Tau and tauopathies

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19-7-2019
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Abstract

The aim of this thesis is to find an answer to several questions regarding tau and tauopathies. The first two question being: “What are tauopathies and how do these neurodegenerative diseases develop?” and “What are the differences of tau protein structure, -fold and -spreading in different tauopathies such as Pick’s disease and Alzheimer’s disease and how do these differences contribute to the different characteristics of these diseases?” In this thesis, the answer to the last question will be given by discussing information regarding the genetics behind the tau protein, the tau structure and function and the ability of tau to cause neurodegenerative diseases. Both Alzheimer’s disease and Pick’s disease, and the differences between them, will be discussed. In the end, the question “Can this information lead to new therapeutic strategies?” will be answered.

By studying information regarding this questions, it has become clear that there is a lot of information regarding the tau protein and the general underlying mechanism causing tauopathies such as Alzheimer’s disease and Pick’s disease. However, apart from the different tau protein folds in Alzheimer’s disease and Pick’s disease, there are at the moment no other disease-specific characteristics that might be the potential cause of different characteristics in tauopathies.

There are several therapeutic strategies suggested that mostly target the general mechanism underlying tauopathies. However, as of this moment the most promising strategy seems to be tau immunotherapy. In contrast to the other strategies proposed, tau immunotherapy is more specific and might be able to target individual tauopathies in the future.

The questions stated can not yet be answered to satisfaction. It is clear that a lot more research has to be done regarding tauopathies. Recent studies have payed more attention to tau protein structure and fold, but more tauopathies have to be included in the future to be able to gain knowledge about the underlying tau mechanisms in different tauopathies. Additionally, that might give more insight in how tauopathies and other neurodegenerative diseases develop and how these diseases can be treated or prevented.

Introduction

Tauopathies
In short, tauopathies are neurodegenerative diseases characterized by abnormal accumulation of the tau protein in the brain. Tauopathies are neurodegenerative diseases that show heterogeneity morphologically, biochemically and clinically (Kovacs, 2015; Tan et al., 2017).
More then twenty different tauopathies can nowadays be distinguished (Ling, 2018). This includes Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, Pick's disease, frontotemporal dementia with parkinsonism linked to chromosome 17, Huntington's disease and agyrophilic grain disease (Wang et al., 2016). Most research regarding tauopathies have included Alzheimer's disease, since this is the most common neurodegenerative disease (Williams, 2006).
Alzheimer's disease is a secondary tauopathy. This means that the disease is not solely caused by tau protein aggregation. Other proteins also play an important role in the development of this disease. A primary tauopathy is caused solely by tau protein aggregation. The most commonly discussed example of a primary tauopathy is Pick's disease. In the underlying mechanism of this tauopathy, no other proteins are involved (Kovacs, 2015).
Both the fact that Alzheimer's disease and Pick's disease are different forms of tauopathies and the fact that they are the most discussed tauopathies in recent studies regarding tau, is the reason the focus of this thesis will be on Alzheimer's disease and Pick's disease.

Alzheimer's disease
Alzheimer's disease is the most common neurodegenerative disease. Patients with Alzheimer's disease suffer from cognitive decline because of tau protein aggregation in neuronal cells and extracellularly deposited beta-amyloid in the cerebral cortex, but also in other parts of the brain (Falcon et al., 2018 [2]). Common symptoms are memory impairment and impairment in language, visuospatial function and executive function (Williams, 2006).
Since both beta-amyloid and tau protein are involved in Alzheimer's disease, it is called a secondary tauopathy (Abisambra et al., 2011; Castellani et al., 2019).

Pick's disease
Pick's disease is a neurodegenerative disease characterized by frontotemporal dementia (Falcon et al., 2018 [1]) and the expression of Pick bodies in neuronal cells, which gain a round or horseshoe shape and consist of tau protein (Ikeda et al., 2017). Symptoms include changes in personality with abnormal behaviour and speech disorder with aphasia (Amano et al., 1999; Williams, 2006).
Since Pick's disease is characterized only by the accumulation of tau protein, it is called a primary tauopathy (Kovacs, 2015).

