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Glucose metabolism and insulin receptor signal transduction in Alzheimer disease

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Abstract

Nosologically, Alzheimer disease is not a single disorder in spite of a common clinical phenotype. Etiologically, two different types or even more exist. (1) In a minority of about 5% or less of all cases, Alzheimer disease is due to mutations of three genes, resulting in the permanent generation of βA4. (2) The great majority (95% or more) of cases of Alzheimer disease are sporadic in origin, with old age as main risk factor, supporting the view that susceptibility genes and aging contribute to age-related sporadic Alzheimer disease. However, disturbances in the neuronal insulin signal transduction pathway may be of central pathophysiological significance. In early-onset familial Alzheimer disease, the inhibition of neuronal insulin receptor function may be due to competitive binding of amyloid beta (Aβ) to the insulin receptor. In late-onset sporadic Alzheimer disease, the neuronal insulin receptor may be desensitized by inhibition of receptor function at different sites by noradrenaline and/or cortisol, the levels of which both increase with increasing age. The consequences of the inhibition of neuronal insulin signal transduction may be largely identical to those of disturbances of oxidative energy metabolism and related metabolism, and of hyperphosphorylation of tau-protein. As far as the metabolism of amyloid precursor protein (APP) in late-onset sporadic Alzheimer disease is concerned, neuronal insulin receptor dysfunction may result in the intracellular accumulation of Aβ and in subsequent cellular damage. In this context, the desensitization of the neuronal insulin receptor in late-onset sporadic Alzheimer disease is different from that occurring in normal aging and early-onset familial Alzheimer disease. In late-onset sporadic Alzheimer disease changes in the brain are similar to those caused by non-insulin-dependent diabetes mellitus.

Keywords: Brain; Glucose/energy metabolism; Alzheimer disease; Insulin; Insulin receptor; Glucose

1. Introduction

Nosologically, Alzheimer disease is not a single disorder. Evidence has been provided that a small proportion of 5% or less (326 families world-wide) of all Alzheimer cases are caused by missense mutations in presenilin genes 1 or 2 on chromosomes 14 and 1, or in the amyloid precursor protein (APP) gene on chromosome 21, leading to autosomal dominant familial Alzheimer disease with an early onset (Pericak-Vance and Haines, 1995; Tilley et al., 1998; for review, see Rocchi et al., 2003). This difference in inheritance forms the basis of the amyloid cascade hypothesis of Alzheimer disease, which explains the genetically induced increased formation of the APP derivative βA4, which aggregates to form amyloid and plaques (Hardy and Selkoe, 2002). In contrast, the great majority of all Alzheimer cases (95% or more) are sporadic in origin and of late onset. βA4 has not been proven to be necessary for the generation and the development of sporadic Alzheimer disease (Joseph et al., 2001). Thus, the amyloid cascade hypothesis may not apply to sporadic Alzheimer disease.

Susceptibility genes may contribute to the generation of sporadic Alzheimer disease. Best known are allelic abnormalities of the apolipoprotein E (APOE) gene on chromosome 19 which are responsible for both anticipated onset and increase in severity of both inherited and sporadic Alzheimer disease. The are other potential candidate susceptibility genes for sporadic Alzheimer disease (Rocchi et al., 2003). Another aspect not yet considered is the change in the gene expression profile in the brain with aging and particularly the expression of genes for some ATP-ases and proteins with a protective function and active in synaptic transmission (Whittemore et al., 1986; Parhad et al., 1995; Salehi et al., 1996; Wu and Lee, 1997; Hung et al., 2000; Jiang et al., 2001; Cho et al., 2002). The age-related changes

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in the profile of susceptibility genes may participate in the origin of disorders that become manifest late in life and which have a chronic and progressive course. Such a genetic predisposition together with age-related risk factors may then cause the disease (Holness et al., 2000). Age has been found to be a major risk factor for sporadic Alzheimer disease because of multiple changes at the cellular and molecular level (for review, see Hoyer, 1995, 2000c).

Oxidative energy metabolism is important for the undisturbed function and structure of the brain. Both the neurotransmitter acetylcholine and the membrane sterol constituent cholesterol are derived from the glucose metabolite, acetyl-CoA (Gibson et al., 1975; Michikawa and Yanagisawa, 1999). ATP is formed from glucose only, and is essential to most cellular and molecular activities such as protein synthesis, sorting, transport and degradation of proteins, and maintenance of synaptic transmission (for review, see Hoyer, 2000a). ATP is of particular functional significance in the maintenance of intra/extracellular ion homeostasis (Erecinska and Silver, 1989), and the correct folding of proteins, and in keeping the endoplasmic reticulum and Golgi apparatus at a pH of 6 (Seksek et al., 1995; Verde et al., 1995). ATP-dependent processes such as binding of chaperones to the unfolded state of proteins, its promotion to correct folding and assembly of secretory proteins take place in the lumen of the endoplasmic reticulum (Dorner et al., 1990). It thus becomes obvious that the neuronal glucose/energy metabolism is of central significance to normal cellular and molecular reactions.

