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Modification of membrane lipids protects neurons against insulin resistance in models of Alzheimer's disease

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Abstract: Alzheimer's disease is a degenerative disease of the central nervous system, which leads to severe deficits in memory and orientation by a progressive loss of neurons and synapses. Soluble β-amyloid oligomers are highly neurotoxic precursors of β-amyloid fibrils that accumulate in Alzheimer's disease. Binding of β-amyloid oligomers to synaptic insulin receptors leads to neuronal insulin resistance, which significantly contributes to cognitive impairments.

Insulin receptors are located in the cell membrane, which consists of a lipid bilayer and contains high amounts of glycosylated lipids, the so-called gangliosides. Gangliosides regulate insulin receptor activity via dynamic molecular interactions and facilitate the β-amyloid oligomer-induced insulin resistance. Thus, inhibiting ganglioside biosynthesis can protect neurons from the detrimental effects of β-amyloid oligomers.

Keywords: Alzheimer's disease, insulin resistance, gangliosides, neurodegeneration, caveolin-1

Alzheimer's disease

Alzheimer's disease, which was initially described by Alois Alzheimer in 1906, is characterized by two pathological changes in the brain; senile plaques, consisting of β-amyloid (Aβ) peptides, are found outside the neurons and neurofibrillary tangles, consisting of hyperphosphorytaled tau protein, are found inside the neurons (Alzheimer, 1907).

Amyloid plaques are built up by large amounts of accumulated and aggregated Aβ. Aβ is generated from the amyloid precursor protein (APP). APP is an integral membrane protein that is ubiquitously expressed throughout the body (Slunt et al., 1994). The sequential cleavage of APP by membrane-bound β- and γ-secretases (presenilins 1/2) gives rise to Aβ fragments. These fragments display variable sizes, ranging from 35 to 42 amino acids. Under physiological conditions, only very low amounts of Aβ are produced and they are rapidly cleared. In the case of Alzheimer's disease, Aβ production is no longer appropriately regulated and leads to an accumulation of specifically $A\beta_{40}$ and $A\beta_{42}$ in the brain. $A\beta_{40}$ and $A\beta_{42}$ are prone to form aggregating Aβ fibrils, which are subsequently deposited in the form of Aβ plaques in the extracellular space (Simons et al., 1996). Therapeutic efforts aiming at diminishing the plaque load were not able to ameliorate the symptoms of Alzheimer's disease (Head et al., 2008). In this respect, several studies demonstrated that there is no direct correlation between the occurrence of Aβ plaques and the severity of disease symptoms (Bennett, 2006; Katzman et al., 1988). However, researchers have been able to explain these seemingly paradoxical findings. Current results indicate that small soluble oligomeric Aβ aggregates are highly neurotoxic and may therefore be causative for the onset of Alzheimer's disease symptoms. Oligomeric Aβ aggregates are precursors of Aβ fibrils and comprise soluble aggregates of variable sizes, termed **a**myloid-β-**d**erived **d**iffusible **l**igands (ADDLs) (Lambert et al., 1998). ADDLs bind to synapses, where they interfere with the transmission of information, ultimately leading to synaptic dysfunction and neurodegeneration.

What causes the majority of the Alzheimer's disease cases is not known. These are therefore termed "sporadic Alzheimer's disease". The risk of developing sporadic Alzheimer's disease increases with age. Moreover, environmental factors, an unhealthy lifestyle and certain pre-existing conditions, such as type 2 diabetes, are considered potential risk factors for sporadic Alzheimer's disease. In a minority of cases (less than 1%), however, inheritable

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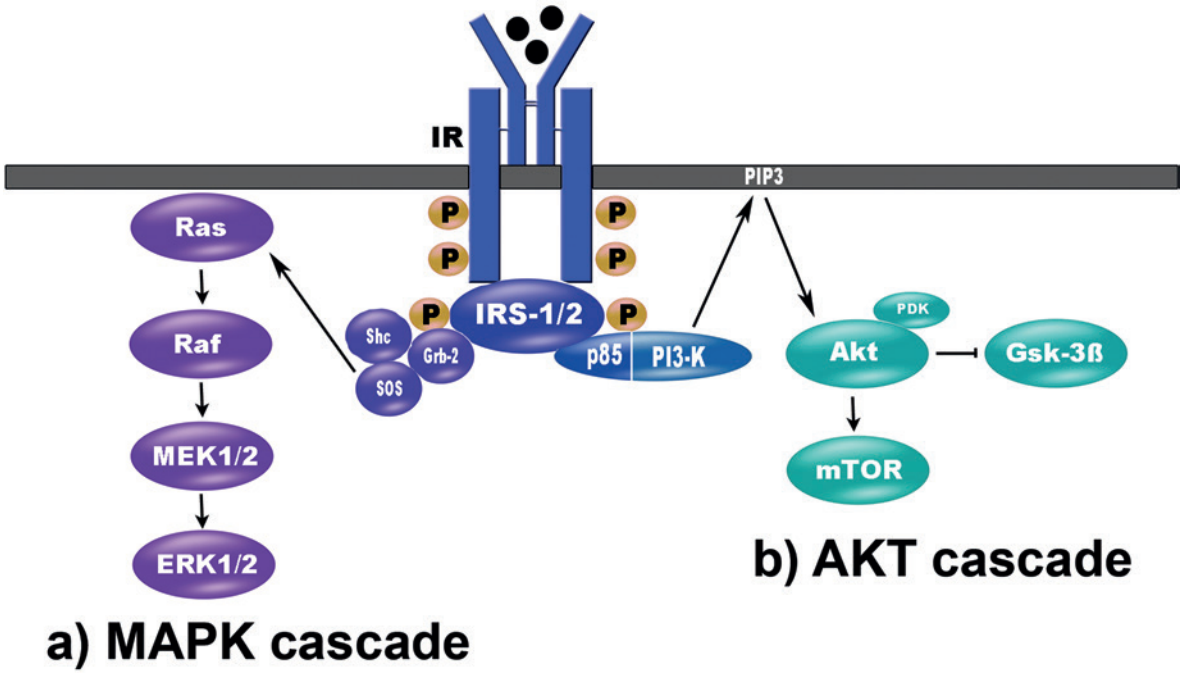