In this thesis, different aspects and characteristics of tauopathies will be described. Hopefully, an answer can be given to the question how these aspects and characteristics differ between different tauopathies such as Alzheimer's disease and Pick's disease. This will then give more insight in how different tauopathies develop and why they develop differently even though the general underlying pathological mechanism is the same.
The following questions will be investigated:

1. What are tauopathies and how do these neurodegenerative diseases develop?
2. What are the differences of tau protein structure, -fold and -spreading in different tauopathies such as Pick's disease and Alzheimer's disease, and how do these differences contribute to the different characteristics of these diseases?
3. Can this information lead to new therapeutic strategies?

Tau protein

Genetics

The tau protein is encoded by a single gene located on chromosome 17q21. This gene is called the microtubule-associated protein tau gene (MAPT). The MAPT gene contains 16 exons and can form six different tau isoforms by alternative splicing of exons 2, 3 and 10 (Arendt et al., 2016; Tan et al., 2017; Andreadis et al., 1992) (Figure 1).

Previously, it had been found that mutations in the MAPT gene cause some forms of frontotemporal dementia with parkinsonism linked to chromosome 17, which is a disease that is also part of the tauopathy family. These findings proved that dysfunction in tau, by mutation of the MAPT gene, was linked to neurodegenerative disease (Strang et al., 2019). Until today, more than 50 MAPT mutations have been found which cause several tauopathies (Ghetti et al., 2015). These mutations will later be further discussed.

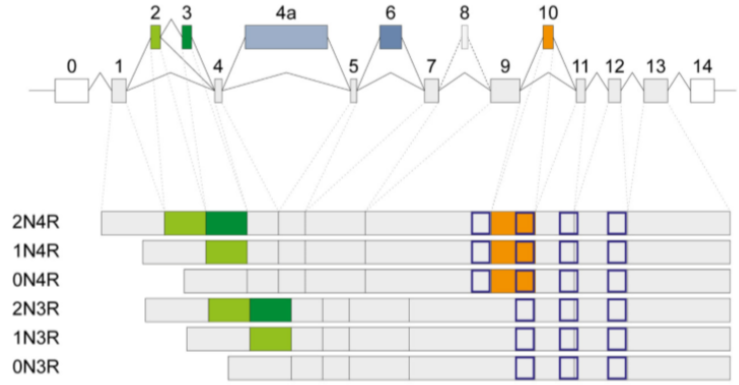

Figure 1: The MAPT gene codes for six different tau isoforms by alternative splicing of exons 2, 3 and 10 (Arendt et al., 2016).

Tau protein isoforms

In the adult human brain, six tau protein isoforms are expressed. As stated above, these isoforms are formed by alternative splicing of exons 2, 3 and 10 of the MAPT gene. The six tau protein isoforms are called 0N/3R, 0N/4R, 1N/3R, 1N/4R, 2N/3R, 2N/4R, 3N/3R and 3N/4R, where the "R" represents the number of microtubule-binding repeats and the "N" represents the number of N-terminal inserts. The microtubule-binding repeats are encoded by MAPT gene exons 9-12 (Tan et al., 2018; Goedert et al., 1989; Tapia-Rojas et al., 2019; Wang et al., 2008) (Figure 1).