There is increasing evidence that neuronal glucose energy metabolism is antagonistically controlled by insulin and cortisol. This short review, therefore, focuses on the ways in which disturbances of the neuronal insulin signal transduction cascade contribute to the cellular and molecular abnormalities occurring in the brain in Alzheimer disease.

2. Insulin and insulin receptor signaling in the brain

2.1. Insulin production, insulin receptor distribution

Substantial evidence has been gathered in support of both the transport of peripheral (pancreatic) insulin to the brain and its production in the central nervous system (Plata-Salaman, 1991; Wozniak et al., 1993). Insulin gene expression and insulin synthesis have been demonstrated in mammalian neuronal cells. Insulin mRNA is distributed in a highly specific pattern with the highest density in pyramidal cells of the hippocampus and a high density in the medial prefrontal cortex, the enthorinal cortex, perirhinal cortex, thalamus and the granule cell layer of the olfactory bulb. Neither insulin mRNA nor insulin synthesis is observed in glia cells (Devaskar et al., 1994). The presence of glucose-responsive neurons in discrete brain areas suggests the existence of a "glucose sensing" mechanism in the brain similar to that found in β-cells of the pancreas. The glucose transport protein 2 (GLUT 2), coupled with glucokinase, participates in the glucose-sensing mechanism of insulin secretion. GLUT 2 mRNA has been found in some brain areas (Leloup et al., 1994, 1998).

Insulin receptors are dispersed throughout the brain in a highly specific pattern, with the highest density being detected in the olfactory bulb, hypothalamus, cerebral cortex, and hippocampus (Hill et al., 1986; Unger et al., 1991). Two different types of insulin receptors have been found in adult mammalian brain: a peripheral type detected in lower density on glia cells, and a neuron-specific brain type detected in high density on neurons (Adamo et al., 1989). It has been shown that the location of phosphotyrosine-containing proteins corresponds to the distribution of the insulin receptor (Moss et al., 1990). It has also been established that the insulin receptor substrate (IRS)-1 co-localizes with these phosphotyrosines. IRS-1 and the insulin receptor are co-expressed in discrete neuron populations in the rat hippocampus and olfactory bulb whereas their proteins have the highest density in the synaptic neuropil (Baskin et al., 1994). Insulin receptor substrate-1 transfers the receptor signal to a wide spectrum of cellular and molecular compounds (for review, see White and Kahn, 1994).

2.2. Insulin receptor regulation

The major molecular structure and most of the biochemical properties of the neuronal insulin receptor are indistinguishable from those of the receptor found in non-nervous tissues. However, some differences have become apparent in that both the α- and β-subunits of the neuronal insulin receptor have a slightly lower molecular weight than their counterparts in non-nervous tissues (Heidenreich et al., 1983). Unlike the insulin receptor in non-nervous tissues, the neuronal insulin receptor does not undergo down-regulation after exposure to high concentrations of insulin (Zahniser et al., 1984).

Binding of insulin to the α-subunit of its receptor induces autophosphorylation of the intracellular β-subunit and subsequent phosphorylation of the intrinsic tyrosine residues of the receptor, leading to activation. Receptor inactivation can be regulated by the action of phosphotyrosine phosphatases (Häring, 1991; Goldstein, 1993). Interestingly, glucocorticoids and catecholamines have also been reported to cause insulin receptor desensitization either by inhibition of phosphorylation of the tyrosine residues or by phosphorylation of serine residues (Häring et al., 1986; Giorgino et al., 1993).

2.3. Insulin/insulin receptor action

2.3.1. Glucose/energy metabolism

Acute stimulation of the cerebral insulin receptor can be achieved with a single intracerebroventricular injection of insulin. This procedure leads to a dose-dependent stimula-

tion of the glycolytic key enzymes hexokinase and phosphofructokinase in the cerebral cortex (Hoyer et al., 1993). Also, insulin has acute stimulatory effects on brain pyruvate dehydrogenase (Rinaudo et al., 1987) and choline acetyltransferase (Kyriakis et al., 1987). These data indicate that both glycolytic flux and pyruvate oxidation in the brain are stimulated by insulin, paralleling the effect of the hormone in non-nervous tissue. Short-term (1 day) or long-term (7 and 21 days) intracerebroventricular infusion of insulin has a discrete anabolic effect on energy metabolism in the hippocampus, as shown by an 11% increase in the concentration of creatine phosphate, the storage form of ATP (Henneberg and Hoyer, 1994). In contrast, inhibition of the neuronal insulin receptor causes severe abnormalities in oxidative energy metabolism and a cholinergic deafferentiation accompanied by behavioral disturbances (Nitsch and Hoyer, 1991; Hellweg et al., 1992; Plaschke and Hoyer, 1993; Duelli et al., 1994; Prickaerts et al., 1995; Lannert and Hoyer, 1998).

Interestingly, insulin and the activation of the insulin receptor have been described to control the expression of a key regulator of cellular DNA repair, the xeroderma pigmentosum complementation group enzyme D (XPD) (Merkel et al., 2003).

