REVIEW

Neuroprotective effects of the Alzheimer’s disease-related gene seladin-1

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Abstract

The endocrine and the nervous system are closely correlated throughout life, starting from the embryo and until the late stages of life. Alzheimer’s disease (AD) is the most common neurodegenerative disease associated with ageing. Unfortunately, an effective way to prevent or to cure this disease does not exist, so far. There is evidence that estrogens exert neuroprotective properties, although their efficacy against AD is still a matter of debate. In 2000 a new neuroprotective gene, i.e. seladin-1 (for SElective AD INdicator-1) was identified and found to be down regulated in AD vulnerable brain regions. Seladin-1 inhibits the activation of caspase-3, a key modulator of apoptosis. This protein has also enzymatic activity. In fact, it has been demonstrated that the seladin-1 gene encodes 3β-hydroxysterol Δ-24-reductase, which catalyzes the synthesis of cholesterol from desmosterol. In recent years, it has been demonstrated that an appropriate amount of membrane cholesterol determines the generation of a barrier against toxic insults and prevents the production of β-amyloid, the histopathological hallmark of AD. This review will summarize the studies that have been focused on the characterization of the biological properties of seladin-1 since its first identification. In particular, the relationship between seladin-1-mediated neuroprotection and estrogens, IGF1 and thyroid hormones, will be described and discussed.

Journal of Molecular Endocrinology (2008) 41, 251–261

Introduction

A tight interplay between the endocrine and the nervous system occurs throughout life, starting from the embryo. Hormones play a role in promoting brain development at the beginning of life and contribute to maintain brain homeostasis until the senile age. With regard to the latter issue, although the neuroprotective role of estrogen is well established, their usefulness in preventing or treating the most common neurodegenerative disease associated with ageing, i.e. Alzheimer’s disease (AD), is still a debated question. The identification of the seladin-1 (SElective AD INdicator-1) gene as a novel neuroprotective factor opened a new scenario on the complex molecular network involving the endocrine and the nervous system. Seladin-1 is the human homolog of the plant DIMINUTO/DWARF1 gene, primarily described in Arabidopsis thaliana (Takahashi et al. 1995, Klahre et al. 1998). This review will sumarize the experimental data obtained in the last few years regarding the characterization of the biological properties of seladin-1 and the relationship of this protein with the endocrine system.

The identification and characterization of seladin-1

The seladin-1 gene was first identified in 2000 by using a differential mRNA display approach to identify genes that were differentially expressed in selective vulnerable brain regions in AD (Greeve et al. 2000), such as the hippocampus, the amygdala, the inferior temporal cortex and the entorhinal cortex (Selkoe 2001). Among the over 30 genes differentially expressed in AD vulnerable brain regions versus unaffected areas, the authors identified a novel cDNA (thereafter named seladin-1) with a markedly reduced expression in the inferior temporal cortex of AD patients compared with the frontal cortex, obtained shortly postmortem. Conversely, seladin-1 was evenly expressed in the brain of unaffected individuals. Later on, we demonstrated that this gene is abundantly expressed in stem cells, whereas the level of expression markedly decreases when these cells are induced to differentiate into mature neurons (Benvenuti et al. 2006). This finding led us to hypothesize that defective seladin-1 expression detected in AD vulnerable brain regions might be linked to an impaired neuronal stem cell
compartment, that could be a potential risk factor to develop this disease. The seladin-1 gene (GenBank accession number AF261758) spans 46.4 kb, maps to chromosome 1p31.1–p33, and comprises nine exons and eight introns; it encodes an open reading frame of 516 amino acid residues. Seladin-1 is located in the endoplasmic reticulum and, although to a lesser extent, in the Golgi apparatus (Greeve et al. 2000).