Fig. 1: Insulin receptor signal transduction. Binding of insulin to the IR induces auto-phosphorylation at various tyrosine residues. Subsequently, adapter molecules (insulin receptor substrate-1 (IRS-1) and IRS-2) are activated by binding to the autophosphorylated IR. Two different signaling cascades can be elicited depending on the adapter molecules: **a)** AKT pathway: The regulatory sub-unit of PI-3-kinase (p85) is activated by interacting with IRS-1 and catalyzes the formation of *phosphatidyl-inositol-3,4,5-triphosphate* (PIP3). Subsequently, PIP3 activates the kinase PKD, which in turn phosphorylates and activates AKT (*protein kinase B*). This pathway regulates processes such as glucose uptake as well as protein and lipid biosynthesis. **b)** MAP-kinase ERK1/2 pathway: In this case, the adapter proteins Grb-2 and mSOS are recruited by IRS-1 and IRS-2. This complex activates the GTPase Ras and, subsequently, further kinases (Raf-1, MEK 1/2). Finally, MAP-kinase ERK1/2 is activated. This signaling pathway regulates cell growth, cell differentiation, and cell viability. *(Fig. 1 modified from Herzer et al., 2016)*.

genetic mutations are known to elicit an aggressive and early-onset disease variant, termed familial Alzheimer's disease (FAD). FAD is caused by various mutations in the genes encoding either APP or presenilin 1/2. Alzheimer's disease mouse models have been generated with the help of these FAD mutations. So-called 5xFAD mice harbor three different mutations in the APP gene and two mutations in the presenilin-1 gene. These mice display a rapid onset of β-amyloid plaque accumulation at the age of 8 weeks as well as cognitive impairments at the age of 9 months (Oakley et al., 2006).

The neuronal insulin receptor

The peptide hormone insulin plays an important role in blood glucose regulation. It is secreted by the pancreas and distributed by the blood stream throughout the body. Insulin binds to insulin receptors (IR) located in plasma cell membranes. Insulin binding induces IR auto-phosphorylation and a change in conformation. In its active form, the IR is able to recruit and bind intracellular adapter molecules that activate further intracellular signaling cascades (Fig. 1). These signals induce the translocation of glucose transporters (GLUT4) into the cell membrane and thus enable the cell to utilize glucose for energy generation. Liver and muscle cells as well as adipocytes express high amounts of IR.

It has been known for a long time that IR are also expressed in various areas of the brain. Among the regions displaying the highest IR expression are the hypothalamus, the hippocampus, the frontal cortex, and the olfactory bulbs (Marks and Eastman, 1990). The bigger part of the IR is expressed at synaptic terminals (Schwartz et al., 1992). The neuronal IR has a lower molecular weight than the peripheral IR. Moreover, in contrast to the peripheral IR, increasing concentrations of insulin do not decrease neuronal IR levels on the cell surface (Heidenreich et al., 1983). One of the initial physiological functions that was described for the neuronal IR was the regulation of energy homeostasis and body weight. In order to accomplish this,

peripheral insulin binds to IR present in specific hypothalamic neuronal populations and, in conjunction with the adipokine leptin, adjusts the neuronal activity as well as the neuronal firing rate. This in turn directly influences the feeding behavior and the energy expenditure of the body.

In addition to the regulation of body energy homeostasis, the IR also exerts neurotrophic functions. Several studies have demonstrated that IR signaling stimulates neuronal survival as well as axonal growth and synapse formation (Chiu and Cline, 2010; Wozniak et al., 1993). Specifically, they have shown an IR signal-dependent stimulation of cognitive processes and memory formation in the hippocampus and the prefrontal cortex. These brain regions express large amounts of IR and display high synaptic plasticity. Experiments in rats showed that an inactivation of the neuronal IR by intracerebroventricular injection of streptozotocin leads to impairments in learning and memory formation (Zhao and Alkon, 2001). In line with this, synaptogenesis in the hippocampus was also reduced (Biessels et al., 1996; Lannert and Hoyer, 1998). Conversely, cognitive training increased IR expression in the hippocampus of rats.