2.3.2. Insulin, the APP and derivatives

Insulin/insulin receptor-mediated signal transduction controls the activity of several enzymes in a cascade-like manner. Phosphatidylinositol 3-kinase is insulin-regulated and activates protein kinase B (Alessi and Cohen, 1998; Vanhaesebroeck and Alessi, 2000). This latter enzyme inhibits glycogen synthase kinase (GSK)-3 (Cross et al., 1995), which regulates (GSK-3α) the production of amyloid-β peptides (Phiel et al., 2003). Recent studies have provided clear evidence that βA4 is generated intracellularly in the endoplasmic reticulum/intermediate compartment of the Golgi apparatus (Cook et al., 1997; Hartmann et al., 1997; Wild-Bode et al., 1997; Xu et al., 1997; Greenfield et al., 1999), in a reaction that is ATP-dependent (see above: Dorner et al., 1990; Seksek et al., 1995; Verde et al., 1995).

The intracellular accumulation of both βA (1–40) and βA (1–42) is reduced by accelerating βAPP/βA transport from the trans-Golgi network to the plasma membrane assisted by mitogen-activated protein kinase signaling. This effect, the promotion of βAPP secretion from the intracellular to the extracellular space and the inhibition of its degradation by insulin-degrading enzyme, is mediated by insulin and the tyrosine kinase activity of the insulin receptor (Gasparini et al., 2001). The same holds true for APP release into the extracellular space, which is dependent on the activation of phosphatidylinositol-3 kinase (Solano et al., 2000). Further evidence had been provided for the release of APP derivatives into the extracellular space mediated by the activation of the acetylcholinergic muscarinic m1 and m3 receptors (Nitsch et al., 1992a). Preliminary findings of our group point to the regulation of the expression of muscarinic acetylcholine receptor mRNA by the action of the insulin receptor (unpublished results).

APP potentiates the activity of neurotrophic factors (Wallace et al., 1997a) via the insulin signaling pathway (Wallace et al., 1997b). Both derivatives of APP, Aβ-(1–40) and Aβ-(1–42) reduce the binding of insulin to its receptor by decreasing the affinity of insulin binding, resulting in a reduced receptor autophosphorylation (Xie et al., 2002).

2.3.3. Insulin-degrading enzyme (IDE)

IDE maps on chromosome 10. It is a cytosolic metalloendoprotease which is expressed differently in different tissues (Duckworth, 1988). IDE mRNA increases from the first postnatal week to adulthood, when levels are high in several organs (Kuo et al., 1993). IDE degrades different groups of substrates. Insulin, transforming growth factor α, atrial natriuretic peptide and insulin-like growth factor II are high-affinity substrates with $k_m \sim 0.1$ μM. In contrast, substrates such as glucagon, epidermal growth factor, insulin-like growth factor I, β-endorphin and Aβ analogues show a lower affinity at k_m>2 μM (Kurochkin and Goto, 1994; Perez et al., 2000; Farris et al., 2003). That is, with respect to insulin and Aβ, the degrading capacity of IDE is different and depends on the intracellular metabolic state. In normal human brain, IDE is the main soluble β-amyloid degrading enzyme at neutral pH (Kurochkin and Goto, 1994), but the greatest β-amyloid degrading activity occurs between pH4 and 5. This indicates that IDE may act as an "amyloidase", preventing the accumulation of amyloidogenic derivatives (McDermott and Gibson, 1997), the extracellular level of which is regulated by neuronal IDE (Vekrellis et al., 2000). In a physiological rat cortical cell system, IDE was shown to eliminate the neurotoxic effects of both Aβ-(1–40) and Aβ-(1–42) and to prevent the deposition of Aβ-(1–40) onto a synthetic amyloid (Mukherjee et al., 2000). Excess insulin inhibits the degradation of both Aβ-(1–40) and Aβ-(1–42) nearly completely, and both Aβ derivatives inhibit insulin degradation in a dose-dependent manner (Perez et al., 2000).

2.3.4. Insulin and tau-protein

The tau-protein stably phosphorylated at five epitopes belongs to a family of microtubule-associated proteins that stimulate the generation and stabilization of microtubules (for review, see Watanabe et al., 1993). The phosphorylation and dephosphorylation of tau-protein at threonine and serine residues are regulated by several protein kinases and by protein phosphatases. Among the tau-phosphorylating protein kinases are the ATP-dependent PK^{erk36} and PK^{erk40} (Röder and Ingram, 1991), protein kinase-1-glycogen synthase kinase-3β (Ishiguro et al., 1992, 1993) and the protein kinase FA/glycogen synthase-kinase-3α (Mandelkow et al., 1992), which all work in an insulin-dependent manner (Cross et al., 1995; 1997; Hong and Lee, 1997; Lesort et al., 1999). Dephosphorylation of tau-protein is performed by several protein phosphatases (Gong et al., 1994; Wang et al.,

