The Biological Basis for Alzheimer's Disease

By
Jessica Macaluso
ID: 913592841
HDE 117/ENT 117
Longevity

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SUMMARY

Dementia is a chronic ailment that results in severe alterations to the brain. Many forms of dementia exist such as Lewy body dementia, frontotemporal dementia, Wernicke-Korsakoff syndrome, and Alzheimer's disease. Alzheimer's disease is the most prevalent form of dementia and affects millions worldwide every year. Common symptoms of this disease include impaired thinking or an inability to make proper judgements. This currently incurable disease is caused by significant neuronal death in the brain due to of the accumulation of two neurodegenerative proteins: intercellular amyloid-beta plaques and intracellular tau tangles. The interaction of these two proteins creates a feedback loop that facilitates the continual destruction of nerve cells in the brain. Because the destruction of nerve cells disrupts the neuronal connections in the brain, Alzheimer's disease results in significant memory deficits as well as impaired cognition. Moreover, with the use of human models and transgenic mouse models, researchers have been able to analyze the role of biology, genetics, and physiology in Alzheimer's disease. For example, mutations in the presenilin 1 (PSEN1) gene or the amyloid precursor protein (APP) gene predispose an individual to acquire early-onset Alzheimer's disease. Likewise, an individual can have an increased likelihood of developing late-onset Alzheimer's disease if they carry the ApoE4 variant of the apolipoprotein E (ApoE) gene. In summary, researchers are amply investigating Alzheimer's disease from a variety of biological faucets in an effort to treat or even cure this form of dementia.

INTRODUCTION

Many efforts have been made to prevent Alzheimer's disease, but it is a challenge to understand the basic biology and clinical pathophysiology of this elusive neurodegenerative disease. A significant amount of research has been dedicated to creating therapeutic drugs to help prevent or completely halt the progression of the disease, but to no avail. The central consequence of this currently incurable disease is neuronal death, and therefore, a significant loss of grey matter in the brain. The most notable areas of loss include the medial temporal lobe (i.e. the hippocampus and the entorhinal cortex) as well as multiple cortices within the different brain lobes (Salmon & Bondi, 2009). Coronal slices of the brain of individuals without Alzheimer's disease compared to individuals with Alzheimer's disease clearly display the destructive nature of the disease (Vinters, 2015) [see Figure 1].

There are three major risk factors affiliated with Alzheimer's disease: age, gender, and genetics (Riedel et al., 2016). Age is the most notable risk factor and therefore a fundamental driver for the development and progression of the disease. Past research shows that the risk to develop Alzheimer's disease grows exponentially after one's sixties. In addition, the incident of Alzheimer's disease is more common in females, especially after one is seventy-five years old (see Figure 2). Globally, women typically live four and a half years longer compared to men and are therefore more at risk at developing this age-related dementia. Also, an individual's genetics affect one's likelihood of developing Alzheimer's disease. Examples of deterministic early-onset genes include mutations in the presenilin-1 (PSEN1) gene, the presenilin-2 (PSEN2) gene, and the amyloid precursor protein (APP) gene (De Strooper, 2007). The most well-known late-onset Alzheimer's disease gene is the Apolipoprotein E (ApoE) gene (Riedel et al., 2016). Collectively, this triad of risk factors allows one to better measure people's likelihood of acquiring Alzheimer's disease.

The most widely studied biological dysfunctions of Alzheimer's disease include amyloid-beta proteins and neurofibrillary tau tangles. Initially, amyloid-beta proteins dominated in Alzheimer's disease research, but, in recent years, a greater effort has been put into investigating the role of tau tangles in relation to Alzheimer's disease. Many different clinical trials are ongoing in an attempt to prevent or even treat Alzheimer's disease. Furthermore, with the use of positron-emission tomography (PET) tracers, new avenues of research have been created and utilized regarding these tau neurofibrillary fibers. With these advances, researchers hope to detect Alzheimer's disease earlier on, specifically from a biological level.

OVERVIEW

Background

In 1907 psychiatrist Alois Alzheimer would come to discover pathological changes (i.e. amyloid-beta plaques and neurofibrillary tau tangles) in the postmortem brain that are now known today as Alzheimer's disease (Zott et al, 2018). Alzheimer's disease is the most abundant form of dementia, a chronic disease or disorder that negatively impacts

cognitive and social functioning because of brain dysfunction (Salmon & Bondi, 2009). Alzheimer's disease is distinct from other forms of dementia (i.e. vascular dementia, dementia with Lewy bodies, semantic dementia, etc.) due to its progressive nature, significant memory deterioration, and destruction of nerve cells. Because an increasing number of people are living to older ages, the prevalence of Alzheimer's disease continues to rise; approximately forty-six million people worldwide suffer from dementia (James & Bennett, 2019).

Moreover, researcher De Strooper reported evidence of biomarkers associated with the development of Alzheimer's disease. For instance, mutations in the presenilin-1 (PSEN1) gene or the amyloid precursor protein (APP) gene can result in early-onset Alzheimer's disease (De Strooper, 2007). In addition, Vinters stated that certain genetic variants of the Apolipoprotein E (ApoE) gene result in an increased risk of Alzheimer's disease development, concluding that one can be biologically predisposed to acquire Alzheimer's disease (Vinters, 2015). Through neuroimaging, cerebrospinal fluid testing, and blood testing, the role of biomarkers and their impact on the brain can be observed (see Table 1).

Implications for the Brain and Cognition

Alzheimer's disease causes many negative consequences on the brain such as neuronal atrophy, synaptic loss, and an accumulation of proteins in the medial temporal lobe (i.e. the hippocampus and the entorhinal cortex) as well as within the cortices of the frontal, parietal, and temporal lobes (Salmon & Bondi, 2009). As a result, one who suffers from this disease will display significant amnesia and substantial impairments regarding abstract reasoning, executive function, attention, and spatial awareness. Furthermore, impairments in episodic memory typically arise first and are therefore indicators of early progression of the disease; the hippocampus is a region in the brain that has been studied robustly regarding memory, especially episodic memory (Tulving, 2002). Episodic memory is a neurocognitive system that is a subset of long-term memory. Essentially, episodic memory allows humans to remember their past experiences.