Apart from the brain, seladin-1 expression has been also detected in many different organs, including endocrine organs, such as the adrenal gland (Greeve et al. 2000, Sarkar et al. 2001, Luciani et al. 2004, Battista et al. 2007), the pituitary gland (Greeve et al. 2000, Luciani et al. 2005), the thyroid gland (Greeve et al. 2000), the prostate (Dong et al. 2005, Hendriksen et al. 2006, Biancolella et al. 2007, Bonaccorsi et al. 2008), the ovary (Greeve et al. 2000, Fuller et al. 2005), and the testis (Greeve et al. 2000).

With regard to its biological effects, seladin-1 was originally found to confer resistance against β-amyloid and oxidative stress-induced apoptosis and to effectively inhibit the activation of caspase-3, a key mediator of the apoptotic process. Interestingly, in PC12 cells (rat adrenal pheochromocytoma) that were selected for resistance against β-amyloid toxicity, the level of expression of seladin-1 was remarkably high (Greeve et al. 2000). A subsequent study demonstrated that the down-regulation of seladin-1 expression in vulnerable AD brain areas is paralleled by an increase in the amount of hyper-phosphorylated tau, a protein component of neuro-fibrillary tangles (Iivonen et al. 2002). The anti-apoptotic effect of seladin-1 has also been associated to a more aggressive behavior and to a defective response to pharmacological treatment in human neoplasia. For instance, in pituitary tumors we have detected markedly higher levels of expression of seladin-1 in non-functioning adenomas compared with GH-secreting adenomas. Accordingly, the somatostatin analogue octreotide was able to activate caspase-3 and to induce apoptosis in primary cell cultures obtained from GH-secreting adenomas, but not from non-functioning adenomas (Luciani et al. 2005). Our conclusion was that seladin-1 may be viewed as one of the factors that confer resistance to pharmacological intervention in this subset of pituitary tumors. In another study, higher levels of expression of seladin-1 in melanoma metastases compared with primary tumors, were associated with resistance against oxidative stress-induced apoptosis (Di Stasi et al. 2005). Very recently, it has been demonstrated that the ability of seladin-1 to protect against apoptosis elicited by oxidative stress may be related to the scavenger activity of this protein (Lu et al. 2008). The authors of the study showed that intracellular generation of reactive oxygen species (ROS) in response to H₂O₂ was diminished in embryonic mouse fibroblasts expressing seladin-1, compared with cells in which the expression had been abolished, thus suggesting a ROS-scavenging activity for this protein. This hypothesis was validated by the observation that intact seladin-1 was associated with high H₂O₂-scavenging activity, whereas an N-terminal deletion caused the loss of this activity. Although the literature unequivocally recognizes the anti-apoptotic property of seladin-1, one single study addressed this protein as a key mediator of Ras-induced senescence (Wu et al. 2004). In this study it was shown that, following oncogenic and oxidative stress, seladin-1 binds p53 in fibroblasts and displaces E3 ubiquitin ligase Mdm2 from p53, thus resulting in p53 accumulation. Ablation of seladin-1 caused the bypass of Ras-induced senescence, and allowed Ras to transform cells. Wild-type seladin-1 cells, but not mutants that disrupt its association with either p53 or Mdm2, were able to suppress the transformed phenotype. These results showed an unanticipated role for seladin-1 in integrating cellular response to oncogenic and oxidative stress. A very recent publication has possibly clarified the apparent discrepancy between the role of seladin-1 in preventing apoptosis on the one hand, and its association with increased levels of p53 on the other hand. Neuroblastoma cells were subjected to acute or chronic oxidative stress. Following acute stress, seladin-1 expression increased and the over expression conferred resistance to H₂O₂-induced toxicity. Conversely, chronic exposure to oxidative stress diminished the expression of seladin-1, but the protective effect was maintained. In fact, reduced seladin-1 levels prevented apoptosis in a p53-dependent manner, via increased p53 ubiquitination and degradation (Kuehnle et al. 2008).