Normal function of tau

The microtubule-binding domain of the tau protein contains either three or four microtubule binding repeats, hence the names of 3R and 4R tau. These repeats bind to microtubules and promote microtubule assembly and thereby stabilization of microtubules. For the initiation of microtubule assembly, nucleation of tubulin is needed. Tau promotes this tubulin nucleation. Via this mechanism, the tau protein helps maintain the normal morphology of neurons. Along with this, tau plays a key role in axonal transport and cell signaling (Wang et al., 2008), which is regulated via different mechanisms. The first mechanism, described by Dixit et al. (2008), is the competition for binding to microtubules of tau with kinesin or dynein motors. This competition reduces the frequency of binding, the motile fraction and the run length of kinesin and dynein. This slows down both the anterograde and retrograde transport along the axon. The second mechanism described is how tau reduces the number of motors that are involved with cargoes, and therefore interferes with and reduces the axonal transport of cargoes (Vershinin et al., 2007). Thereby, tau also affects the axonal transport of cargoes by competing with these cargoes for available kinesin (Konzack et al., 2007). As a fourth mechanism, it is described how tau regulates the release of cargo vesicles from kinesin chains. Tau activates protein phosphatase 1 and glycogen synthase kinase 3β and thereby regulates the release of the cargo vesicles (Kanaan et al., 2011). The fifth mechanism is described by Magnani et al. (2007) and is the ability of tau to facilitate association of dynactin to microtubules. This association causes

stabilization of the interaction of dynein with microtubules and therefore supports transport via dynein.
Additionally, tau seems to be playing an important role in axonal elongation and maturation. In cultured rat neurons where tau was knocked out, there was an inhibition of neurite formation. In contrast, when tau was overexpressed in these same neurons, the formation of neurites was strongly activated, even in non-neurite cells (Knops et al., 1991).

Posttranslational modifications of tau
Posttranslational modifications of tau include phosphorylation, ubiquitination, truncation, glycosylation, glycation, methylation, sumoylation, prolyl-isomerization and acetylation. Although usually posttranslational modifications are linked to pathology, it is important to realise that these modifications are also present under physiological conditions. The most common modification is phosphorylation, and under physiological conditions this causes reduced binding to microtubules. The other posttranslational modification mechanisms all have their own physiological function in the human brain, mostly influencing binding of tau to microtubules, tau metabolism, tau turnover and tau aggregation (Tapia-Rojas et al., 2019; Wang et al., 1996; Martin et al., 2011; Hanger et al., 2007; Kuhla et al., 2007). Next to a role in physiological function, these posttranslational modifications of tau protein also play a role in pathological function (Figure 2).
Tau phosphorylation is regulated by different kinases and phosphatases. Three classes of protein-kinases are able to phosphorylate tau: 1) proline-directed serine/threonine-protein kinases; 2) non-proline-directed serine/threonine-protein kinases; 3) tyrosine kinases (Martin et al., 2011). There are several phosphatases that can dephosphorylate tau in the brain (Liu et al., 2005). Whether the phosphorylation maintains a physiological and does not transform into a pathological condition, depends on the balance between the kinases and phosphatases activity (Tapia-Rojas et al., 2019). Hyperphosphorylation of tau by the kinases affects normal cellular distribution of tau in adult and developing neurons. It thereby reduces the affinity of tau for microtubules which results in the destabilization of neurons (Hanger et al., 2007).