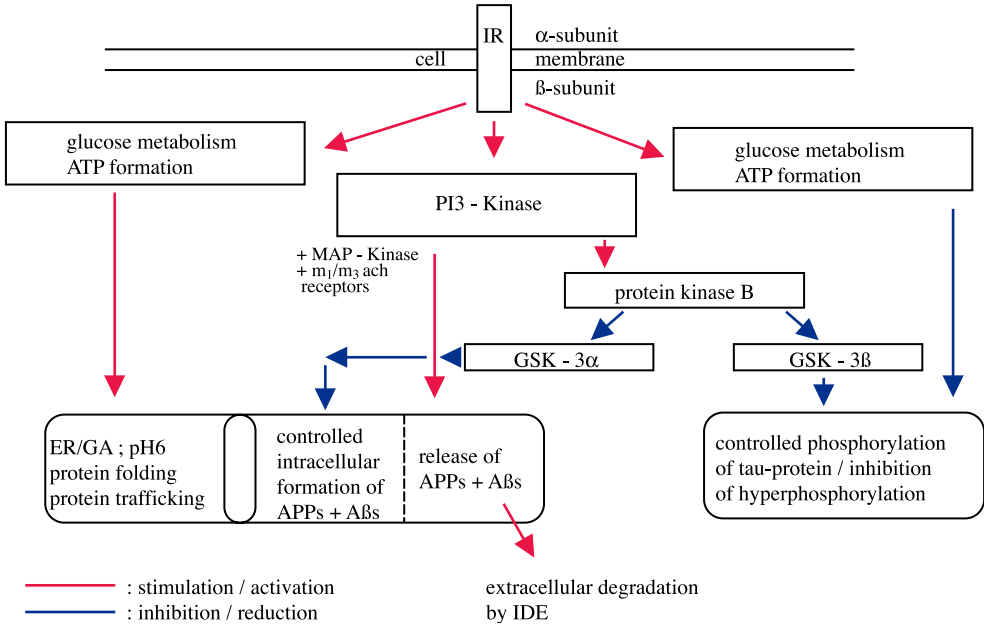

Fig. 1. Schematic survey of the insulin/insulin receptor controlled formation of ATP, the metabolism of APP including the formation of APPs and Aβs, and formation of phosphorylated tau-protein under normal conditions (for details, see text). PI3-kinase, phosphatidylinositol 3-kinase; GSK, glycogen synthase kinase; APPs, secreted form of APP; Aβs, APP derivatives Aβ (1–40)/(1–42); ER, endoplasmic reticulum; GA, Golgi apparatus; IR, insulin receptor; IDE, insulin-degrading enzyme; m1/m3 ach, muscarinergic acetylcholine receptors.

1995). Insulin has a dual effect. After a short period of insulin treatment (1 min), tau-protein phosphorylation and glycogen synthase kinase-3β activity are increased (Lesort et al., 1999). In contrast, prolonged exposure to insulin induced a down-regulation of the glycogen synthase kinase-3β activity (Cross et al., 1997; Hong and Lee, 1997).

These data provide clear evidence that the metabolism of APP, the intracellular formation of secreted APP (APPs) and amyloid-β peptides, and the release of APPs and Aβs into the extracellular space, as well as the balanced phosphorylation of tau-protein, are under control of insulin/insulin receptor signal transduction including the action of ATP and acetylcholine (Fig. 1).

3. Alzheimer disease

As pointed out in detail above (see Introduction), nosologically, Alzheimer disease is not a single disorder. However, beside nosologically differences, some pathophysiological similarities exist between the genetically caused early-onset (familial) type and the late-onset sporadic type of the disease.

3.1. Early-onset familial AD

The genetic abnormalities on chromosomes 1, or 14, or 21 are all characterized by the permanent generation of Aβ-(1–40) and, in particular Aβ-(1–42), beginning early in life (Hardy and Selkoe, 2002). Both these derivatives of APP reduce the binding of insulin to its receptor and receptor autophosphorylation (Xie et al., 2002). The disruption of autophosphorylation by ATP may result in a decrease/lack of receptor tyrosine kinase activity and, thus, in a failure of postreceptor effects exerted via insulin receptor substrate-1 (Chou et al., 1987). This dysfunction of the insulin signal transduction cascade may cause a drastic fall in the cerebral metabolism of glucose in familial Alzheimer disease, whereas the cerebral metabolism of oxygen and cerebral blood flow remain normal (Hoyer et al., 1988, 1991). Regionally, in "presenile" cases, glucose utilization is primarily perturbed in frontal and parietotemporal areas (Mielke et al., 1992).

The deficit in neuronal glucose availability may be partially and transiently balanced by the utilization of endogenous brain substrates to meet the energy demand of the brain, namely, amino acids and fatty acids. In early-onset familial Alzheimer disease, glucoplastic amino acids, in particular glutamate, are used for energy formation (Hoyer and Nitsch, 1989) to maintain ATP concentrations at a normal level (Hoyer, 1992). As a side effect of glumatate utilization, neurotoxic ammonia is formed in the brain (Hoyer et al., 1990) and inhibits mitochondrial dehydrogenases such as α-ketoglutarate dehydrogenase, isocitrate dehydrogenase and malate dehydrogenase (Lai and Cooper, 1991). In aged transgenic mice overexpressing the Swedish mutation of human APP, mRNA for the (brain) phosphofructokinase is decreased in Aβ plaque-associated neurons, but is up-regulated in reactive astrocytes, causing an overall undiminished enzyme activity in brain cortex and hippocampus. These data point to an impairment of cerebral glucose metabolism as a consequence of a long-lasting β-

amyloid burden (Bigl et al., 2003). It is unknown as yet whether or not fatty acids from cell membranes are utilized for energy formation, too, to compensate for the deficit in brain glucose. Since there is no energy depletion (see above), membrane properties may not change (Wu et al., 1996).