Seladin-1 as an enzyme

A fundamental step forward in unraveling the biological properties of seladin-1 was represented by the demonstration that this protein has also a specific enzymatic activity, which was found to be markedly reduced in desmosterolosis, a rare autosomal recessive disorder characterized by multiple congenital anomalies (FitzPatrick et al. 1998). Patients with desmosterolosis have elevated plasma levels of the cholesterol precursor desmosterol and this abnormality suggested a deficiency of the enzyme 3β-hydroxysterol Δ-24-reductase (DHCR24), which catalyzes the reduction of the Δ²⁴ double bond in desmosterol to produce cholesterol (Fig. 1). Waterham and colleagues identified the human DHCR24 cDNA, which appeared identical to seladin-1 (Waterham et al. 2001). DHCR24 activity was confirmed in vitro by enzymatic assay following heterologous expression of the DHCR24 cDNA in Saccharomyces cerevisiae. Conversely, in constructs containing mutant DHCR24 alleles from patients with desmosterolosis the conversion from desmosterol into cholesterol was absent or markedly reduced. Desmosterolosis belongs to a group.
of several inherited disorders, linked to enzyme defects in the cholesterol biosynthetic pathway at the post-squalene level, which have been described in recent years (Herman 2003). These genetic diseases are characterized by major developmental malformations and in most cases determine severe neuropsychological alterations, suggesting an important role for cholesterol in brain homeostasis.

Figure 1 Cholesterol biosynthesis from squalene. Deficiencies of the circled enzymes are responsible for different inherited disorders of cholesterol biosynthesis. DHCR24, 3β-hydroxysterol Δ²⁴-reductase (desmosterolosis); SC14DM, 3β-hydroxysterol C₁₄ demethylase; DHCR14, 3β-hydroxysterol Δ¹⁴-reductase (Greenberg skeletal dysplasia); SC4DM, 3β-hydroxysterol C₄ demethylase complex (including a 3β-hydroxysteroid dehydrogenase defective in CHILD syndrome); SΔ8 > 7, 3β-hydroxysterol Δ⁸-Δ⁷ isomerase (Conradi Hunermann syndrome); SΔ⁶DS, 3β-hydroxysterol Δ⁶-desaturase (lathosterolosis); and DHCR7, 3β-hydroxysterol Δ⁷-reductase (Smith–Lemli–Opiz syndrome). Modified from Peri et al. (2005).
Interestingly, the DIMINUTO/DWARF1 gene, the plant homolog of seladin-1, encodes an enzyme involved in the biosynthetic pathway of the most active brassinosteroid, brassinolide (Klahre et al. 1998). Brassinosteroids are a class of sterols plant hormones that can be considered as the counterpart of animal steroid hormones. They regulate gene expression, stimulate cell division and differentiation, modulate reproductive biology and promote cell elongation (Clouse & Sasse 1998). Accordingly, DIMINUTO/DWARF1 mutants showed a reduced height compared with the wild-type plant, due a severe reduction in cell length (Takahashi et al. 1995).