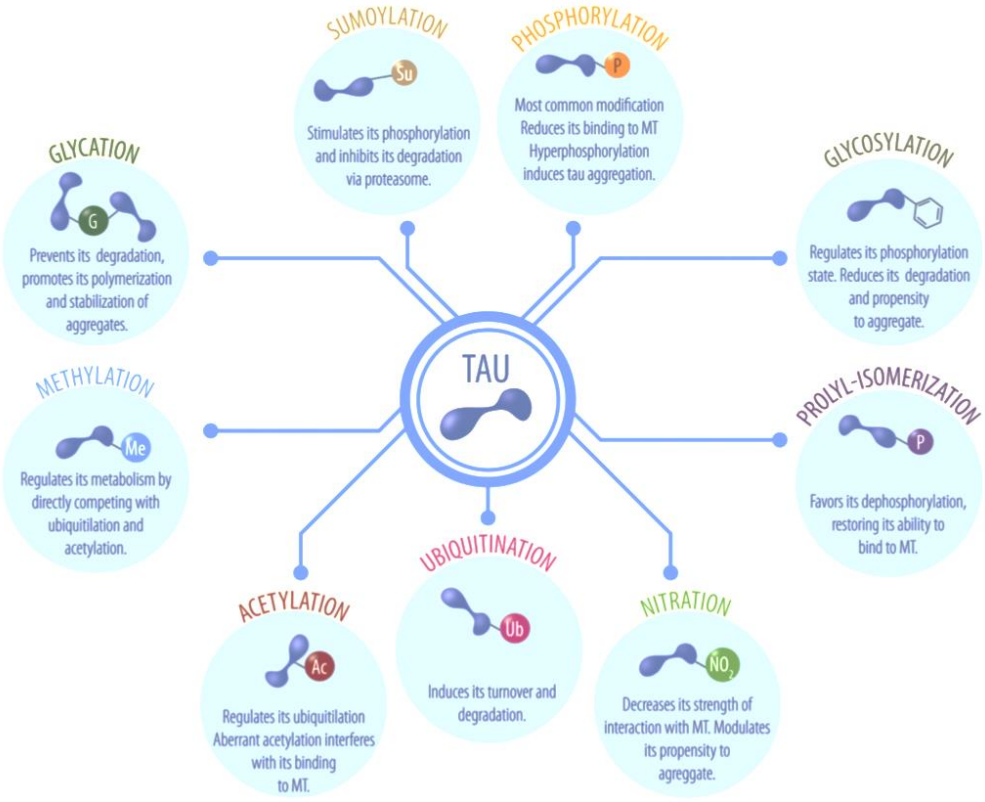

Figure 2: Posttranslational modifications of tau (Tapia-Rojas et al., 2019).

Tau protein structure and fold in Alzheimer's disease and Pick's disease

In Alzheimer's disease, all six isoforms of the tau protein are expressed. This means that both 3R and 4R tau are present in the brains of patients with Alzheimer's disease. On the contrary, in Pick's disease only 3R tau is present, thus only three tau protein isoforms are expressed in these patient's brains. By the use of cryo-electron microscopy, two types of tau filaments were distinguished in both Alzheimer's disease and Pick's disease, and these tau filaments also differ between these diseases. In Alzheimer's disease, straight filaments (SFs) and paired helical filaments (PHFs) can be distinguished, whereas in Pick's disease narrow Pick filaments (NPFs) and wide Pick filaments (WPFs) can be distinguished (Fitzpatrick et al., 2017; Falcon et al., 2018 [1]).

The PHFs and SFs in Alzheimer's disease consist of two protofilaments with C-shaped subunits (Figure 3). The cores of the two protofilaments in PHFs and SFs are similar, and consist primarily of microtubule-binding repeats R3 and R4 of 4R tau. Both filaments differ in the way the protofilaments make contact with each other. In PHFs, the protofilaments make contact in a symmetrical way, whereas in SFs, the protofilaments contact each other in an asymmetrical way. The association of the protofilaments is through cross-β-packing and β-helices (Fitzpatrick et al., 2017).

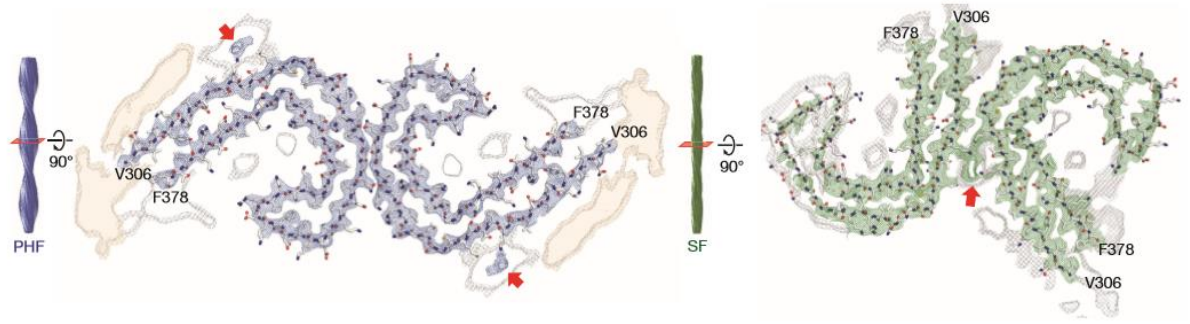

Figure 3: Cryo-electron microscopy pictures of a PHF (left) and a SF (right) in Alzheimer's disease (Fitzpatrick et al., 2017).