The genetically induced continuous formation of Aβ-(1–40)/(1–42), and its consequences, form the core of the amyloid cascade hypothesis (Hardy and Selkoe, 2002). The way in which the Aβs may damage insulin signal transduction mechanisms and contribute to the formation of hypophosphorylated tau-protein is depicted in Fig. 2.

3.2. Late-onset sporadic Alzheimer disease

3.2.1. Aging as risk factor

In contrast to early-onset familial Alzheimer disease, aging is the main risk factor for late-onset sporadic Alzheimer disease. Aging of the brain is associated with a multitude of inherent changes in cerebral glucose/energy metabolism, its control, and related pathways at cellular, molecular and genetic levels. Numerous changes are accentuated by stress. Beside changes in single parameters, functional imbalances of regulative systems may develop, such as

- energy production (reduced) and energy turnover (increased),
- insulin action (reduced) and cortisol action (increased) due to a shift in the hypothalamic pituitary–adrenal axis to an increased basal tone (Cizza et al., 1994).
- acetylcholine action (reduced) and noradrenaline action (increased), indicating sympathetic tone, obviously also reducing insulin secretion after glucose stimulation (Balbo et al., 2002).
- shift in the gene expression profile from anabolic (reduced) to catabolic (increased) in distinct brain areas such as cortex, hippocampus and hypothalamus (see Introduction and Hoyer, 2000b,c and references herein for more details).

These changes/shifts may indicate an uncoupling of the synchronization of biological systems (Mirollo and Strogatz, 1990). This may correspond to an increase in entropy, which is an elemental, inherent principle of chemical and biological processes (Hess, 1983, 1990; Prigogini, 1989;).