The identification of the ε4 allelic variant of the apolipoprotein E as a major genetic risk factor for AD suggests a role for cholesterol in the pathogenesis of this disease, although this is still an open and controversial issue, at present. The published literature is divided between those who support the idea that cholesterol may favor the onset of the disease and those who, on the contrary, believe that cholesterol may play a protective role against AD. In particular, on the one hand some reports showed that elevated cholesterol levels increase β-amyloid formation in in vitro systems and in animal models of AD (Yanagisawa 2002, Herman 2003, Puglielli et al. 2003). Accordingly, epidemiological studies suggest that statin therapy may provide protection against AD, although the clinical benefit of statins might be also due to their cholesterol-independent effects on cerebral circulation and inflammation (Reiss et al. 2004). Furthermore, it has to be said that most of the commercially available statins do not cross the blood–brain barrier. This observation appears to be in agreement with the opinion of those who, on the other hand, support the idea that cholesterol may actually be good for the brain. It has to be considered that the central nervous system contains as much as 25% of the total amount of unesterified cholesterol in the entire body, which is mostly produced via local de novo synthesis. Keeping this in mind, it is not surprising that several studies pointed out the fact that the intracellular content of cholesterol, particularly the amount contained in the cell membrane, should be addressed much more than the plasma levels (Yanagisawa 2002). In this new scenario, the dichotomy between the view of cholesterol as a neurotoxic or a neuroprotective factor might thus be only apparent. If cell cholesterol is considered, an appropriate amount in the cell membrane would create a barrier against toxic insults, whereas a cholesterol-depleted membrane would ease the interaction with toxic factors such as β-amyloid, which may generate for instance an anomalous number of calcium channels leading to the accumulation of toxic levels of calcium (Fig. 2; Arispe & Doh 2002). Accordingly, reduced membrane lipids in the cortex of AD transgenic mice have been detected (Yao et al. 2008). We have very recently provided evidence that over expression of seladin-1, as well as PEG-cholesterol treatment, increases resistance to β-amyloid toxicity and prevents calcium influx in neuroblastoma cells, whereas the exposure to a selective inhibitor of DHCR24 blunts these effects, similarly to cholesterol depletion with methyl-β-cyclo-dextrin (Cecchi et al. 2008). The amount of cell cholesterol may also affect amyloidogenesis. It has been shown that in membranes from AD patients, or in rodent hippocampal neurons with a moderate reduction of membrane cholesterol, the interaction between the amyloidogenic enzyme β-secretase and amyloid precursor protein (APP) is facilitated, thus leading to elevated production of β-amyloid (Fig. 3; Abad-Rodriguez et al. 2004). Similarly, seladin-1

![Figure 2](https://www.endocrinology-journals.org) Interaction between β-amyloid and the cell membrane. In the presence of reduced membrane cholesterol, the insertion of β-amyloid is eased by the fluidity of the membrane (left). Thus, β-amyloid generates open channels through which Ca<sup>2+</sup> ions flow across the membrane is allowed. Conversely, the β-amyloid insertion process is prevented by the stiffness of a cholesterol-enriched membrane (right). From Arispe & Doh (2002), modified.
deficient mouse brains had reduced levels of cholesterol, that were associated with increased cleavage of APP by β-secretase and high levels of β-amyloid. Conversely, seladin-1 over expression increased cholesterol levels and reduced APP processing in neuroblastoma cells (Crameri et al. 2006). These results suggest that loss of membrane cholesterol in neurons contributes both to increased membrane interaction with β-amyloid and to excessive amyloidogenesis in AD. Thus, the reduced expression of seladin-1 in AD vulnerable regions is in keeping with the ‘membrane integrity’ theory. Overall, the experimental findings on the neuroprotective role of seladin-1 are clearly in favor of the hypothesis that an optimal amount of cholesterol may be critical for brain homeostasis. In this view, the role of statins in neuroprotective strategies might be limited to their vasoprotective and/or anti-inflammatory effects.

Mice with a targeted disruption of the DHCR24 gene have been generated (Wechsler et al. 2003). As expected, plasma and tissues of DHCR24−/− mice contained virtually no cholesterol, whereas desmosterol accumulation was observed. These animals were around 25% smaller in size than DHCR24+/+ and DHCR24+/− littermates at birth. In contrast to initial reports, it was subsequently demonstrated that these animals do not survive until adulthood: in fact, they show a lethal dermopathy at birth, associated with retention of epidermal water in agreement with similar observations in patients with desmosterolosis, and die within a few hours (Mirza et al. 2006, 2008).