As shown in Fig. 1, IR stimulation activates both the MAP-kinase/ERK1,2 and the AKT pathways. Research findings indicate that particularly the MAP-kinase/ERK1,2-dependent signaling stimulates synaptic function and neuronal wiring, independent of glucose regulation. These results have put the neuronal IR into the focus of researchers who intend to counteract the cognitive decline that accompanies neurodegenerative diseases.

Alzheimer's disease, neuroinflammation, and neuronal insulin resistance

In recent years, several hypotheses about the etiology and progression of sporadic Alzheimer's disease have been put forward. This review will mainly cover the connections between neuronal insulin resistance and Alzheimer's disease.

Obesity and type 2 diabetes are suspected to increase the risk of developing Alzheimer's disease (Walker and Harrison, 2015). In 2012, researchers showed that obesity and high fat diet elicit neuroinflammation (Thaler et al., 2012). Characteristic hallmarks of neuroinflammation are morphological changes of glial cells (astrogliosis and microgliosis) as well as increases in pro-inflammatory cytokines (e.g. TNF-α and IL-1β). In 2013, the "inflammation hypothesis of Alzheimer's disease" was put forward, suggesting that neuroinflammatory processes in the brain facilitate pathophysiological changes typical of Alzheimer's disease (Krstic and Knuesel, 2013). For example, neuroinflammation disturbs the physiological microglial function to an extent that these cells are no longer able to appropriately clear cellular debris, including misfolded or inadequately degraded proteins. This leads to synaptic destabilization. Moreover, neuroinflammation triggers the generation of neurotoxic ADDLs in the brain. ADDL binding to synaptic transmembrane receptors interferes with their physiological activity. Additionally, ADDLs promote IR loss from the neuronal cell surface (De Felice et al., 2009). Besides disturbing the cell's glucose homeostasis, a loss of insulin signaling also reduces synaptic function and promotes the degeneration of affected neurons.

In fact, lower insulin-dependent signaling and reduced IR levels were found in brains of Alzheimer's disease patients (Steen et al., 2005). A therapeutic approach to counterbalance the loss of IR signaling by intranasal application of insulin indeed improved the short-term memory (Reger et al., 2006). However, it was not possible to maintain these improvements for a longer period, perhaps due to a decreased insulin sensitivity in the affected neurons.

Besides more general processes such as APP cleavage (Clement et al., 2010), the lipid composition of the neuronal membrane affects IR activity and sensitivity (Herzer et al., 2015; Kabayama et al., 2007). Thus, we have developed a novel research approach by showing that an altered membrane lipid composition and a concomitant increase of neuronal insulin sensitivity can protect neurons in various models of Alzheimer's disease.

Membrane lipids modulate neuronal receptors

A major part of the cellular signal transduction originates at transmembrane receptors embedded in the plasma cell membrane. Pathological changes in transmembrane proteins, such as irreversible protein modifications due to increased oxidative stress, contribute to cell death in neurodegenerative diseases (Hajieva et al., 2015). Besides well-known lipids like phospholipids and cholesterol, the membrane also contains so-called glycosphingolipids. In addition to their hydrophobic membrane anchor, glycosphingolipids contain a hydrophilic head group consisting of variable carbohydrate residues.