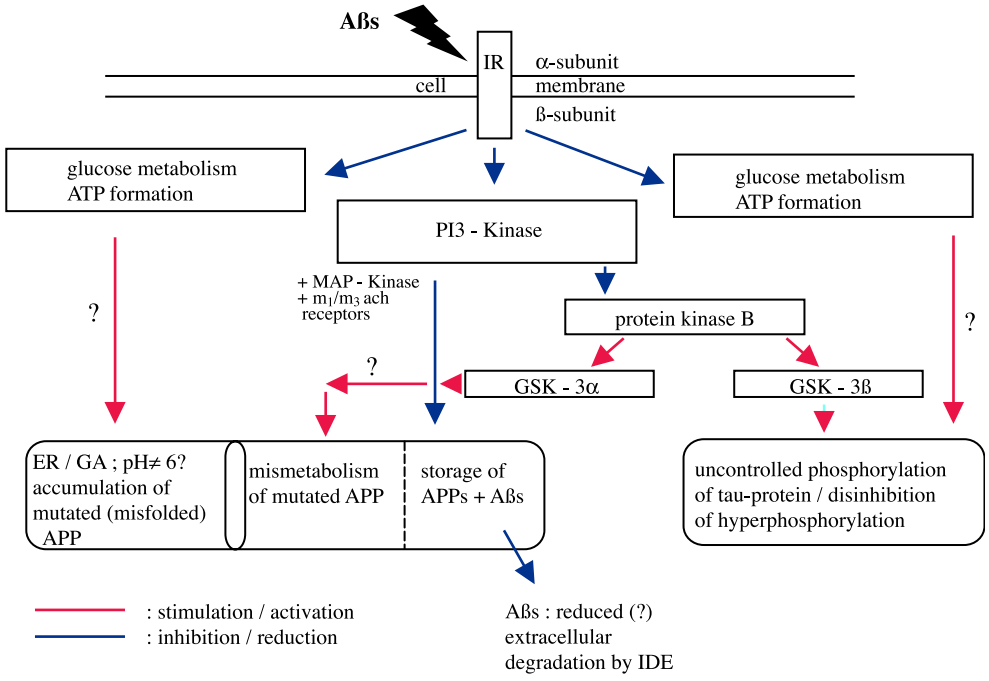

Fig. 2. Scheme showing the consequences of inhibition of the neuronal insulin receptor function in early-onset familial Alzheimer disease. The permanently generated Aβs inhibit the binding of insulin to its receptor at the α-subunit, resulting in dysfunction of the neuronal insulin receptor (Xie et al., 2002). The activation of PI3-kinase may be reduced, as is the activity of protein kinase B (Alessi and Cohen, 1998; Vanhaesebroeck and Alessi, 2000). As a consequence, the activities of both GSK-3α and GSK-3β might be disinhibited. It is not yet known whether GSK-3α influences the intracellular metabolism of the mutated APP. Disinhibition of GSK-3β may contribute to the hyperphosphorylation of tau-protein. (Cross et al., 1995; 1997; Hong and Lee, 1997; Lesort et al., 1999, Phiel et al., 2003). The inhibition of insulin receptor function, causing reduced PI3-kinase activity, may alter the metabolism of APP (Petanceska and Gandy, 1999), and may hamper the release of APPs and Aβs from the intracellular to the extracellular compartment (Solano et al., 2000; Gasparini et al., 2001). Although brain glucose utilization is markedly reduced in early-onset familial Alzheimer disease (Hoyer et al., 1988), ATP is available at a nearly normal concentration (Hoyer, 1992). It is not yet known whether or not the disturbance in neuronal glucose metabolism damages the function of the ER/GA and contributes to the hyperphosphorylation of tau-protein, as may be expected if there is a deficit in ATP (Röder and Ingram, 1991). Otherwise, mutated (misfolded) proteins down-regulate the "unfolded protein response" which has been assumed to occur in familial Alzheimer disease (Imaizumi et al., 2001). Abbrevations: see Fig. 1.

In the physical sciences, the term criticality is used to describe a self-organized metalabile steady state (metalabile equilibrium in entropy). Additional internal or external events, even events that are ineffective on their own, may change the biological and/or biophysical properties of the aging brain. Such events may shift a system from supercriticality to criticality to subcriticality/catastrophy (Bak et al., 1988; Held et al., 1990) and an increase in entropy. These principles can be assumed to be valid in medical terms, i.e. in age-related chronic diseases such as sporadic Alzheimer disease (Hoyer, 2000c), where susceptibilty genes and age-related risk factors can be considered critical "events" (Holness et al., 2000).

3.2.2. Reduction in neuronal activity

Morphologically, there is clear evidence that a major abnormality in sporadic Alzheimer disease brain may be a diminished neuronal activity as a consequence of metabolic abnormalities (for review, see Salehi and Swaab, 1999). This will be discussed in more detail below.

3.2.3. Glucose metabolism

Early and severe abnormalities of cerebral glucose metabolism parallel worsening of the symptoms of dementia. Cerebral oxygen utilization is less severely diminished than glucose utilization (Hoyer et al., 1991; Fukuyama et al., 1994). In contrast to early-onset Alzheimer disease, the late-onset type is associated with less prominent local abnormalities in glucose utilization but instead with abnormalities distributed over all cortical areas, and particularly in parietotemporal and frontal association cortices (Mielke et al., 1992; Herholz et al., 2002) and especially in severe dementia (Foster et al., 1984; Duara et al., 1986). This hypometabolism in the cerebral cortex is particularly pronounced in structures with both high glucose demands and insulin sensitivity (for review, see Henneberg and Hoyer, 1995).

These abnormalities in cerebral glucose utilization include a diminished activity of key glycolytic enzymes (Bigl et al., 1996, 1999, 2000), and of the key dehydrogenating enzyme complexes pyruvate dehydrogenase (Perry et al., 1980; Sorbi et al., 1983), and α-ketoglutarate dehydrogenase (Mastrogiacomo et al., 1993). Reduced pyruvate dehydrogenase activity results in a decreased level of acetyl-CoA, and together with the diminished activity of choline acetyltransferase, the synthesis of acetylcholine in the presynaptic neuron is markedly reduced (Sims et al., 1983a). In this respect, it is noteworthy that the degeneration of the cholinergic system correlates with the progression of mental disturbances in patients with Alzheimer disease (Baskin et al., 1999). A decreased concentration of acetyl-CoA may also decrease the formation of intracellular cholesterol (Michikawa and Yanagisawa, 1999). Cholesterol is the main sterol in membranes and is important for normal cell function. Cholesterol levels are markedly decreased in brain membranes and in the CSF of patients with Alzheimer disease. (Svennerholm and Gottfries, 1994; Mulder et al., 1998; Eckert et al., 2000).

3.2.4. Glucose-related metabolism

The above-mentioned dysbalance between (less) diminished cerebral oxygen consumption and (more markedly) reduced glucose consumption may indicate that substrates other than glucose are oxidized to form energy. In all probability, glucoplastic amino acids are utilized, as they are in early-onset Alzheimer disease (see above). However, this will have to be proven for sporadic Alzheimer disease. Fatty acids from membranes may be partially and transiently used to compensate for the glucose deficit (Nitsch et al., 1992b; Pettegrew et al., 1995).

3.2.5. ATP availability

A decisive pathophysiological consequence of the markedly perturbed glucose metabolism is a decrease in ATP production from glucose by around 50% in the beginning of sporadic Alzheimer disease. The oxidative utilization of substrates other than glucose restores ATP formation to 80% of normal, but thereafter ATP levels decrease throughout the course of the disease (Hoyer, 1992). A fall in ATP formation in the sporadic Alzheimer disease brain has also been demonstrated by other investigators (Sims et al., 1983b; Brown et al., 1989). This energy deficit may compromise ATP-dependent processes in a hierarchical manner (Buttgereit and Brand, 1995) including cellular and molecular mechanisms in particular in the endoplasmic reticulum and Golgi apparatus (see Introduction). A depletion of cellular ATP prevents the dissociation of chaperone/protein complexes and thus blocks secretion of these proteins (Dorner et al., 1990). Misfolded or malfolded protein complexes accumulate in the endoplasmic reticulum and are indicative of "endoplasmic reticulum stress" (Kaufman, 1999). Additionally, ATP depletion results in the degradation of membrane phospholipids (Sun et al., 1993).