**Seladin-1 as a new effector of estrogen receptor (ER)-mediated neuroprotection**

There is well established in vitro evidence that estrogens exert neurotropic and neuroprotective effects by stimulating the expression of neurotropins and cell-survival factors, enhancing synaptic plasticity, and acting as an antioxidant factor (Behl 2003, Maggi et al. 2004, Turgeon et al. 2006). AD is more common in women and it is known that decreased estrogen levels after menopause are a risk factor for the disease (Paganini-Hill & Henderson 1994). Thus, estrogen therapy has been considered a rationale option for the treatment of this disease. Despite the lack of general consensus, several studies indicated that estrogen treatment may decrease the risk or delay the onset of AD in post-menopausal women (Fillit 2002). Although the data from the Women’s Health Initiative Memory Study trial indicated that hormone replacement therapy (HRT) has no benefit (Rapp et al. 2003, Shumaker et al. 2003), it has to be considered that a number of factors may determine the efficacy of estrogens or HRT, such as age, the menopausal status, the route of administration and the dose, the starting cognitive function, and the presence of pre-existing risk factors (i.e. smoking, apolipoprotein E genotype; MacLusky 2004, Turgeon et al. 2006). In particular, there seems to be a critical time for estrogen treatment. In fact, early and prolonged therapy has been found to produce the maximum benefit in terms of reduced risk for AD (Resnick & Henderson 2002, Zandi et al. 2002). In addition, estrogen therapy is not the same as HRT and the type of progestogen used may determine the outcome of the therapeutic intervention (Schumacher et al. 2007). The neuroprotective role of the selective ER modulators (SERMs) has been less extensively investigated. Nonetheless, a neuroprotective effect of tamoxifen and raloxifene has been observed (Dhandapani & Brann 2002) and a beneficial role of tamoxifen and raloxifene against β-amyloid toxicity has been demonstrated in rat neurons (O’Neill et al. 2004a,b). The Multiple Outcomes of Raloxifene Evaluation trial evaluated the cognitive function in more than 5000 women with osteoporosis who were assigned to receive...
raloxifene (60 mg or 120 mg) or placebo daily for 3 years. Compared with those taking placebo, women receiving 120 mg/day of raloxifene had a 33% lower risk of mild cognitive impairment and somewhat lower risks of AD and any cognitive impairment (Yaffe et al. 2005).

In order to establish whether seladin-1 may be involved in estrogen-mediated neuroprotection, we have taken advantage of a unique cell model of human fetal neuronal precursor, that expresses both ER α and β (Barni et al. 1999). These fetal neuroepithelial cells (FNC) are long-term cell cultures from human fetal (8–12 weeks of gestational age) olfactory epithelium, that were established, cloned and propagated by Vannelli et al. (1995). FNC cells express both neuronal and olfactory markers that are typical of maturing olfactory receptor neurons, are electrically excitable and following exposure to a number of different aromatic chemicals show a specific increase in intracellular cAMP, indicating some degree of functional maturity (Vannelli et al. 1995). Thus, FNC cells appear to originate from the stem cell compartment that generates mature olfactory receptor neurons.

Preliminarily, we confirmed the protective role of estrogens/SERMs in the brain. In fact, 17β-estradiol was able to stimulate cell proliferation (100 pM and 100 nM) and to effectively counteract β-amyloid- and H2O2-mediated toxicity (100 pM, 10-100 nM; Benvenuti et al. 2005). In agreement with 17β-estradiol, also the SERM tamoxifen (100 pM–100 nM) effectively protected FNC cells from the toxic effects of β-amyloid, whereas partially different results were observed with raloxifene. In fact, cell viability after exposure to β-amyloid was preserved at low concentrations of raloxifene (100 pM and 1 nM). Conversely, 10 and 100 nM did not exert protective effects. In addition, we demonstrated that the protective action of estrogens in FNC cells was associated with a counteracting effect against β-amyloid-induced apoptosis, as demonstrated by the strong inhibition of the activation of caspase-3. In the same study, we also demonstrated that FNC cells constitutively express seladin-1 and that 17β-estradiol (10 pM–100 nM), tamoxifen (1 nM), raloxifene (1 nM), and a selective ERα agonist (propylpyrazole-triol; 10 nM) significantly increased the amount of mRNA. However, a selective ERβ agonist (diarylpropionitrile; 10 nM) did not affect seladin-1 expression, whereas higher concentrations of raloxifene (10–100 nM) determined a marked reduction. These findings, and in particular the parallelism between the concentrations of raloxifene that conferred neuroprotection on the one hand, and stimulated seladin-1 expression on the other hand, led us to hypothesize that seladin-1 might be a mediator of the neuroprotective effects of estrogens/SERMs.