As the disease continues to progress, additional aspects of the brain deteriorate: the frontal, the parietal, and the temporal lobes (Salmon & Bondi, 2009). Because of this brain destruction and disconnection, patients experience a broad loss of knowledge and impaired language abilities such as verbal learning and the naming of objects. Through a study comparing ninety-eight patients with early Alzheimer's disease with ninety-eight normal control subjects, researchers Salmon and Bondi compared the two groups results across multiple tests: the California Verbal Learning Test, the category fluency text, a portion of the Trail-Making Test, and a deferred recall measure. Their results clearly display key characteristics affiliated with Alzheimer's disease: declining episodic memory, executive function, and semantic memory (see Figure 3). In addition, researchers Martyr and Clare reported a moderate association between one's instrumental activities of daily living abilities and executive function (Martyr & Clare, 2012). Instrumental activities of daily living occur in everyday function and allow an individual to live independently. Examples

of instrumental activities of daily living include shopping, using a telephone, or managing one's finances. In the meta-analysis, instrumental activities of daily living were assessed with questionnaires as well as through informants. Executive function capabilities were examined with a variety of tests such as the clock drawing task or the Stroop task. Strong associations were reported between multiple executive tasks (i.e. block design, category fluency, and the Wisconsin Card Sorting Test) and activities of daily living. In conclusion, both executive function and activities of daily living are impaired by the progression of Alzheimer's disease.

PROTEINS

Amyloid-Beta Plaques

Various cellular proteins such as amyloid-beta are affiliated with the neurological deterioration of the brain in Alzheimer's disease. For example, rather than remain in their typically soluble form, these proteins instead accumulate into an insoluble cross-beta structure known as amyloid (Andreeva et al, 2017). While amyloid-beta plaques are characteristic of normative aging, a significant number of plaques is a trademark for many neurodegenerative pathologies such as Alzheimer's disease.

The improper folding of these amyloid-beta peptides outside of the nerve cells cause significant and irreversible damage to the human central nervous system (i.e. the brain and the spinal cord). These neurotoxic effects are a consequence of multiple cell signaling cascades resulting in abnormal proteins. The propagation of incorrectly folded proteins occurs at the 42-residue of human amyloid-beta proteins (Xiao et al., 2015). An accumulation of these proteins results in the destruction of nerve cell synapses, causing both memory and cognition deficits (Bloom, 2014). Furthermore, the damage to synapses can even result in neuronal death. To help mediate the correct folding of proteins, molecular chaperones work to moderate the aggregation of amyloid-beta peptides (Graham et al, 2017). By lowering the prevalence of misfolded proteins, neurons can be saved from degradation. Even still, more research is necessary to fully understand the degree chaperones aid in Alzheimer's disease prevention.

Moreover, supplementary research with both human and mice models has been performed to observe the role of amyloid-beta proteins and its triggering of neurofibrillary tau tangles to change from a normal to a diseased state. Researcher Bloom deduces that over twelve researchers and their colleagues have reported evidence of an interaction between amyloid-beta plaques and neurofibrillary tau tangles (Bloom, 2014) [see Table 2].

Tau Tangles

Similar to amyloid-beta peptides, tau tangles are a key hallmark for Alzheimer's disease. Neurofibrillary tau tangles are initially soluble but become insoluble once they are diseased. Unlike amyloid-beta proteins, tau tangles exist outside of the nerve cells. Like amyloid-beta proteins, a significant accumulation of these tau tangles will have detrimental memory and cognition loss due to neuronal death. Bloom argues in favor of a feedback

loop. Meaning, once tau tangles are made toxic, they will further enhance the toxicity of amyloid-beta plaques (see Figure 4).

Furthermore, positron emission tomography (PET) tracers have allowed for in vivo characterization of not only amyloid-beta protein accumulation, but tau tangle accumulation as well. Huijbers and colleagues observed that as tau tangles accumulate, participants show characteristics of Alzheimer's disease: hippocampal hyperactivity and a drop in encoding success (Huijbers et al, 2019). Participants at risk for dementia had more difficulty encoding the faces of unfamiliar individuals that those with normal cognition (see Figure 5).

GENETICS AND PHYSIOLOGY

Human Models

Early Onset: PSEN Genes and APP Gene

Familial Alzheimer's disease has been linked to genes such as presenilin-1 (PSEN1) and the closely related presenilin-2 (PSEN2) [De Strooper, 2007]. Regarding age of onset, mutations in PSEN1 and PSEN2 cause early-onset Alzheimer's disease compared to the ApoE4 variant affiliated with late-onset. While there is variability with age of onset, PSEN1 mutations can lead to cognitive decline in individuals as early as before thirty years old (Larner & Doran, 2005). Presenilin genes are catalytic portions of the gamma-secretase enzyme that cleaves amyloid precursor proteins (APP) into amyloid-beta oligomers of various lengths (De Strooper, 2007) [see Figure 6]. When PSEN1 and PSEN2 are inactive, no amyloid-beta peptides are formed. Normal functioning of presenilin genes allows for a normative amount of amyloid-beta plaques as one ages. Therefore, mutations in presenilin genes leads to an abundant production of amyloid-beta plaques and results in Alzheimer's disease pathogenesis. Mutations in PSEN1 have been studied most in depth out of the two presenilin genes, therefore researchers know the most about PSEN1 and the different mutations in PSEN1 that cause aberrant amyloid-beta protein production. A majority of PSEN1 mutations are missense mutations where a single amino acid is changed in the PSEN1 gene. PSEN1 mutations can also occur because of insertions, deletions, or splicing.

In addition, mutations in the amyloid precursor protein gene have been affiliated with Alzheimer's disease, specifically early-onset. Due to alternative splicing, the APP gene exists in three major isoforms in the human genome: APP695, APP751, and APP770 (Zhang et al., 2011). APP751 and APP770 both contain a Kunitz Protease Inhibitor (KPI) while APP695 does not include this fifty-six amino acid domain. The APP isoforms containing the KPI sequence are affiliated with an increase in amyloid-beta proteins and therefore Alzheimer's disease pathogenesis. The biological function of APP remains largely unknown, but researchers propose proper functioning of APP results in neuronal outgrowth and synaptogenesis. Therefore, improper processing of the APP gene could plausibly disrupt neuronal communication and therefore result in Alzheimer's disease pathologies such as an abundance of amyloid-beta protein accumulation.

In contrast, Jonsson and colleagues discovered an APP gene coding mutation that serves as a protective factor against Alzheimer's disease (Jonsson et al., 2012). A majority of APP coding mutations result in the overproduction of the more toxic amyloid-beta 1-42 peptide compared to the less harmful amyloid-beta 1-40 peptide. This is not the case with the A673T coding substitution; the A673T substitution reduces amyloid-beta protein production by approximately forty percent. With the A673T coding substitution, amyloid-beta proteins can be cleaved properly and therefore are not in a neurotoxic state. Consequently, mutations in the APP gene do not always result in excessive amyloid-beta peptides and can sometimes work to counter Alzheimer's disease development.