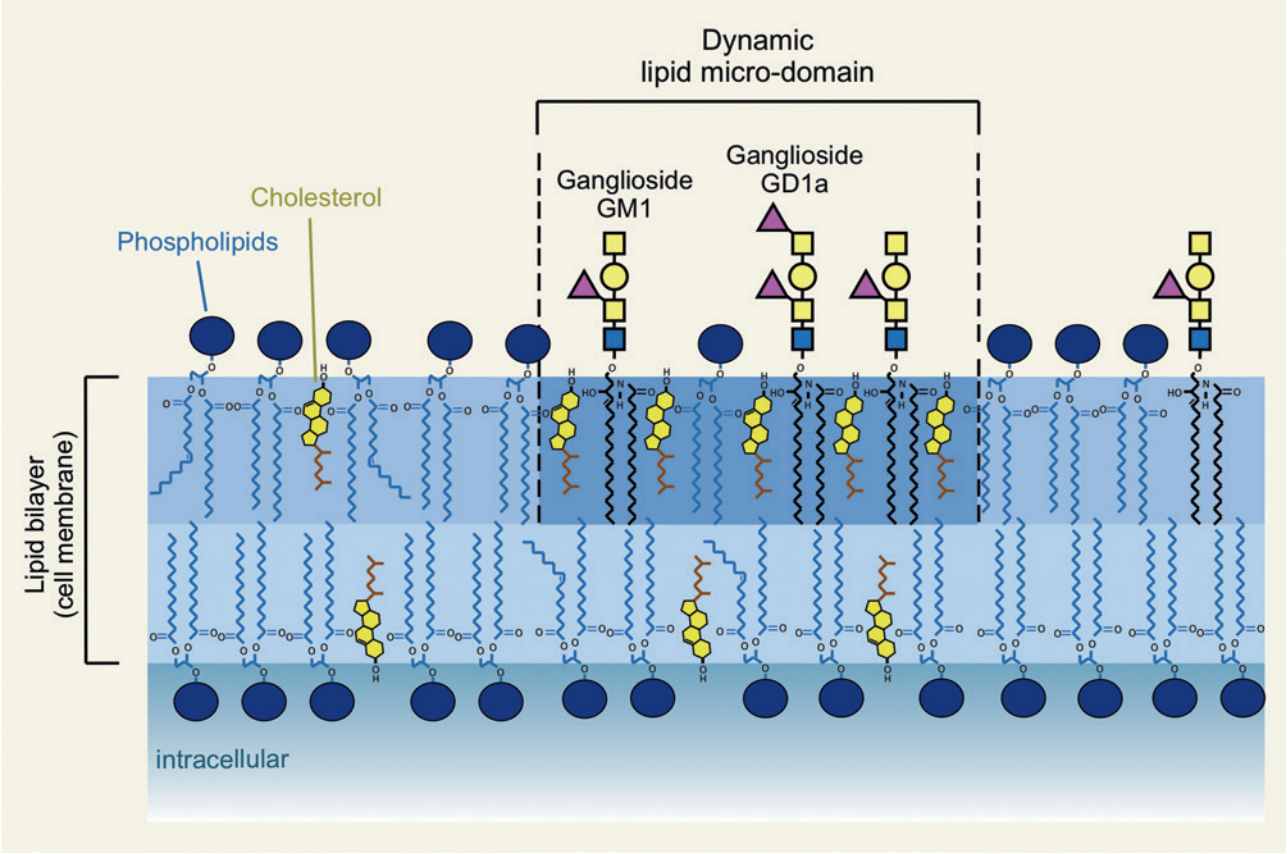

Fig. 2: Scheme of the neuronal membrane. The cell membrane is composed of a lipid bilayer. Phospholipids and cholesterol are the main components. Specific glycosylated lipids, the so-called gangliosides, are located in the outer leaflet of the cell membrane. They take part in the formation of so-called lipid micro-domains, which are characterized by a high content of gangliosides and cholesterol. Important cellular processes, such as transmembrane receptor signal transduction, are mainly taking place in lipid micro-domains.

Gangliosides, a sub-class of glycosphingolipids, are highly expressed in the central nervous system and located in the outer leaflet of the plasma cell membrane (Fig. 2 and Excursion 1). Gangliosides play an important role in postnatal brain development (Jennemann et al., 2005) and modulate the activity of transmembrane receptors in adult neurons (Nordström et al., 2013).

The cell membrane contains so-called lipid micro-domains (Fig. 2), which are characterized by high amounts of sphingolipids and cholesterol, but also by specific proteins, such as caveolin-1 and transmembrane receptors. Within these dynamic nano structures, important membrane processes, such as signal transduction, endo-, and exocytosis take place (Inokuchi, 2010). Gangliosides contribute to the formation of these membrane micro-domains (Fig. 2). We could show that gangliosides modulate the activity and sensitivity of transmembrane receptors by dynamic molecular interactions. In the following sections, we describe how alterations in neuronal ganglioside biosynthesis influences both neuronal insulin sensitivity and disease progression in a mouse model of Alzheimer's disease.

Inhibition of ganglioside biosynthesis increases the insulin sensitivity of hippocampal neurons

Already a decade ago, it was observed that ganglioside GM3 acts as a natural inhibitor of IR in white adipocytes (Kabayama et al., 2007). In line with these findings, an inhibition of ganglioside biosynthesis successfully counteracted liver steatosis and high blood glucose levels in obese mice (Zhao et al., 2009). Contrary to liver and fat cells, neurons mainly synthesize complex gangliosides. Since individual ganglioside species are not redundant and able to regulate receptors differentially, we initially needed to investigate if ganglioside depletion was able

to increase the insulin sensitivity of neurons and thereby protect them from the detrimental effects of ADDLs.

For our experiments on cultivated hippocampal neurons, we inhibited the key enzyme in ganglioside biosynthesis, the glucosylceramide synthase (GCS), with the help of a pharmacologic inhibitor GENZ-123346 (GENZ) (Richards et al., 2012) (Fig. 3a). We indeed observed an increased insulin-dependent signal transduction in GENZ-treated neurons (Herzer et al., 2016). Since the ERK1/2 signaling pathway stimulates neuronal survival and cognitive function, the specific elevation in ERK1/2-dependent signaling in GENZ-treated cells is noteworthy in regard to Alzheimer's disease. Interestingly, the GENZ treatment does not only elevate IR signal transduction, but also the amount of IR in treated neurons (Herzer et al., 2016). Consequently, we have investigated if the inhibition of ganglioside biosynthesis and the concomitant increased insulin sensitivity can indeed protect neurons in models of Alzheimer's disease.