Noteworthy, this hypothesis was supported by an additional very recent study. In fact, we demonstrated that, upon silencing seladin-1 expression by small interfering RNA (siRNA) methodology, the protective effect against β-amyloid and oxidative stress toxicity exerted by 17β-estradiol was lost (Fig. 4). The specificity of these results was validated by the observation that in cells exposed to control siRNA the protective effects of 17β-estradiol were maintained (Luciani et al. 2008). Furthermore, a computer assisted analysis revealed the presence of half-palindromic estrogen responsive elements (EREs) upstream of the coding region of the seladin-1 gene. A region spanning around 1500 bp was cloned in a luciferase reporter vector, which was transiently co-transfected with the ER α in CHO cells. The exposure to 17β-estradiol, as well

Figure 4 (A) Effect of 17β-estradiol (E2; 10 nM for 48 h) against β-amyloid (BA; 100 nM for 18 h) toxicity in FNC (white columns) or in FNC cells subjected to seladin-1-specific siRNA (grey columns). (B) Effect of 17β-estradiol (10 nM for 48 h) against oxidative stress (200 μM H2O2 for 20 h) in FNC (white columns) or in FNC cells subjected to seladin-1-specific siRNA (grey columns). The results were expressed as mean percentage ± S.E.M. of viable cells/well in three different experiments. *P<0.05 versus the corresponding untreated control cells; # = P<0.05 versus the corresponding cells exposed to β-amyloid (A) or to H2O2 (B). Modified from Luciani et al. (2008).
as to raloxifene and tamoxifen increased luciferase activity, thus suggesting a functional role for the half EREs of the *seladin-1* gene. Overall, these additional data provided a direct demonstration that seladin-1 is a fundamental mediator of the neuroprotective effects of estrogens.