3.2.6. Insulin/insulin receptor signal transduction

The abnormalities in neuronal glucose metabolism and in glucose-related metabolism are assumed to be caused by a disturbance in the control of glucose utilization at the level of insulin signal transduction. Although insulin concentration and the activity of insulin receptor tyrosine kinase are diminished, and CSF insulin concentrations are also decreased in Alzheimer disease (Craft et al., 1998), these changes are not significantly different from these in age-matched healthy adults older than 60 years. Thus, these abnormalities may be age-related rather than disease-related. However, insulin receptor density is up-regulated in Alzheimer disease (Frölich et al., 1998), indicating an impairment of the insulin signal transduction cascade similar to that seen in non-insulin-dependent diabetes mellitus. So, the hypothesis was forwarded that sporadic Alzheimer disease is the brain equivalent of non-insulin-dependent diabetes mellitus (Hoyer, 1998). The blood of patients with sporadic

Alzheimer disease has a diabetes mellitus-like pattern: basal arterial glucose concentration is slightly but significantly decreased, but the plasma insulin concentration is enhanced, and insulin-mediated glucose disposal was diminished (Bucht et al., 1983; Craft et al., 1998, 1999).

The causes of both the desensitization of the neuronal insulin receptor and the decrease in insulin concentration in sporadic Alzheimer disease brain are speculative at present. With respect to insulin signaling system in general, IDE is discussed as a candidate contributing to insulin dysfunction and the accumulation of Aβs. In this context, it may be of significance that the affinity of IDE for its substrates insulin and Aβ is different in control subjects and in patients with mild Alzheimer disease (Craft et al., 2000; see also Section 2.3.3). In the Alzheimer brain, the Aβ-degrading capacity of IDE is about 50% of that of control brains, but insulin degradation decreases by about 30% only (Perez et al., 2000). Decreased IDE mRNA and IDE activity have been found in the hippocampus of sporadic Alzheimer disease brains (Cook et al., 2003); however, in neurons adjacent to senile plaques, IDE is up-regulated (Bernstein et al., 1999). The different changes in the degrading capacity of IDE for Aβ and insulin in sporadic Alzheimer disease brain may explain the accumulation of Aβ, but not the diminished insulin concentration found in postmortem sporadic Alzheimer disease brain and CSF (Craft et al., 1998, Frölich et al., 1998). In IDE −/− mice, an increased cerebral accumulation of Aβ accompanies glucose intolerance and increased insulin concentrations in serum (Farris et al., 2003). This pattern is in accord with findings in patients with sporadic Alzheimer disease. However, it would have to be shown that the brain insulin concentration is low in IDE −/− mice as is the case in brain and CSF from patients with sporadic Alzheimer disease. If so, the IDE gene would be an important susceptibility gene in sporadic Alzheimer disease.

As mentioned above, the up-regulation of insulin receptor density associated with reduced activity of insulin receptor tyrosine kinase may indicate a densensitization of the neuronal insulin receptor. As in non-nervous tissues, both cortisol and catecholamines may be candidates for insulin receptor desensitization (Häring et al., 1986; Gior-