Inhibition of ganglioside biosynthesis protects neurons against the detrimental effects of ADDLs

Neuronal insulin resistance is one of the highly complex pathological features of Alzheimer's disease, leading to impaired synaptic function and neurodegeneration. Neurotoxic ADDLs, which are generated during Alzheimer's disease, induce the loss of dendritic IR and thereby contribute to insulin resistance (De Felice et al., 2009). Thus, an important aim was to find out if the inhibition of ganglioside biosynthesis by GENZ could protect hippocampal neurons from ADDL stress. We indeed observe the following neuroprotective effects when treating these neurons with GENZ (Herzer et al., 2016):

Viability. The MTT viability assay measures the metabolic activity of the cells. The required enzyme activity correlates with cell viability. ADDLs significantly reduce the viability of hippocampal neurons. However, a preceding GENZ treatment increases the viability of neurons, which are exposed to ADDLs (Fig. 3b).

Cell surface IR. ADDLs induce a loss of IR at the neuronal cell surface. However, this can be counteracted by GENZ treatment.

Insulin-dependent signal transduction. The loss of surface IR ultimately impairs insulin-dependent signal transduction. The innovative proximity ligation assay (PLA®, Duolink®) detects phosphorylated and thereby active IR

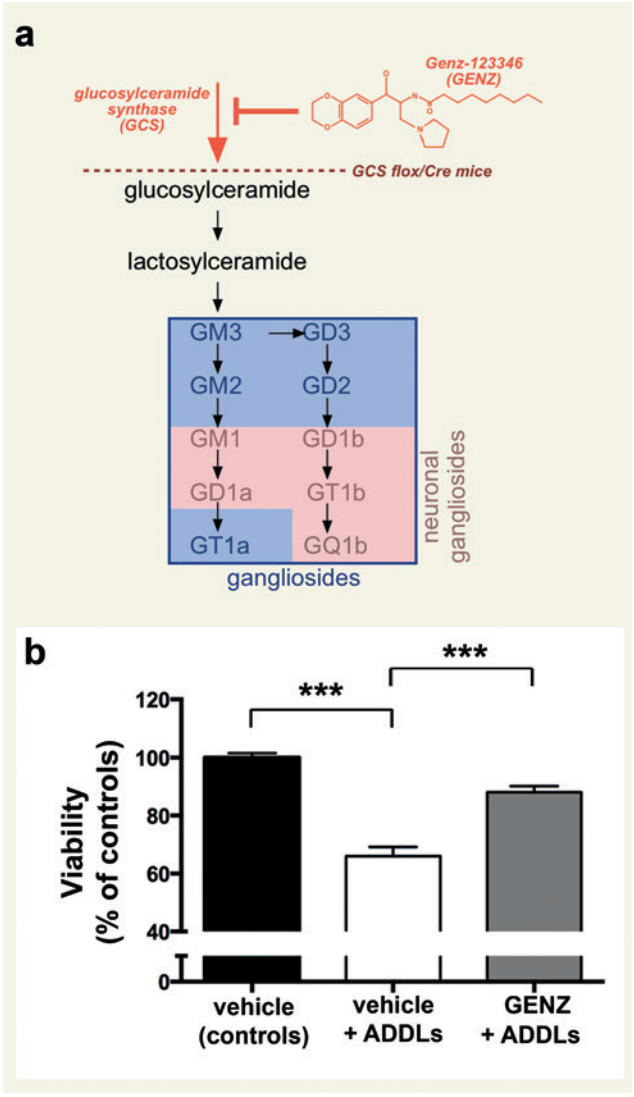

Fig. 3: Inhibiting ganglioside biosynthesis protects neurons against neurotoxic oligomeric β-amyloid species (ADDLs). **a** Glucosylceramide synthase (GCS) is the key enzyme in ganglioside biosynthesis. Ganglioside biosynthesis can be inhibited either pharmacologically by the ceramide analogue GENZ-123346 (GENZ) or genetically by cell-specific deletion of the *Ugcg* allele (*Ugcg* flox/flox//Cre mice). The promoter regulating the expression of the Cre recombinase determines the target cells where ganglioside biosynthesis will be shut down. **b** ADDL exposure reduces neuronal viability. However, GENZ-treated neurons are more resistant towards the detrimental effects of ADDLs *(Fig. 3.b) modified from Herzer et al., 2016).*

along the dendrites of cultivated neurons (Fig. 4.a.). In line with results from other groups (De Felice et al., 2009), the PLA® shows that ADDLs impair the insulin-stimulated phosphorylation of dendritic IR. However, this detrimental effect can be counteracted by GENZ treatment (Fig. 4.b.).