**Seladin-1 as a mediator of the pro-survival effects of IGF1**

There is strong evidence that the insulin-like growth factor (IGF) system plays an important role in the nervous system by favoring for instance neuronal development, metabolism, survival, and regeneration (Matthews & Feldman 1996, Russo et al. 2004, 2005, Mendez et al. 2005). Conversely, high glucose concentrations may be detrimental to nerves and it is generally accepted that one of the mechanisms leading to diabetic neuropathy may be related to a direct or an indirect effect of glucose levels. Glucose may cause a number of alterations in nervous cells, including for instance altered transcription and translation, ion channel dysfunction, altered axonal transport, demyelination, AGE formation and impaired neurotrophic support (Tomlinson & Gardiner 2008). There is evidence that intermittent high glucose concentrations, as it may occur in poorly controlled diabetes, may be more detrimental to cells than constant high glucose, as observed in endothelial, mesangial, renal tubular cells and fibroblasts (Piconi et al. 2006). However, no previous study had assessed the effect of intermittent high glucose on i) neuronal cell growth and on ii) the IGF system. Furthermore, there are no reports regarding a possible relationship between the IGF system and seladin-1. In view of the reported evidence of a tight link between estrogens and the IGF family in the nervous system in terms of neuronal cell differentiation, survival and regeneration (Mendez et al. 2005, 2006), we reasoned that a relationship between seladin-1 and the IGF1 system might occur, similar to the previously demonstrated association between seladin-1 and estrogens. Thus, very recently we have addressed these issues using again FNC as the *in vitro* cell model. We demonstrated that these cells express IGF1 receptor (IGF1R) and synthesize and release in the culture medium IGF1, IGFBP2 and -4, but not -1, -3, -5 and -6 (Giannini et al. 2008). The exposure to IGF1 (1–100 nM) stimulated cell growth, reduced apoptosis and increased the release of IGFBP2, whereas it decreased the amount of IGFBP4. It is known that IGFBP2 may facilitate the binding of IGF1 to its receptor (Brooker et al. 2000), whereas IGFBP4 is generally considered as a potent inhibitor of the biological effects of IGF1 (Mazerbourg et al. 2004). Conversely, intermittent (20 mM or 10 mM, alternatively), but not constant (20 mM), high glucose concentrations significantly reduced FNC cell growth, increased apoptosis and disrupted the IGF system, as demonstrated by the marked reduction of IGF1 and IGFBP2 release. The addition of IGF1 to the culture medium counteracted the effects of intermittent high glucose on cell proliferation and apoptosis. Interestingly, we found that IGF1 significantly increased seladin-1 expression, whereas high glucose markedly reduced it. Finally, 17β-estradiol (10 nM) treatment determined a ninefold increase of the release of IGF1 in the culture medium, indicating that a cross-talk between estrogens and IGF1 occurs in FNC cells. Overall, these results suggest that seladin-1 might be a mediator of the pro-survival effects of IGF1 in the nervous system, although the exact mechanism of action needs to be addressed in future studies, designed for instance to evaluate the effects of IGF1 and high glucose after silencing seladin-1 expression. In addition, these findings indicate that the disruption of the IGF system may be one of the mechanisms through which glucose toxicity causes diabetic neuropathy. An interplay between seladin-1, estrogens and IGF1 may also be envisaged. In particular, both IGF1 and 17β-estradiol directly stimulate the expression of this neuroprotective factor; furthermore, the latter hormone appears to have also an indirect stimulatory effect, by increasing the release of IGF1, which on turn can bind to IGF1R via an autocrine loop (Fig. 5). It remains to be elucidated whether IGF1-induced seladin-1 expression is a direct consequence of IGF1/IGF1R binding or is mediated via an interaction between IGF1R and ER.
Seladin-1 as a mediator of the effects of thyroid hormones (TH) in promoting brain development

It is well known that TH play a fundamental role during fetal life, particularly in promoting brain development. TH affect the expression of genes, that are related, for instance, to cell migration (i.e. reelin, laminin, tenasin C), myelination (i.e. myelin basic protein, proteolipid protein, myelin associated glycoprotein) and neuronal differentiation (i.e. nerve growth factor (NGF), brain-derived neurotropic factor (BDNF); König & Neto 2002, Santisteban & Bernal 2005). Accordingly, it has been shown that early maternal hypothyroxinemia alters fetal brain histogenesis and cytoarchitecture in rats (Lavado-Autric et al. 2003), and unrecognized hypothyroidism in women in the first trimester of pregnancy may adversely affect the neuropsychological development of the progeny (Haddow et al. 1999, Pop et al. 2003, Morreale de Escobar et al. 2004). There is also evidence both in embryonic and adult mammals supporting a key role of TH in the development and maintenance of basal forebrain cholinergic neurons typically involved in AD (Patel et al. 1987, Calzá et al. 1997). Therefore, we hypothesized that seladin-1 might be a mediator of the effects of TH in the brain. In particular, we addressed the potential role of this factor during the development of the nervous system. To this purpose we used FNC cells and human mesenchymal stem cells (hMSC) as cell models representing neuronal precursors. The choice of hMSC was based on the fact that these cells, that are much more easily obtainable than neuronal stem cells, may be readily differentiated into neurons (Woodbury et al. 2000, Sanchez-Ramos 2002, Benvenuti et al. 2006). We first demonstrated that both FNC and hMSC express TH receptors and that T3 was able to promote the differentiation into a neuronal phenotype, as assessed by morphological, immunocytochemical and electrophysiological evidence (Benvenuti et al. 2008). In addition, T3, and to a lesser extent T4, significantly increased the expression of seladin-1 in both cell types and effectively counteracted camptothecin-induced apoptosis. However, in hMSC that had been differentiated into mature neurons (hMSC-n), the expression of seladin-1 was significantly lower than in undifferentiated cells and was not affected by TH (Fig. 6). This finding is in keeping with similar observations from in vivo studies performed in experimental animals showing that most of the TH-regulated genes are responsive only during a limited time interval of brain development (König & Neto 2002). The biological role played by the increased expression of seladin-1 induced by TH in neuronal precursors remains to be fully elucidated and additional