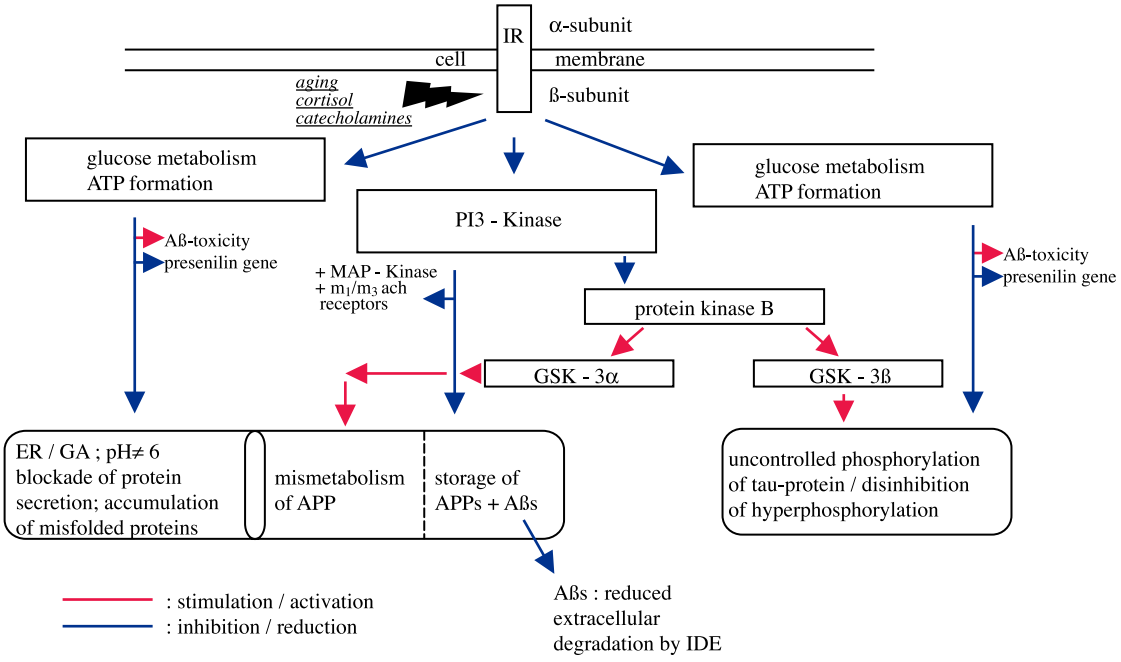

Fig. 3. Scheme showing the consequences of inhibition of neuronal insulin receptor function in late-onset sporadic Alzheimer disease. The age-related increase in both cortisol and noradrenaline levels in the CNS inhibits the β-subunit of the neuronal insulin receptor at different sites, leading to receptor desensitization (see text). As a result, the activation of PI3-kinase may be reduced, as is the activity of protein kinase B (Alessi and Cohen, 1998; Vanhaesebroeck and Alessi, 2000). As a consequence, the activities of both GSK-3α and GSK-3β may be disinhibited, leading to the mismetabolism of APP (GSK-3α) and to the hyperphosporylation of tau-protein (GSK-3β) (Cross et al., 1995; 1997; Hong and Lee, 1997; Lesort et al., 1999; Phiel et al., 2003). The inhibition of the insulin receptor function causes reduced PI3-kinase activity and may alter the metabolism of APP (Petanceska and Gandy, 1999) and may hamper the release of APPs and Aβs from the intracellular to the extracellular compartment (Solano et al., 2000; Gasparini et al., 2001). Aβs accumulate in neurons (Gouras et al., 2000) which then undergo lysis to form amyloid plaques (D'Andrea et al., 2001). Cerebral glucose metabolism is severely perturbed (Hoyer et al., 1991 and text), including the presynaptic cholinergic system (Sims et al., 1983a; Wurtman, 1992). The function of the acetylcholinergic m1 and m3 receptors is reduced, causing a diminished release of APP derivatives (Nitsch et al., 1992a). ATP formation is significantly reduced with reduction increasing with the course of the disease (Hoyer, 1992). The reduced ATP availability damages the function of the ER/GA (Dorner et al., 1990; Seksek et al., 1995; Verde et al., 1995; Kaufman, 1999), increases the toxicity of Aβ (Arias et al., 2002), down-regulates the presenilin 2 gene (Ghidoni et al., 2003), and contributes to the hyperphosphorylation of tau-protein (Röder and Ingram, 1991). Thus, disturbances in the neuronal insulin receptor signaling pathway are associated with reduced neuronal glucose/energy metabolism and work in a detrimental concerted action in sporadic Alzheimer disease to damage cellular and molecular mechanisms and to disrupt the metabolism of APP, leading to an increased formation of Aβs, and tau-protein hyperphosphorylation. Abbreviations: see Fig. 1.

gino et al., 1993). Levels of cortisol in the CSF are much higher in patients with sporadic Alzheimer disease than in healthy and middle-age/aged adults (Swaab et al., 1994). This may be caused by a disinhibition of the hypothalamic–pituitary–adrenal axis, leading to an increase of its basal tone and to hypercortisolemia (Sapolsky et al., 1986; Cizza et al., 1994; Lupien et al., 1994), which may compromise the function of the neuronal insulin receptor via its dysregulation of the phosphorylation of tyrosine residues in the receptor. It is tempting to assume that both prenatal and early postnatal stress can cause long-term changes in the hypothalamic–pituitary–adrenal axis associated with long-lasting hypercortisolemia (King and Edwards, 1999; Vallée et al., 1999), thereby rendering genes more susceptible to environmental risk factors later in life, particularly aging (Holness et al., 2000).

Additionally, CSF noradrenaline concentrations are higher in patients with sporadic Alzheimer disease than in controls and correlate with the severity of dementia (Peskind et al., 1998). This high level up-regulates the cAMP messenger system (Martinez et al., 1999), which may desensitize the neuronal insulin receptor via its phosphorylation of serine/threonine residues (Häring, 1991; Häring et al., 1986).

It is thus obvious that in both pathological conditions, early-onset familial Alzheimer disease and late-onset sporadic Alzheimer disease, damage to the insulin signal transduction cascade may be an early and dramatic event. However, the underlying cause of the damage may be different: an insulin binding deficit at the α-subunit of the insulin receptor in early-onset familial Alzheimer disease, and desensitization via the β-subunit of the insulin receptor in late-onset sporadic Alzheimer diseases (for synopsis, see Fig. 3). The consequences of the disturbance at different sites of the neuronal insulin signal transduction cascade may be largely identical.

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