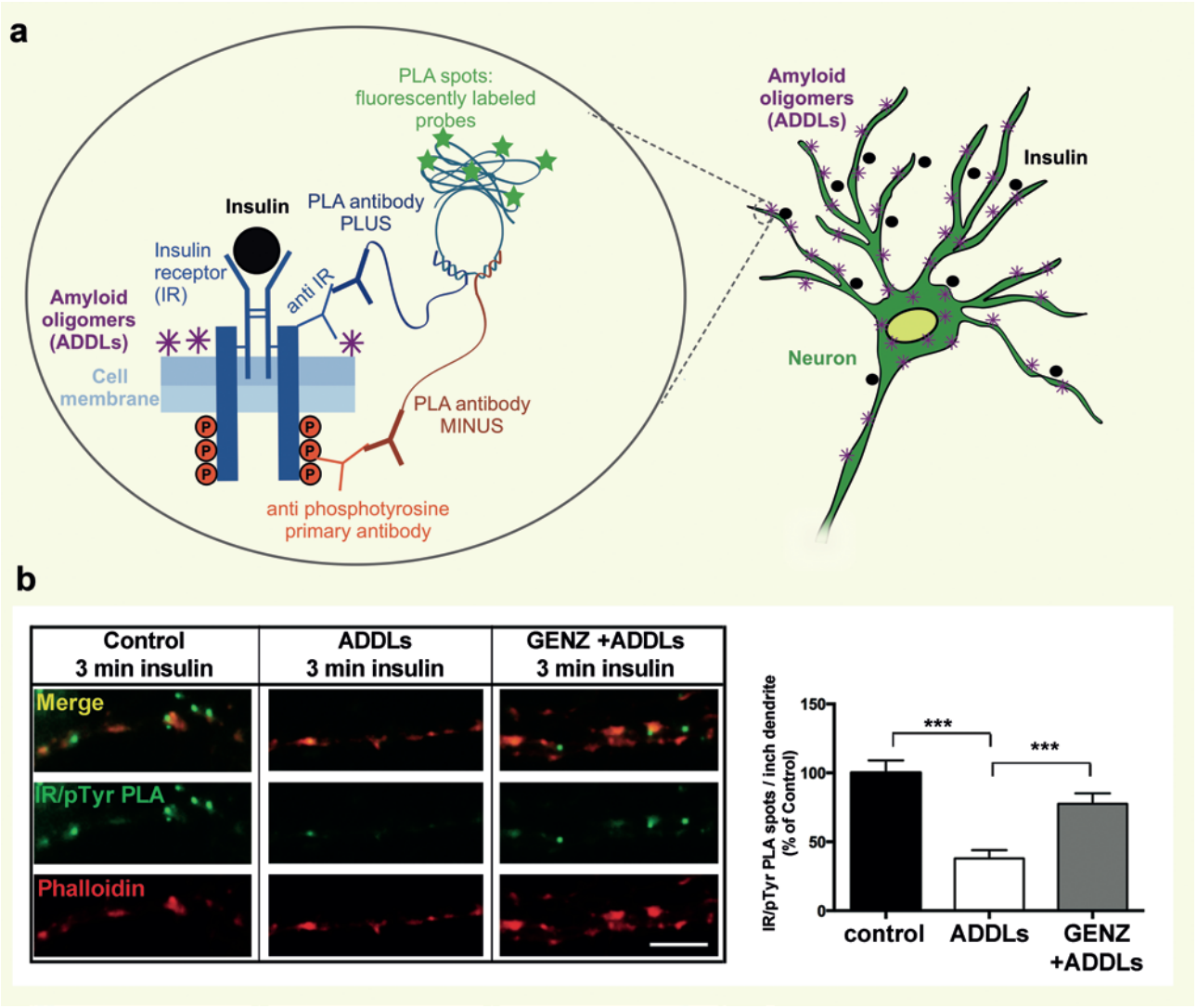

Fig. 4: Insulin sensitivity is increased in GENZ-treated cells in a model of Alzheimer's disease. **a** Molecular interactions can be visualized by the innovative technology proximity ligation assay (PLA®). The PLA® enables the detection of interaction partners by primary antibodies (two different host species) and oligonucleotide-coupled PLA® secondary antibodies. The adapter oligonucleotides will be ligated and form a template for the subsequent "rolling circle amplification" step. The amplicon will then be visualized by a fluorescently labeled probe. Phosphorylated and thus active IR can be visualized by PLA® along the dendrites. **b** Cultivated neurons are exposed to neurotoxic β-amyloid oligomers (ADDLs) in a model of Alzheimer's disease. The PLA® shows a decline in insulin-stimulated IR phosphorylation after ADDL exposure. However, the inhibition of ganglioside biosynthesis by GENZ maintains the insulin sensitivity of ADDL-exposed neurons *(Fig. 4.b) modified from Herzer et al., 2016)*.

Reduction of caveolin-1 by GENZ stabilizes IR levels on the neuronal cell surface

Caveolae, formed by the protein caveolin-1, are specialized membrane micro-domains in which endocytosis takes place. Moreover, high amounts of cholesterol and sphingolipids are found in caveolae. Interestingly, ganglioside-deficient neurons display less caveolin-1 and, consequently, a lower number of caveolae (Herzer et al., 2016).