Figure 6 Effect of T3 and T4 on the amount of seladin-1 mRNA levels in FNC, hMSC and hMSC-derived neurons (hMSC-n), as assessed by real-time RT-PCR. * P<0.05 versus untreated cells (C). From Benvenuti et al. (2008), modified.

Figure 7 Model representing the hypothesized role of seladin-1 during brain development. TH stimulates the expression of seladin-1, that may contribute to maintainenance of a pool of undifferentiated and self-renewing neuronal precursors. In addition, TH induces the expression of genes, that promotes the differentiation of neuronal precursors into mature neurons.
studies performed, for instance, in seladin-1 ‘silenced’ cells, will probably provide an answer to this question. However, bearing in mind the well established anti-apoptotic activity of seladin-1, we hypothesized that one of the functions associated with the increased seladin-1 levels in the developing brain may be to protect neuronal precursor cells from death. From this point of view, seladin-1 might therefore be regarded as a factor, which helps in maintaining a pool of young and self-renewing multipotent cells, to be then made available to other TH-regulated genes, which are able to promote the differentiation toward a neuronal phenotype (Fig. 7).

Conclusions

The experimental data summarized in this review suggest that the role of seladin-1 in the nervous system may extend beyond its originally recognized neuroprotective effect against AD. Since its first identification, seladin-1 (and perhaps this name should be no longer considered appropriate) has opened a new possible scenario on several very interesting issues, including for instance: i) the role of cell cholesterol and, in a broader view, of cholesterol-enriched membrane microdomains (i.e. lipid rafts) in neuroprotection; ii) the role of hormone-mediated neuroprotection in preventing or in treating neurodegenerative diseases; iii) the relationship between the IGF system and diabetic neuropathy, as well as other neuropathies; iv) stem cell-based neurogenesis and the role of TH in brain development. Obviously, these issues need further thorough investigation in order to fully elucidate both the role of seladin-1 in maintaining nervous cells homeostasis and the alterations leading to pathological conditions affecting the nervous system, aiming to possibly identify new areas of pharmacological intervention.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The experimental studies presented in this review were partially supported by a grant from Ente Cassa di Risparmio di Firenze and by a grant from Ministero dell’Istruzione, dell’Università e della Ricerca.

Acknowledgements

The authors wish to thank the following collaborators at the Department of Clinical Physiopathology, University of Florence, Italy, for their tireless support: Des Susanna Benvenuti, Paola Luciani, Ilaria Cellai, Cristina Deledda, Silvana Baglioni, Giovanna Danza, Fabiana Rosati, Matteo Morello, Francesca Dichiara, Corinna Giuliani, Stefano Giannini, and Anna Pezzatini. The support provided by colleagues at the Department of Anatomy, Histology, and Forensic Medicine, the Department of Biochemical Sciences, the Department of Physiological Sciences, the Department of Haematology, the Institute of Dermatology and Venereology at the University of Florence and at the Careggi University Hospital, Florence, and the continuous collaboration with the Institute of Endocrine Sciences and the Laboratory of Developmental Neuroendocrinology, Department of Endocrinology, Centre of Excellence on Neurodegenerative Diseases, University of Milan, and the Department of Endocrinology and Metabolism, University of Pisa are also acknowledged. The authors wish to thank Eli Lilly for kindly providing raloxifene.

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Journal of Molecular Endocrinology (2008) 41, 251–261

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Received in final form 26 August 2008
Accepted 31 August 2008
Made available online as an Accepted Preprint 31 August 2008

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