Furthermore, the splitting of the preplate, which occurs when waves of newly born neurons migrate through the first-born generation of neurons, does not occur.

Reelin affects APP processing; addition of reelin enhanced the interaction between APP and Dab1 and resulted in reduced production of Aβ (Hoe et al. 2006). Dab1 is required for multiple steps of neuronal migration. At the final steps of neuronal migration, Dab1 downregulation is important. The inability to downregulate Dab1 resulted in an overmigration phenotype (Feng et al. 2007). Therefore, it may be possible to relate the overmigration phenotype observed in the brain of the triple APP family members to their interaction with Dab1. A strong confirmation to this assumption came from a different study where endogenous APP levels were reduced by in utero electroporation (Young-Pearse et al. 2007). Acute reduction of APP strongly inhibited neuronal migration. Importantly, overexpression of Dab1 was able to rescue the phenotype of APP knockdown, suggesting that Dab1 acts downstream of APP in the function of cortical plate entry. Coreduction of APP and Dab1 resulted in a pronounced retardation of neuronal migration. Furthermore, Dab1 needed to be present for APP overexpression to accelerate neuronal migration. Collectively, the above-mentioned data strongly suggest that APP family proteins have a role in affecting the neuronal migration related reelin signaling pathway. A specific function for Dab1 in postnatal migration of interneuron precursors from the SVZ to the olfactory bulb has been demonstrated (Andrade et al. 2007). In mice lacking Dab1, the rostral migratory stream is essentially absent and neuroblasts accumulate in the SVZ.

The proliferation and migration of neuronal progenitor cells to the SVZ were severely impaired in APP mutant mice or mice infused with Aβ (Haughey et al. 2002). All APP family member gene products are highly expressed in the olfactory system (Loffler and Huber 1992; Clarris et al. 1995; Utsumi et al. 1998; Genter et al. 2003) and play a role there (Clarris et al. 1995; Thinakaran et al. 1995; Strubel et al. 1998). In addition, olfactory mucosa and olfactory bulb contain high levels of β-amyloid and amyloid precursor proteins in patients with Alzheimer’s disease, Parkinson’s disease, and Down syndrome (Yamagishi et al. 1994; Crino et al. 1995). In summary, APP proteins are likely to participate in regulation of migration of precursor neurons to the olfactory bulb, which in turn will be influenced in case of APP mutations.

Presenilin

Linkage analysis studies led to the successful cloning of the 2 related genes PSEN1 and PSEN2 (Levy-Lahad et al. 1995; Sherrington et al. 1995). In Alzheimer’s patients, multiple different mutations have been identified in both the genes. Presenilins are part of the γ-secretase complex, which cleave APP, and other important substrates such as Notch (Zhang et al. 2000), which play an important role in regulation of neuronal migration. Mutations in either presenilins or APP result in an increased ratio between the long (Aβ42) and the short (Aβ40) β-amyloid peptides (reviews: De Strooper 2007; Hardy 2007; Wolfe 2007). Aβ42 is the major Aβ form deposited in the plaques. Conditional knockout of both presenilins results in progressive neurodegeneration in aging mice, accompanied with increased levels of the Cdk5 activator p25 and hyperphosphorylated tau (Saura et al. 2004). PSEN1 roles in the developing brain are numerous. Analysis of Psen1−/− mice revealed its involvement in cell cycle control of neuronal progenitors, leading to premature differentiation mainly at early stages of development (Handle et al. 2000; Yuasa et al. 2002). Following cell cycle exit, neurons migrate to their target position and PSEN1 regulates multiple aspects of neuronal migration. Ectopic clusters of neurons invading the basal membrane were observed in brain sections from PSEN1 deficient mice (Hartmann et al. 1999). This phenotype is similar to type II cobblestone lissencephaly. The rupture of the basal membrane occurs in conjunction with cortical neurons protruding the subarachnoid space (Barkovich et al. 2005). Additional studies indicated abnormalities both in radial glia mediated migration and in tangential migration.
(Handler et al. 2000; Louvi et al. 2004). On top of that, the
structure and organization of the radial glia in Psen1 mutant
tissue is significantly different from that in the wild
type (Louvi et al. 2004). Furthermore, double mutant mice of
Psen1 and Psen2 exhibited early embryonic lethality at
embryonic day 9.5 (Donoviel et al. 1999). The mutant embryos
exhibited multiple patterning defects and abnormal expression of
genets lying downstream of the Notch pathway. The Reelin
and the Notch pathways are interconnected. Reduction of a
Notch downstream gene has been detected in Reeler mice
(Baba et al. 2006). Reeler activated Notch in human neuronal
progenitor cells via a direct interaction of Dab1 with Notch
(Keilani and Sugaya 2008). Furthermore, Reeler mice exhibited
a reduction in the intracellular cleaved form of Notch intracel-
lar domain (NICD) suggesting that loss of Notch
signaling results in migration deficits (Hashimoto-Torii et al.
2008). Support for this notion came from overexpression of
NICD in Reeler mice, which alleviated the migration phenotype.
In vitro studies demonstrated that the possible underlying
mechanism is that reelin signaling inhibits NICD degradation via
DAB1 (Hashimoto-Torii et al. 2008).

Whether Presenilins play a role in migration to the olfactory
bulb has not been directly assessed. Nevertheless, they are
important for tangential migration (Louvi et al. 2004) and are
expressed in the related tissues (Utsumi et al. 1998; Nilsberth
et al. 1999; Yan et al. 2004). Fruit flies lacking the single
Presenilin ortholog exhibit deficits in both visual and olfactory
learning assays (Knight et al. 2007), thus suggesting that this
protein may participate also in synaptic functioning in the
olfaction system. Mice heterozygote for the reeler mutation do
not show the cortical layering phenotype, yet exhibit olfactory
discrimination learning deficits (Larson et al. 2003). Collect-
ively, we believe that Presenilins are likely to participate in
olfaction regulation, which will be impaired in case of
mutations in either of the Presenilin genes.