Upon ligand binding, IR are internalized both in clathrin-coated pits and caveolae. Thus, caveolin-1 can regulate the amount of cell surface IR. Since caveolin-1-levels are increased in the brains of Alzheimer's disease patients (Gaudreault et al., 2004), caveolae are regarded as potentially decisive factors for the development of this disease. With the help pf the PLA®, we are able to show for the

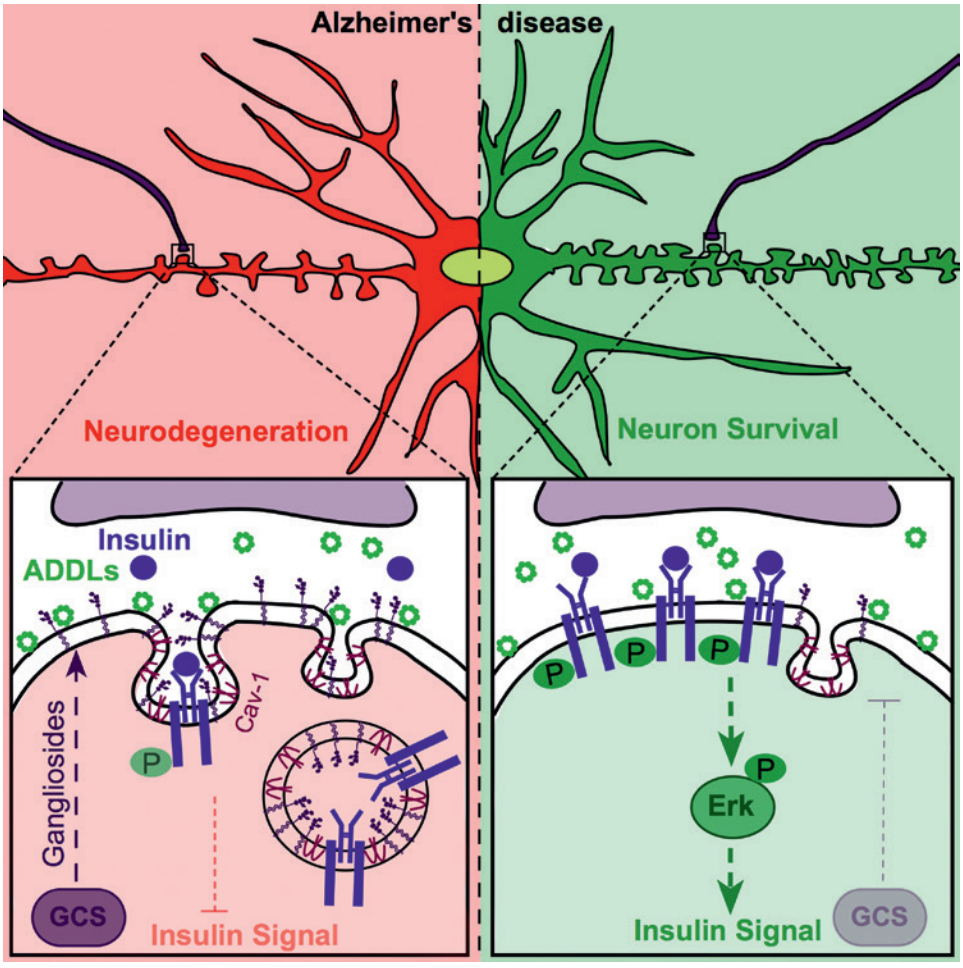

Fig. 5: Inhibition of the ganglioside biosynthesis protects against Alzheimer's disease-induced neurodegeneration and insulin resistance. The results suggest that gangliosides facilitate the β-amyloid-induced IR endocytosis in caveolae and thereby contribute to neurodegeneration (left scheme). However, inhibiting GCS decreases the levels of caveolin-1 and increases the viability and the insulin sensitivity of neurons in a model of Alzheimer's disease (right scheme). We suggest that GCS inhibition also accounts for the increased viability of ganglioside-deficient neurons in our mouse model of Alzheimer's disease *(Fig. 5 modified from Herzer et al., 2016)*.

first time that ADDLs significantly induce direct molecular interactions between *a) caveolin-1 and ganglioside GD1a, b) IR and GD1a, and c) IR and caveolin-1*. We suggest that increased interactions between IR and caveolin-1, mediated by gangliosides, are required for IR endocytosis (Herzer et al., 2016).

Thus, we postulate a novel molecular mechanism by showing that gangliosides in the neuronal cell membrane facilitate Alzheimer's disease-induced insulin resistance by stimulating caveolin-1 expression and its molecular interactions with IR. An inhibition of GCS and a subsequent reduction of caveolae stabilize the IR in neurons exposed to neurotoxic ADDLs (Fig. 5).