Late Onset: ApoE Gene

Research focusing on inherited forms of Alzheimer's disease is currently ongoing, especially in regard to the three genetic variants of the Apolipoprotein E (ApoE) gene: ApoE2, ApoE3, and ApoE4. This gene is found in human blood and can provide a prediction if one is predisposed to acquire late-onset Alzheimer's disease (Andreeva et al, 2017). Over sixty percent of people diagnosed with Alzheimer's disease have at least one ApoE4 allele (Riedel et al., 2016). ApoE is important for proper folding of amyloid-beta proteins and if one carries one or more ApoE4 alleles, there is an increase in amyloid-beta protein formation. As a result, the ApoE4 variant puts an individual more at risk for developing Alzheimer's disease due to improper folding of amyloid-beta proteins.

There are three major hypotheses regarding the impact of the allelic genetic variation of ApoE with preventing or promoting Alzheimer's disease (Huang et al, 2019). Firstly, it has been observed that ApoE2 aids in clearing excessive amyloid-beta plaques in the brain; these proteins are a trademark of Alzheimer's disease. Secondly, the ApoE gene binds to the microglial surface receptor TREM2. The binding of ApoE to this receptor supposedly inhibits proper regulation of microglial functioning, but more research is needed to support this hypothesis. Thirdly, the different ApoE variants impact one's likelihood of developing Alzheimer's disease. Through observation of intracellular neuronal signaling, researchers have dictated that different allelic variants of ApoE put an individual more or less at risk of developing Alzheimer's disease. Through substantial investigation, researchers have deduced that individuals carrying the ApoE4 variation of the allele are most likely to develop Alzheimer's disease, individuals carrying the ApoE2 variation of the allele are least likely to develop Alzheimer's disease, and individuals who carry the ApoE3 variation of the allele have a prevalence of developing Alzheimer's disease somewhere between ApoE2 and ApoE4. Even still, the different effects of the ApoE variants are not fully understood despite extensive research on the topic.

By culturing both human and stem cells, Huang and colleagues attempted to gain a better understanding of the validity of the third proposed hypothesis regarding the ApoE genetic variations. Through gene expression analyses and electrophysiology, they reported that different ApoE variations create a variation of neuronal signaling pathway and that the ApoE gene fosters synaptic creation. Furthermore, their results created additional support for the third hypothesis regarding the ApoE gene.

Moreover, a derivative of rasagiline, known as M-30, has been used as a neuroprotector against Alzheimer's disease (Weinreb et al, 2009). Rasagiline has been administered in several preclinical experiments in an effort to promote anti-Alzheimer's disease activities and treat this common form of dementia (see Figure 7). By activating MAO-A and MAO-B inhibitors, amyloid-beta protein accumulation can be averted. By inhibiting the aggregation of these amyloid-beta plaques, Alzheimer's disease can be treated through the promotion of neuronal survival. In addition, ladostigil has been used to promote neuronal protection and neurorestorative effects (see Figure 8). The use of these two compounds have resulted in scientific findings promoting treatment for Alzheimer's disease.

Despite the sizable efforts put into drug therapy, there is uncertainty regarding the safety and effectiveness of treatments (Graham et al, 2017). Also, it is difficult to design clinical trials due to the ambiguous nature of the disease. Even still, there are currently over fifty active and advanced ongoing clinical trials with efforts to not only provide drug therapy in an attempt prevent Alzheimer's disease.

Transgenic Mice Models

In addition, mice models have been used to suggest risk factors for Alzheimer's disease. Regarding the role of the ApoE gene, if the human ApoE4 allele is expressed in a transgenic mouse, there is an increase of amyloid-beta plaques in the hippocampus (Andreeva et al, 2017). On the other hand, if the human ApoE2 allele is being expressed in a transgenic mouse, there is a decrease in amyloid-beta plaques in the hippocampus.

Furthermore, the disruption of proper calcium storage in transgenic mice models has been suggested to play a role in events leading to Alzheimer's disease (Aloni, et al, 2019). An Alzheimer's disease-associated phenotype was developed in the 3xTg/SPKO mouse model. By using and creating knock-out mice, Alzheimer's disease symptoms were made present on three levels of analysis: behaviorally, electrophysiologically, and morphologically. These 3xTg/SPKO mice were more prone to overproduction of amyloid-beta plaques in the CA1 region of the hippocampus than their wild-type (wt) or SPKO comparison groups and therefore more at risk for Alzheimer's disease development (see Figure 9). In addition, these 3xtG/SPKO mice exhibited a reduction in long-term potentiation and therefore a weakening of neuronal connection and communication within the brain, specifically the hippocampus; this too is characteristic of Alzheimer's disease.

In contrast, other researchers have investigated the role of epigenetics on cognitive decline affiliated with Alzheimer's disease. For example, Graff and colleagues discover that an epigenetic blockage of gene transcription that produces this cognitive impairment is plausibly reversible (Graff et al., 2012). Histone deacetylase 2 (HDAC2) is affiliated with a reduction in histone acetylation of genes critical for proper learning and memory; histone acetylation promotes gene expression and histone deacetylation causes gene repression. With the use of short-hairpin-RNA, histone deacetylase 2 can be effectively knocked down. Thus, the genes affiliated with learning and memory are no longer being repressed and can therefore be properly expressed. With the use of a water maze test, Graff

and colleagues reported evidence that blocking HDAC2 with the use of short-hairpin-RNA, proper learning and memory can be restored. Transgenic mice with the short-hairpin-HDAC2 not only find the water maze target faster, they also remain in the correct quadrant of the maze longer compared to the [CK-p25] transgenic mice experiencing pathologies affiliated with Alzheimer's disease (i.e. neuronal death and increased levels of amyloid-beta proteins) [see Figure 10].

Additionally, transgenic mouse models have been utilized to further analyze the role of neurofibrillary tau tangles. Due to the minimal research in in vivo diseased tau tangles, Min and colleagues focus on how acetylation of the tau protein [through the deletion of protein deacetylase SIRT1] results in toxicity of these proteins (Min et al, 2018). By deleting SIRT1, tau acetylation was increased and caused a significant number of cognitive impairments in the affected transgenic mice models. When the affected mice tried to navigate behavioral tests such as the Y-maze and the Morris water maze, these mice displayed spatial memory impairments and compromised memory retention in probed trials that occurred twenty-four hours after the initial learning of the mazes.