**Tau**

Tau is the major component of tangle filaments. The 2
prototypic lesions of Alzheimer’s disease, the plaques and the
tangles, can occur independent of each other (reviewed by
Selkoe 2001). Tau is a microtubule-associated protein (MAP)
which is best known for its involvement in a group of
neurodegenerative diseases collectively known as tauopa-
thies, of which the most common one is Alzheimer’s disease
(reviews by Mandelkow EM and Mandelkow E 1998; Avila et al.
2004; Rademakers et al. 2004; Ballatore et al. 2007; Hernandez
and Avila 2007). Mutations within the MAPT (tau) locus result
in frontotemporal dementia with Parkinsonism (Hutton et al.
1998; D’Souza et al. 1999). A potential cascade of events
leading to axonal degeneration initiates with a pathological
increase or redistribution of Tau in neurons (Braak H and
Braak E 1991; Mandelkow EM and Mandelkow E 1998; Baas
and Qiang 2005). Accumulation of Tau on the microtubules
blocks the path of motor proteins. Consequently, Tau
hyperphosphorylated and removed from microtubules, where
the hyperphosphorylated form results in neuronal toxicity
(Mocanu et al. 2008). Increased expression of Tau interferes
mainly not only with the activity of anterograde molecular
motors (kinesins) but also with that of the retrograde
molecular motor cytoplasmic dynein (Seitz et al. 2002; Stamer
et al. 2002; Mandelkow et al. 2004; Dixit et al. 2008). An
alternative scenario may be that Tau affects microtubule polarity. Its overexpres-
sion there revealed a surprising mix of polarity of micro-
tubules, which resulted in displacement of transported
organelles (Shemesh et al. 2008).

Reduced activity of molecular motors may be of great
importance in case of neurodegenerative diseases (reviews:
Hirokawa and Takemura 2004; Holzbaur 2004; Stokin and
Goldstein 2006). However, the participation of cytoplasmic
dynein in regulation of neuronal migration is well established.
The realization that cytoplasmic dynein plays a pivotal role in
migratory neurons of the developing brain was appreciated
following the identification of the LIS1 gene associated with
lissencephaly, a severe human neuronal migration disorder
(Reiner et al. 1993). Experiments in the fungus Aspergillus
nidulans suggested an evolutionary conserved role for LIS1
and other LIS1 interacting proteins in regulation of cytoplasmic
dynein during nuclear motility (reviews Morris et al. 1998;
Reiner 2000; Tsai and Gleesos 2005; Ayala et al. 2007).

So far, the role of tau in neuronal migration has yet to be
proven beyond doubt. There is a genetic interaction between the
Reelin pathway and tau hyperphosphorylation (Hiesberger
et al. 1999; Brich et al. 2003). Mice deleted for tau exhibited
a reduction in microtubule density in small caliber axons
(Harada et al. 1994), as well as muscle weakness and memory
disturbances (Ikegami et al. 2000). It has been proposed that
developmental functional redundancy by increase expression of
other MAPs may explain the relatively mild phenotype
(Harada et al. 1994). This hypothesis has been substantiated by
analysis of Map1b Tau double mutant mice, where defects in
axonal elongation and neuronal migration were observed
(Takei et al. 2000). The involvement of Tau in neuronal
migration may also be inferred from analysis of human patients.
Microdeletion of a region encompassing the MAPT gene results
in moderate mental retardation with associated dysmorphic
features (Koolen et al. 2006; Sharp et al. 2006; Shaw-Smith et al.
2006; Varela et al. 2006). The frequency of the microdeletion
syndrome was estimated to be 1:20,000, thus a common
underlying cause for mental retardation. It has been suggested
that the deletion of Tau within this locus is responsible for the
mental retardation phenotype.

Despite the lack of direct evidence linking Tau to migration
to the olfactory bulb, olfactory dysfunction has been noticed in
transgenic mice overexpressing human tau (Macknin et al.
2004). In summary, Tau is likely to participate in regulation of
embryonic and adult neuronal migration. Posttranslational
modifications of Tau and, in particular, phosphorylation and
dephosphorylation are key for its activity in dynamic processes.
Tau phosphorylation status is also abnormal in case of
Alzheimer’s disease. Therefore, we propose that Tau may also
be involved in neuronal migration aberrations in case of
Alzheimer’s disease.

**Concluding Comments**

The best studied niche of adult neurogenesis is in the SVZ from
which newborn neurons migrate to the olfactory bulb (Lois and
2007). As outlined above, protein products associated with
Alzheimer’s disease play an active role in regulation of neuronal migration. It has been suggested that anosmia can be a predictor of neurodegenerative diseases such as Alzheimer’s and Parkinson among different populations (Suzuki et al. 2004; Elbenstein et al. 2005; Tabert et al. 2005; Handley et al. 2006; Kjelvik et al. 2007; reviews: Albers et al. 2006; Hawkes 2006; Galvan and Bredesen 2007). Furthermore, olfactory dysfunction may assist in distinguishing Alzheimer’s disease from depression patients (Graves et al. 1999; Pentzek et al. 2007). In summary, the presented data are consistent with the notion that genes involved in neurodegeneration function during several stages of neuronal migration. It is therefore conceivable that abnormal neuronal migration may contribute to olfactory dysfunction in Alzheimer’s disease.

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