Cryo-electron microscopy in Pick's disease showed the two different Pick filaments, and revealed that indeed, these filaments only consist of 3R tau. NPFs consist of only one protofilament, which very much differs from the PHFs and SFs in Alzheimer's disease. The WPFs consist of two NPFs, which associate at their distal tips and make tight contact through Van der Waals interactions. At their distal tips, the NPFs have a flat surface at a hairpin turn, which provides the interface for the formation of WPFs (Figure 4). Previously it was not known why, in contrast to the filaments in Alzheimer's disease, the filaments in Pick's disease only consist of 3R tau, which lacks the second microtubule-binding repeat. Different structures in the Pick filament have been pointed out which may cause this difference. Firstly, there is a structure in the Pick filament, ranging from the lysine at position 254 to the lysine at position 274, which is inaccessible to residues from the second microtubule-binding repeat of 4R tau. Secondly, since a threonine in the filament structure, at position 263, is located very close to the backbone of the opposite strand, a bulky sidechain from 4R tau cannot be accommodated. Also, the interaction of an isoleucine from 3R tau at position 260 with its leucine at position 375 and isoleucine at position 360 are stronger than the interaction with a cysteine, at position 291, from 4R tau that would be formed otherwise (Falcon et al., 2018 [1]).

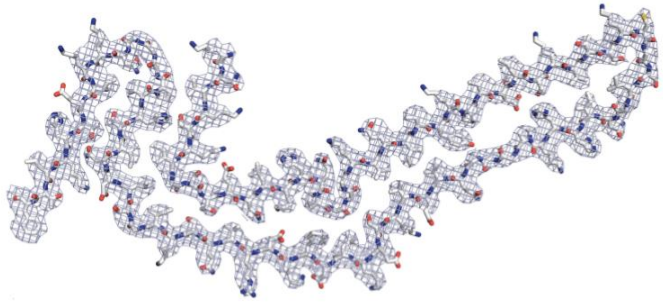

Figure 4: Cryo-electron picture of a NPF. The WPF consist of two NPFs, which associate at the distal (right) tips (Falcon et al., 2018 [1]).

Another big difference between tau filaments in Alzheimer's disease and tau filaments in Pick's disease occurred after cryo-electron microscopy. It showed that the tau filaments from Pick's disease do not have a phosphorylated serine at position 262 and/or 356. The Pick filament structure shows a tight turn which might prevent the phosphorylation of serine at position 262 (Falcon et al., 2018 [1]) (Figure 5).

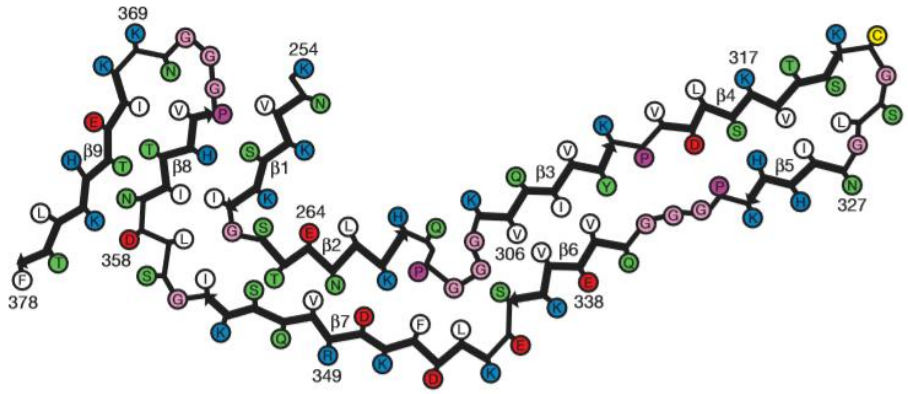

Figure 5: Schematic picture of the NPF fold (Falcon et al., 2018 [1]).