Inhibition of ganglioside biosynthesis also protects Alzheimer's disease mice against neurodegeneration

GCS and subsequent ganglioside biosynthesis can be genetically deleted in adult neurons of a mouse model of Alzheimer's disease (5xFAD mice; Excursion 2). In fact, these animals display a significantly lower neurodegeneration in the cerebral cortex, even though the amyloid plaque burden is not reduced. Moreover, GCS deletion protects Alzheimer's disease mice from the loss of IR in the cerebral cortex.

Our hypothesis suggests that gangliosides facilitate the β-amyloid-induced IR internalization taking place in caveolae. Indeed, molecular interactions between caveolin-1 and IR, which occur in Alzheimer's disease, can be prevented by GCS deletion (Herzer et al., 2016). Thus, key findings from our cell culture work can be confirmed in a mouse model of Alzheimer's disease.

Outlook

It has been suggested for a long time, that membrane lipids not only represent a mechanical barrier, but that they actively modulate signal transduction processes as well as other changes occurring in neurodegenerative diseases. Specifically with regard to Alzheimer's disease, it was shown that membrane fluidity, determined by the lipid composition of cell membranes, influences APP processing (Hajieva et al., 2015). Our results now motivate a novel hypothesis, suggesting that gangliosides in the cell membrane may facilitate the ADDL-induced neuronal insulin resistance and, as a consequence, also neurodegeneration. This indicates that neuronal ganglioside biosynthesis may potentially play a decisive role in the progression of Alzheimer's disease. Inhibiting the key enzyme in ganglioside biosynthesis, the GCS, might therefore potentially constitute a novel therapeutic target against Alzheimer's disease.

However, the hypothesis that modulating GCS expression could possibly influence the course of Alzheimer's disease requires additional empirical support by extensive and purposeful future studies. For example, a hypothesized therapeutic potential of GCS inhibitors, such as GENZ, needs to be evaluated in more detail, specifically in animal models of sporadic Alzheimer's disease. In this regard, it will be most important to evaluate if neuronal GCS inhibition exerts any effect on the cognitive function of affected mice.

Moreover, additional cell types in the brain, particularly glial cells, play an important role in the initiation and progression of Alzheimer's disease. Neuroinflammatory changes elicited by astrocytes and microglia are suspected to facilitate, if not to elicit, sporadic Alzheimer's disease. Thus, it will be a decisive goal to find out how gangliosides in these cells contribute to the onset of neuroinflammation. This can be achieved by combinatorial *in vivo* and *in vitro* experiments featuring GCS inhibition in astrocytes or microglia. Evaluating glial morphology as well as the cognitive function and neuronal connections in affected mice with glial-specific GCS deletion will be a first step in order to find out whether gangliosides are able to modulate neuroinflammation and, subsequently, pathological changes in Alzheimer's disease.

Excursion 1: Gangliosides

Gangliosides are lipids with a specific chemical structure that are found in the outer leaflet of the cell membrane. They were initially isolated from brain tissue in 1942 by Ernst Klenk, who also gave them the name "gangliosides". Besides very high amounts in the brain, gangliosides are found in virtually all cells of the body. They contribute to the formation of dynamic micro-domains in cellular membranes, where they modulate the activity of transmembrane receptors. Gangliosides display a hydrophobic ceramide membrane anchor and a hydrophilic head group consisting of a variable carbohydrate chain. Typically, gangliosides have one or more sialic acid residues in their head groups. Glucosylceramide synthase (GCS) is the key enzyme in ganglioside biosynthesis, which catalyzes the addition of an activated glucosyl moiety to ceramide. The subsequent addition of a galactosyl moiety leads to the formation of the common ganglioside precursor lactosylceramide. Additional carbohydrate moieties are then added by the sequential activity of further enzymes. Through this process, various ganglioside species are formed that differ in the composition of their head groups. Different cell types display different ganglioside expression patterns. Whereas neurons express high amounts of the complex gangliosides GM1, GD1a, GT1b, and GQ1b, astrocytes mainly express gangliosides with simple structures, such as GM3 and GD3.

Excursion 2: Ganglioside-deficient mouse model of Alzheimer's disease

Ganglioside biosynthesis can be inhibited cell-specifically by genetic deletion of the key enzyme of ganglioside biosynthesis (GCS, gene *Ugcg*) (Jennemann et al., 2005). This is accomplished with the help of the so-called Cre-loxP system, which specifically deletes marked ("floxed") DNA sequences. The promoter that regulates Cre expression determines the target cells where the recombinase shall be active. Mice with floxed *Ugcg* alleles are therefore crossbred with animals expressing the cutting enzyme Cre recombinase specifically in forebrain neurons (Nordström et

al., 2013). As Cre activity is inducible by tamoxifen in these mice, ganglioside biosynthesis can be specifically deleted in adult forebrain neurons. Mice harboring a GCS deletion in adult forebrain neurons are then cross-bred with a common mouse model of Alzheimer's disease, the so-called 5xFAD mice (Oakley et al., 2006). 5xFAD mice display an early-onset progressive variant of Alzheimer's disease, as well as β-amyloid deposition and neurodegeneration starting at the age of three months.

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