Despite the crucial data transgenic mice models provide in Alzheimer's disease research, current mice models do not fully mirror the Alzheimer's disease pathologies that are visible in humans (Ashe & Zahs, 2010). For example, transgenic mice with amyloid precursor protein (APP) mutations will develop amyloid-beta plaques and memory deficits, but typically do not have any tau tangles and have minimal neuronal loss. Although these mice do display Alzheimer's disease symptoms comparable to those of human models, the underlying biology varies between the two species. In conclusion, while mice models provide critical information regarding Alzheimer's disease research, researchers have yet to create a transgenic mouse model that fully replicates the biological underpinnings of Alzheimer's disease that are seen in humans.

CONCLUSION

Since its official discovery in 1907, Alzheimer's disease has been a rising issue for the aging population around the world. As longevity increases, the prevalence of Alzheimer's disease rises as well. Despite continual attempts to treat or cure Alzheimer's disease, researchers have been unsuccessful in their efforts to remedy this pathological memory disease. Despite this, the substantial research put into Alzheimer's disease has allowed researchers to discover biomarkers for the disease. Trademarks of Alzheimer's disease include the accretion of two neurodegenerative peptides: amyloid-beta plaques outside the nerve cells and tau tangles within the nerve cells. These two peptides are thought to interact in a feedback loop: diseased tau tangles facilitate the further creation of amyloid-beta proteins. This interaction promotes neurological degeneration and therefore causes memory loss and cognitive impairments for the affected individual. Also, with the use of both human models and transgenic mouse models, researchers have been able to discover the effects of genetics and physiology on the likelihood one will acquire Alzheimer's disease. For example, missense mutations in presenilin-1 (PSEN1) and coding mutations in the amyloid precursor protein (APP) gene can result in an individual

developing early-onset Alzheimer's disease. Likewise, if an individual carries the ApoE4 allelic variant for the apolipoprotein E (ApoE) gene, the likelihood of that individual to acquire Alzheimer's disease is significantly higher than with an individual carrying the ApoE2 allelic variant. In conclusion, over the past century and more specifically in the last twenty-years, researchers have effectively established an extensive biological basis Alzheimer's disease despite its mysterious and aberrant nature.

TABLES

Table 1. Biomarkers of potential value in supporting the clinical diagnosis of Alzheimer's disease/senile dementia of Alzheimer type (Source: Vinters, 2015).

Method	Measures
Thorough neurologic and neuropsychological examination of the subject	Emphasize mental status, memory storage and retrieval, focal signs
Neuroimaging (structural, magnetic resonance imaging)	Ventricular enlargement (ventriculomegaly) Thinning of the cortical ribbon Hippocampal atrophy/enlargement of the temporal horn of the lateral ventricle Brian microbleeds (for cerebral amyloid angiopathy)
Neuroimaging (metabolic)	Pittsburgh compound B (PiB), labeled with ^{18}F or ^{11}C: florbetapir or amyvid [^{18}F]Fluoroethyl-methyl-amino-2-naphthyl-ethylidene malononitrile (FDDNP) [^{18}F]Fluoro-dexoyglucose positron emission tomography Tau markers
Cerebrospinal fluid testing	Amyloid beta 1–42 Total tau and phospho-tau 14-3-3 protein (to rule out spongiform encephalopathy)
Blood testing	Apolipoprotein E isoforms (polymerase chain reaction–based assay) Neuron-specific enolase, S100B (as a measure of brain injury)

Table 2. Tau-dependent effects of Aβ. Abbreviations: Aβ, amyloid-β; AβO, amyloid-β oligomer; APP, amyloid precursor protein; MT, microtubule; NMDA, N-methyl-D-aspartate (Source: Bloom, 2014).

| Study	System	Summary of Main Results
Götz et al,[5] 2001	Mouse	Tangle formation accelerated by injection of Aβ fibrils into the brain
Lewis et al,[6] 2001 and Hurtado et al,[7] 2010	Mouse	Mutant APP expression accelerates tangle formation by mutant tau
Roberson et al,[8] 2007	Mouse	Tau required for learning and memory deficits when plaques are present
Leroy et al,[9] 2012	Mouse	A feedback loop connects Aβ and tau pathologies
Ittner et al,[10] 2010	Mouse	Aβ causes tau-dependent excitotoxicity at NMDA receptors
Rapoport et al,[11] 2002	1° Neurons	Aβ fibrils are cytotoxic
King et al,[12] 2006	1° Neurons	AβOs cause tau-dependent MT loss
Nussbaum et al,[13] 2012	1° Neurons	Pyroglutamylated AβOs cause tau-dependent cytotoxicity
Seward et al,[14] 2013	1° Neurons	AβOs cause tau-dependent, ectopic cell cycle reentry
Shipton et al,[15] 2011	Brain slice	AβOs cause tau-dependent impairment of long-term potentiation
Vossel et al,[16] 2010	1° Neurons	AβOs cause tau-dependent inhibition of mitochondrial transport on MTs
Zempel et al,[17] 2013	1° Neurons	AβOs cause tau-dependent MT severing and synaptic damage in dendrites