The ability of the tau protein to cause tauopathies

Tau aggregation

In different tauopathies, for example and as discussed before Alzheimer's disease and Pick's disease, tau inherits a certain fold (Falcon et al., 2018 [1][2]). However, intrinsically, the tau protein is unfolded and does not have a strong tendency to aggregate (Mykrasch et al., 2009). Along with this, the tau protein has a preference for forming a paperclip-like shape, in which both N- and C-terminals and the microtubule-binding repeat domains approach each other (Jeganathan et al., 2006). The formation of this paperclip-structure most likely prevents tau aggregation. Truncation, a posttranslational modification of tau which has been described before as a mechanism influencing aggregation of tau, prevents the formation of the paperclip-structure. This indicates that truncation of tau promotes aggregation of the protein (Wang et al., 2016). Additionally, interaction with other molecules or mutations of tau could also lead to abnormal aggregation (Jeganathan et al., 2006). The tau aggregates in tauopathies are called neurofibrillary tangles, and are the cause of the neurodegeneration that patients with several tauopathies suffer from. Therefore, the neurofibrillary tangles serve as an important characteristic in, and biomarker for these diseases (Wang et al., 2016).

Hyperphosphorylation of tau

As stated earlier, hyperphosphorylation of tau by kinases affects the normal cellular distribution of tau in adult and developing neurons. It thereby reduces the affinity of tau for microtubules which results in the destabilization of neurons (Hanger et al., 2007; Wang et al., 2016). In the longest tau isoform, there are 85 sites that can potentially be phosphorylated. Some sites are abnormally hyperphosphorylated in tauopathies, these are the 17 threonine-proline or serine-proline motifs. These sites are phosphorylated by signal-transducing proline-directed serine/threonine kinases, in contrast to other sites which are phosphorylated by, among others, cyclic AMP-dependent protein kinase, Ca^{2+}- or calmodulin-dependent protein kinase II or microtubule affinity-regulating kinases (Hanger et al., 2009).

Hyperphosphorylation of tau induces pathology via four different mechanisms. Firstly, hyperphosphorylation of tau can induce incorrect sorting of tau from axons to the somatodendritic compartment, which causes dysfunction of the synapses. Secondly, tau hyperphosphorylation might cause avoidance of tau degradation by proteasomes, since the phosphorylated serine's at positions 262 and 356 cannot be recognized anymore by the C terminus of HSP70-interacting protein-heat shock protein 90 complex which is needed for proteasomal degradation (Dickey et al., 2007). Thirdly, since in Alzheimer's disease it has been found that both hyperphosphorylation and aggregation are elevated, it is considered that phosphorylation of tau enhances tau aggregation (Grundke-Iqbal et al., 1986). Lastly, interaction of tau with its interaction partners may be changed by phosphorylation of tau. Hyperphosphorylated tau is, for example, unable to interact with kinesin-associated protein JUN N-terminal kinase-interacting protein 1, whereas the unphosphorylated tau is able to interact with this interaction partner and thereby forms a kinesin complex which mediates axonal transport (Kanaan et al., 2011).

MAPT gene mutations

More than 20 years ago, mutations in the MAPT gene were identified that correlated with frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). This proved that tau dysfunction on its own was already enough for causing neurodegeneration in the central nervous system (Strang et al., 2019; Spillantini et al., 1998; Poorkaj et al., 1998). It has been stated that the MAPT gene mutations can cause multiple deficiencies regarding cognition, behaviour and motor function (Reed et al., 2001).