FIGURES
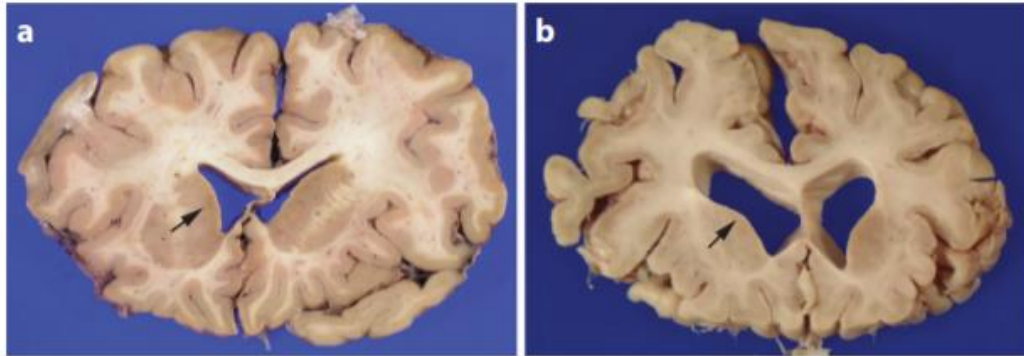
Figure 1. Coronal slices of (fixed) brain from two different patients, one without dementia (panel a) and one with (panel b); slices are at comparable coronal levels (near the head of the caudate nucleus). Arrows indicate a relatively normal lateral ventricle in the control case (panel a) versus a markedly enlarged lateral ventricle in the Alzheimer's disease subject (panel b). Cortical thinning is less prominent (Source: Vinters, 2015).
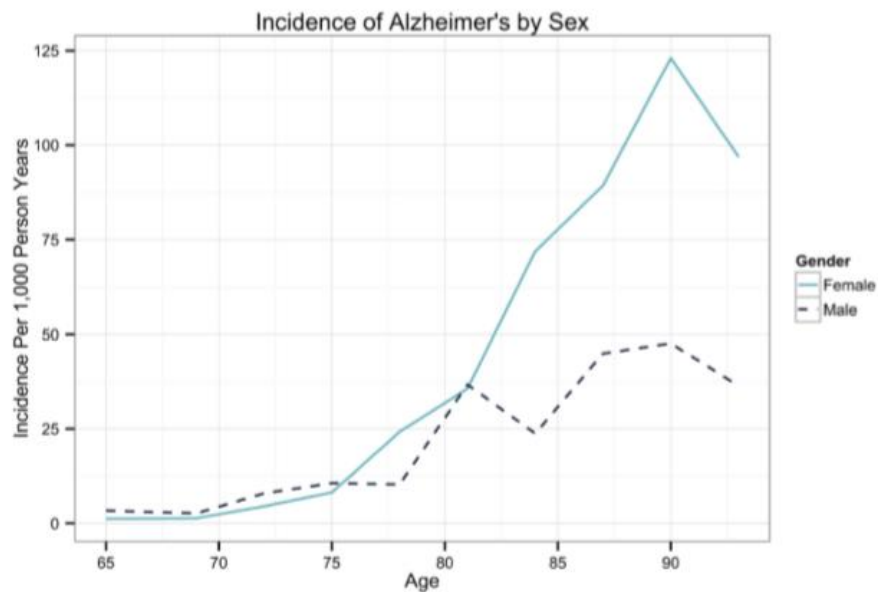
Figure 2. Sex-specific incidence estimates of Alzheimer's per one thousand person years. Obtained with the data from the Cache County Study. Additional data reported in Ruitenberg et al. indicate that men are at greater risk than women for developing earlier onset Alzheimer's disease. However, this sex difference is reversed by age seventy-five, with women at a two-fold greater risk for Alzheimer's disease, thereafter (Source: Riedel et al., 2016).
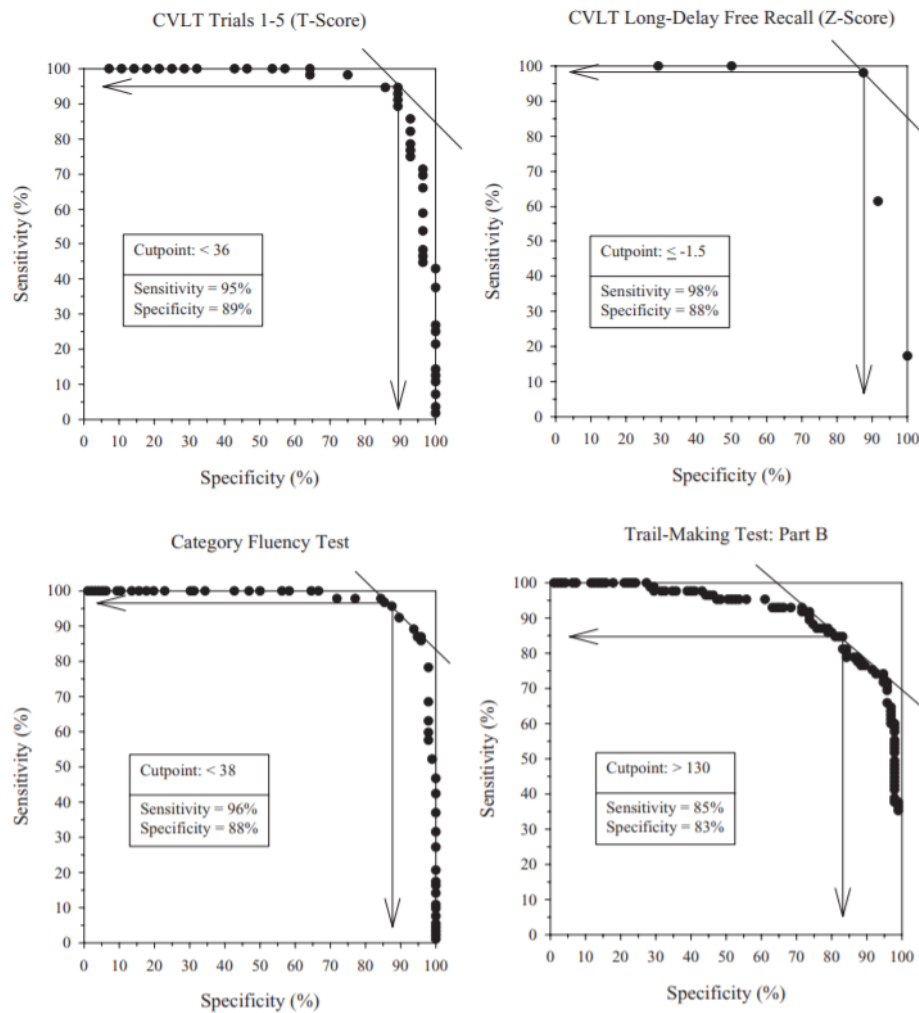
Figure 3. Receiver Operating Characteristic curves comparing sensitivity and specificity for the accurate diagnosis of early Alzheimer's disease (AD) achieved with Trial 1-5 Learning measure from the California Verbal Learning Test (CVLT), the Long-Delay Free Recall measure from the CVLT, the Category Fluency Test (a semantic memory and executive function measure), and Part B of the Trail-Making Test (an executive function measure). The maximally effective cut-point for memory and executive function measures showed excellent sensitivity and specificity in distinguishing between very mild AD and normal aging (Source: Salmon & Bondi, 2009).
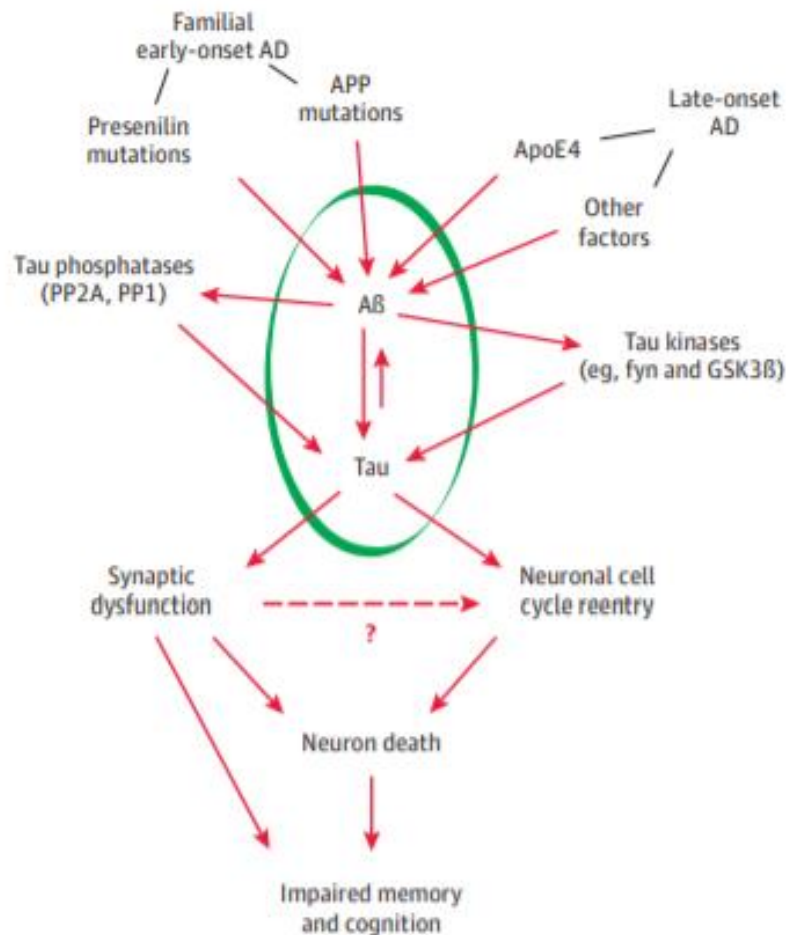
Figure 4. Signaling from amyloid-β (Aβ) through tau drives Alzheimer's disease (AD) progression. Pathological Aβ species accumulates in the brain because of simple genetic insults, such as the rate amyloid precursor protein (APP) and presenilin mutations that cause familial early-onset AD, and the presence of apolipoprotein E4 (ApoE4), the protein product of the ε4 allele of the ApoE gene, which is the strongest genetic risk factor for late-onset AD. Complex genetic interactions and environmental risks, indicated here as other factors, also contribute to the accumulation of toxic Aβ species in late-onset AD. Toxic Aβ species stimulate the formation of pathological tau by modulating protein kinases and phosphatases that regulate tau phosphorylation and by inducing tau misfolding. Toxic forms of tau mediate the synaptic dysfunction and neuron death that underlie memory and cognitive impairment in AD, so the signature adverse effects of Aβ require tau (Source: Bloom, 2014).
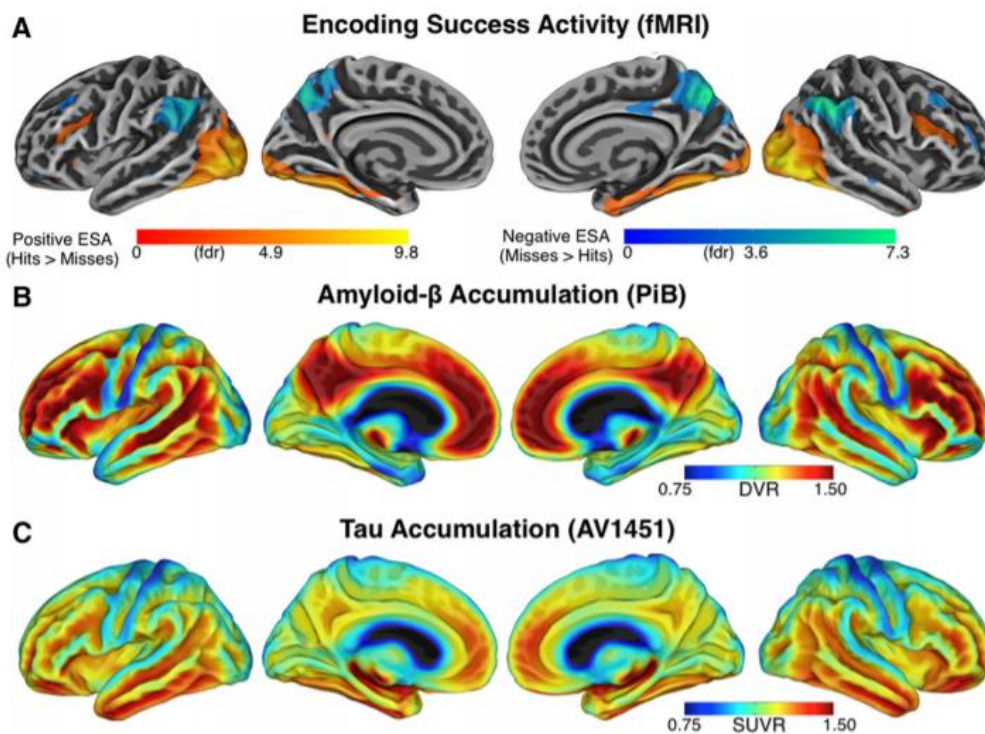