In many tauopathies, the ratio of 3R to 4R tau is altered. Whereas in the brains of healthy individuals the ratio of 3R to 4R tau is approximately one, in various tauopathies such as Pick's disease it is not. It is unclear in which extent the MAPT gene mutations correlate with other tauopathies such as Alzheimer's disease and Pick's disease, but it is clear that MAPT gene mutations are the cause of altered tau physiology. MAPT gene mutations have different effects on tau physiology. Firstly, a

mutation of MAPT causes disruption of the paperclip-structure of tau, which leads to more aggregation and inclusion formation. Secondly, tau mutations within the microtubule-binding repeats can disrupt the interaction between tau and tubulin. This results in the destabilization of microtubules and also an increase in unbound, free tau, which may also enhance tau aggregation. Thirdly, there is a mutation that causes more phosphorylation of tau, compared to the wildtype tau protein. As described earlier, tau hyperphosphorylation causes destabilization of the neurons in the brain. A fourth effect of mutations on tau physiology is that some specific MAPT gene mutations can cause tauopathies with either 3R or 4R tau predominantly expressed, or tauopathies with both isoforms equally expressed. Usually, some certain mutation causes inclusion of exon 10, which causes higher expression of 4R tau. Overproduction of one of the isoforms most likely leads to an excessive quantity of unbound and free tau, which is very prone to aggregate (Ghetti et al., 2015; Strang et al., 2019; Lu et al., 2001).

Prion-like properties of tau

Prions are proteins that can transmit their misfolded shape from the outside to the inside of a cell (Frost et al., 2009). Since tauopathies begin in disease-specific regions but later spread to more brain areas, it has been hypothesized by Frost et al. (2009) that, like prions, extracellular tau aggregates can transmit their misfolded state towards the inside of the cell. Along with that, Seeley et al. (2009) suggested that there is a pathogenic agent that spreads along different neuronal networks. Later, the laboratory of Holmes et al. (2014) also hypothesized that these pathogenic agents are tau aggregates or -seeds.

When tau seeds are added to the outside of cells, they bind to the surface by making contact with heparan sulphate proteoglycans. Then, the tau aggregates are taken up by the cell via macropinocytosis (Holmes et al., 2013). When the tau aggregates are taken up by the cell, it induces fibrillization of full-length tau which is already present in the cell. This fibrillated full-length tau then converts into a misfolded state (Frost et al., 2009).

If these prion-like mechanisms of tau are actually the cause of tauopathies, they should exist in the brains of tauopathy mouse models and brains of human individuals who suffer from tauopathies. This hypothesis has been tested by Holmes et al. (2014). They found that tau seeding activity was detected more than four weeks earlier than the current best histological marker for tau aggregation. The fact that there is an early appearance and development of this tau seeding activity, proves that tau seeds are an underlying mechanism for the progression of tauopathies and that tau seeding activity at least is a very early marker of tauopathies (Holmes et al., 2014).

Therapeutic strategies

Inhibition of kinases

As described above, kinases are able to phosphorylate tau. In contrast, phosphatases dephosphorylate tau. By phosphorylation of tau by the kinases, the normal cellular distribution of tau in adult and developing neurons is affected. This reduces the affinity of tau for microtubules which then results in destabilization of neurons (Hanger et al., 2007). Therefore, inhibition of kinases or activation of phosphatases might be a good therapeutic target to inhibit neurofibrillary degeneration (Iqbal et al., 2004). Noble et al. (2005) described how they inhibited glycogen synthase kinase-3 with lithium chloride. They showed that treatment with lithium chloride caused significant inhibition of glycogen synthase kinase-3 activity. This resulted in less phosphorylation of tau. Thereby, mice that were treated with lithium chloride showed less neuronal degeneration. From all this, Noble et al. (2005) concluded that kinase inhibitors may be an effective therapy against tau pathology.

Microtubule-stabilizing drugs

Michaelis et al. (2005) have previously reported that paclitaxel is a microtubule-stabilizing agent. They state that paclitaxel blocks hyperphosphorylation of tau by beta-amyloid. The paclitaxel cell-cultures survived longer than the cultures not treated with paclitaxel. Thereby, they found that other taxanes also increased the survival of the paclitaxel-treated cell-cultures (Michaelis et al., 2005). Zhang et al. (2005) also proposed paclitaxel as a microtubule-stabilizing drug. They concluded that injections of paclitaxel weekly restored axonal transport and increased microtubule and stable tubulin numbers.