Figure 5. Whole-brain maps illustrating the colocalization of fMRI activity, amyloid-β, and tau accumulation. A, task-evoked fMRI activity across all participants on the cortical surface (p<0.05, FDR-corrected). Warm colors show positive encoding success activity, cool colors show negative encoding success activity. B, the mean amyloid-β accumulation using PET-PiB expressed as DVR across all participants. The red colors indicate areas with high levels of accumulation and blue with low. C, the mean tau accumulation, using PET-AV1451 expressed and SUVR across the subset with tau data (Source: Huijbers et al., 2019).
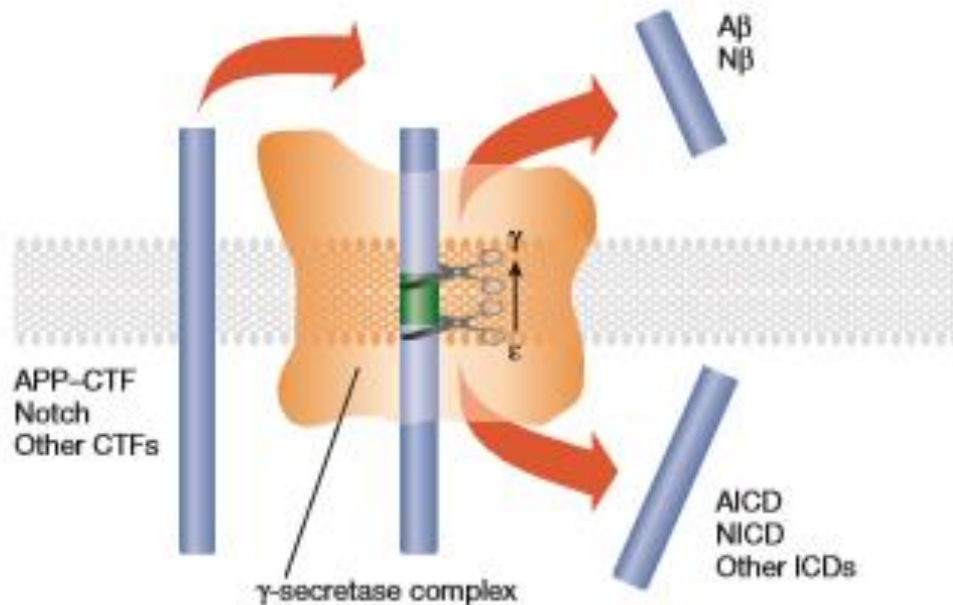
Figure 6. The γ-secretase. "barrel" structure of the γ-secretase (orange). The arrow indicates progressive ε-to-γcleavage of the substrate (blue bars). The possibility of unfolding of the substrate is discussed in the main text, Aβ,amyloid β-peptide; AICD, APP intracellular domain; APP, amyloid precursor protein; CTF, carboxy-terminal fragment; ICD, intracellular domain; Nβ, Notch β-like fragment; NICD, Notch intracellular domain. (Source: De Strooper, 2007).
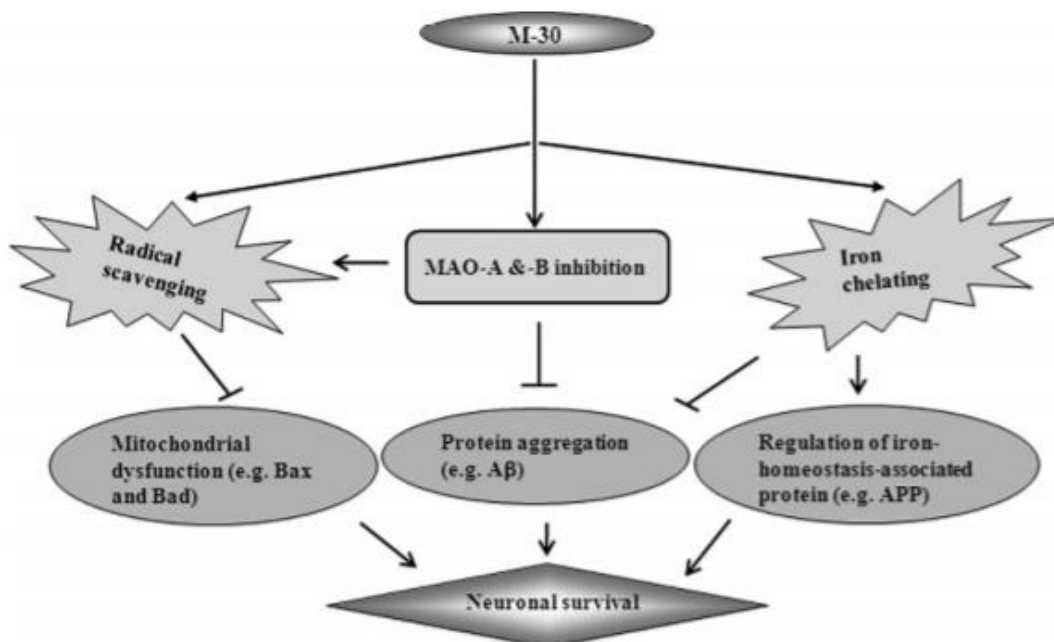
Figure 7. Schematic illustration of the multifactorial effects involved in the neuroprotective mechanism of action of the iron chelator, M-30. APP = amyloid precursor protein; MAO = monoamine oxidase (Source: Weinreb et al., 2009).
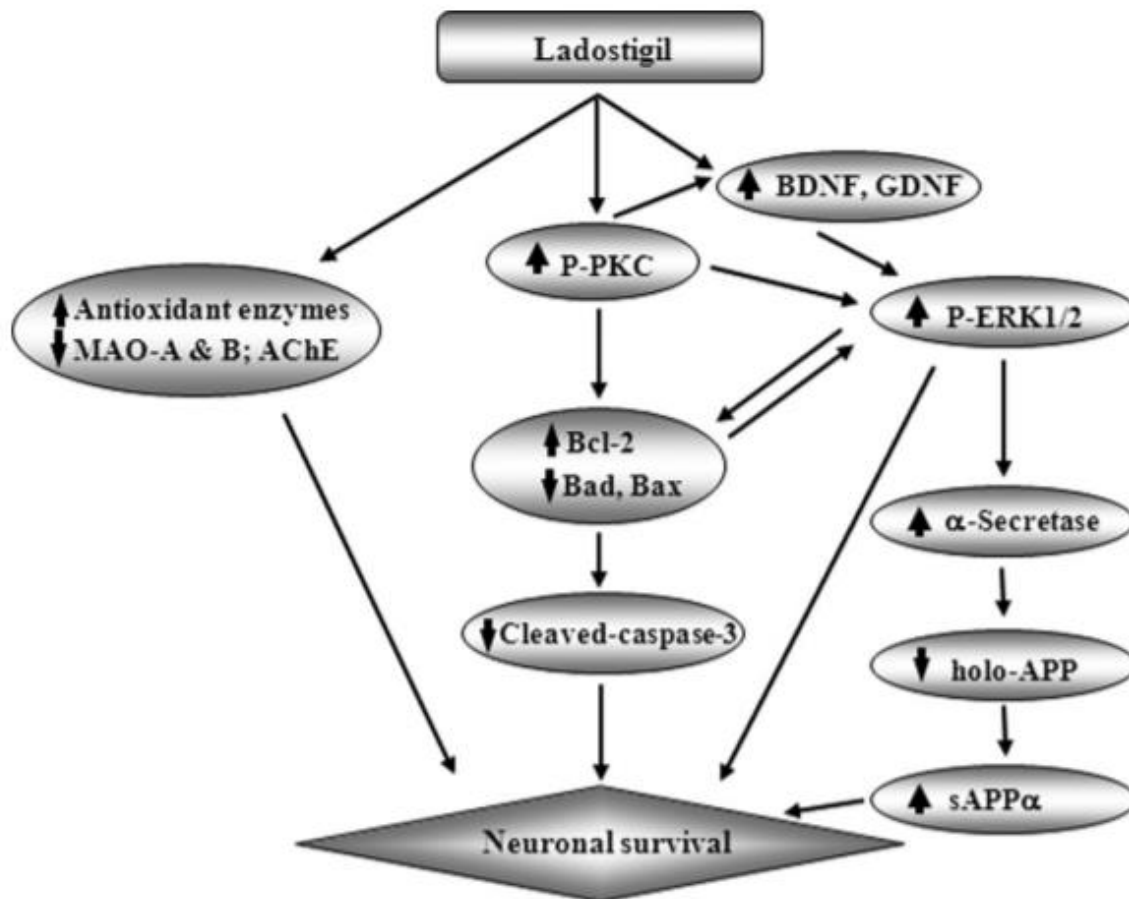
MULTIFUNCTIONAL NEUROPROTECTIVE COMPOUNDS

Figure 8. Schematic overview demonstrating protein and gene targets involved in the neuroprotective activity of ladostigil, with respect to the pathological features described in AD, such as extracellular deposition of Aβ, marked cholinergic cortical afferent dysfunction, lack of trophic factor support and cytotoxic signals that can initiate cell death processes and OS at those neurons and brain areas associated with this disease. AChE = acetyl cholinesterase; APP = amyloid precursor protein; BDNF = brain-derived neurotrophic factor; GDNF = glial cell line-derived neurotrophic factor; MAO = monoamine oxidase; P-PKC = phosphorylated-PKC; P-ERK1/2 = phosphorylated extracellular signal-related kinase 1/2 (Source: Weinreb et al., 2009).
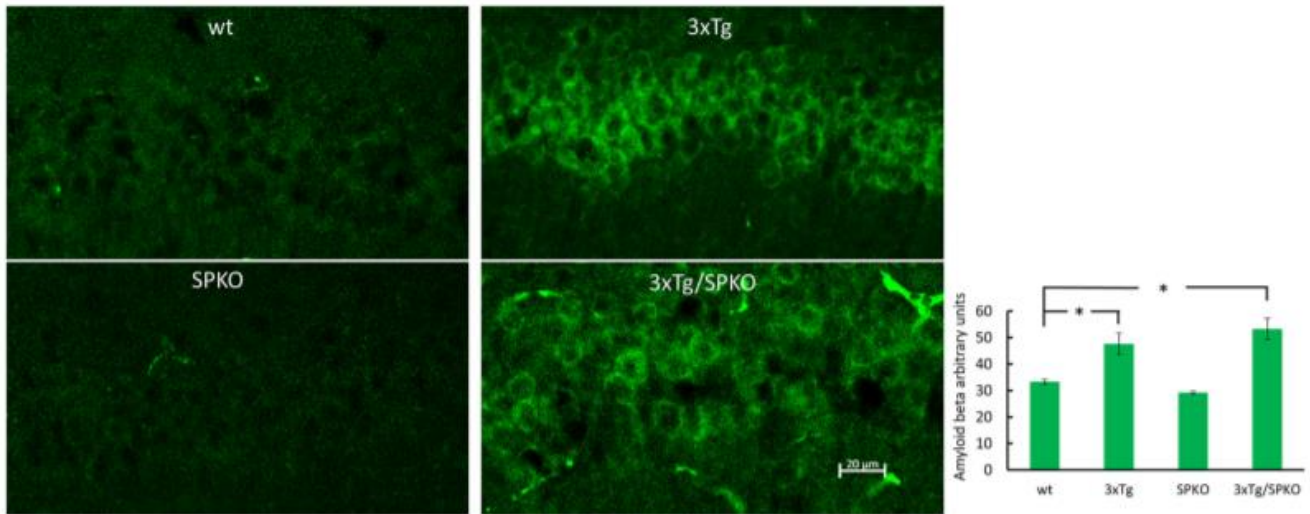
Figure 9. 3xTg and 3xTg/SPKO express more intracellular β-amyloid: representative immunostaining of CA1 area of hippocampal sections immunolabeled for β-amyloid (green). Bar graph showing significant differences between the control and the 3xTg groups and between the wt and 3xTg/SPKO groups found using one-way ANOVA with Tukey HSD post hoc test (wt, 33.39+/-0.81/; 3xTg, 47.68+/-3.9; 3xTg/SPKO, 53.3+/-3.95; F3=8.551; p<0.001; post hoc test: wt vs 3xTg, p=0.0147; wt vs 3xTg/SPKO, p=0.0016). Nine-month-old female mice; n=18 sections taken from 3 animals/group. *p<0.05 (Source: Aloni et al., 2019).
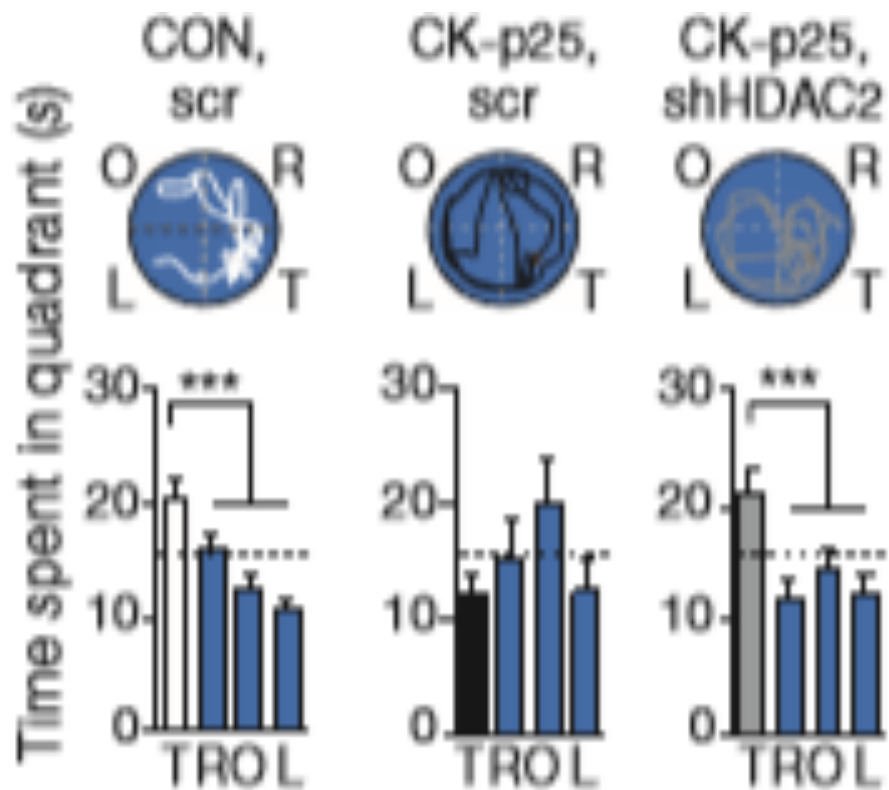
Figure 10. Representative swim traces and time spent per quadrant during the water maze test (T, target quadrant; R, right; O, opposite; L, left of target). *P≤0.05; **P≤0.01; P≤0.001; values are mean +/1 s.e.m. (Source: Graff et al., 2012).

Jessica Macaluso

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