Interference with tau aggregation

Pickhardt et al. (2004) wanted to test whether they could protect neurons by inhibiting tau aggregation or reversing it. They screened 200.000 compounds in search for a tau aggregation inhibitor. In the end, they found 1266 compounds that were positive for tau aggregation inhibition, and 77 of them were able to dissolve existing aggregates. It is very important to note that these inhibitors did not affect the normal function of tau like stabilization of microtubules (Pickhardt et al., 2004).

Tau immunotherapy

Earlier, it had been described that the tau protein spreads to the brain in a prion-like manner. This involves tau to be present extracellularly. Extracellular tau is therefore strongly involved in spreading of tauopathies and is an attractive therapeutic target (Albert et al., 2019).

Asuni et al. (2007) are concerned that the therapeutic approaches described above are lacking in target specificity and thereby form a risk for toxicity. They stress that it is therefore important to also develop other potential therapies, such as immunotherapy. Previously, tau immunotherapy has been described as a beneficial therapy for tauopathies by numerous reports (Asuni et al., 2007; Boutajangout et al., 2011; Castillo-Carranza et al., 2015).

In the study published by Asuni et al. (2007), the goal of the tau immunotherapy was to target pathological tau protein conformers, that exist extracellularly. They found that the tau antibodies that were formed in the brains of the P301L tangle mouse model recognized pathological tau proteins. In the end they concluded that active immunization reduced tau aggregation.

In another study, Boutajangout et al. (2011) also used the P301L mouse model. In this case, they wanted to test passive immunization with tau antibodies. They concluded that also passive immunization with tau antibodies leads to a decrease in tau pathology.

Discussion

In this thesis, I wanted to find an answer to a few questions regarding tau pathology. At first, it was important to gain more information on what tauopathies exactly are and how these neurodegenerative diseases develop. Hereby I wanted to answer question (1) stated in the introduction. Therefore, more information was needed on what the tau protein actually is, what it looks like and what its function is under normal and pathological conditions.
The tau protein is encoded by the MAPT gene, which forms six different tau isoforms by alternative splicing of exons 2, 3 and 10. In the adult human brain, all six tau protein isoforms are expressed. The isoforms differ in the number of microtubule-binding repeats and the number of N-terminal inserts. In normal conditions, the tau protein is mainly important for the stabilization of microtubules. The tau protein promotes microtubule assembly and axonal transport and cell signalling. Thereby it seems to be playing an important role in axonal elongation and maturation.
Several posttranslational modifications of tau alter the functionality of the protein. The most important and most common posttranslational modification is phosphorylation. Phosphorylation of the tau protein is regulated by phosphatases and kinases. It is very important that there is a balance between these two, because a disbalance causes the tau phosphorylation to transform from a physiological into a pathological condition.
It is already known that there is a difference in the underlying tau protein mechanism in different tauopathies, because it has already been found that the tau protein fold in Alzheimer's disease and Pick's disease are not the same. Whereas in Alzheimer's disease they found two tau filaments called straight filaments and paired helical filaments, in Pick's disease they found the narrow Pick filaments and straight Pick filaments. It is not yet clear what exactly is the consequence of these different folds, but the different folds might affect the way the disease develops and spreads in the brain. This might then explain the differences between both tauopathies. To find out how the folding mechanism works in different diseases and whether it actually is a cause of different characteristics in different tauopathies, more research has to be done regarding the tau protein fold in all tauopathies.

Then, I wanted to find an answer to question (2. This included investigating how tauopathies develop and whether this development differs between different tauopathies.
The main mechanism which causes tauopathies, is the aggregation of tau. Intrinsically, the tau protein does not have a strong tendency to aggregate, but this is altered by a posttranslational mechanism called truncation. Truncation prevents formation of a paperclip-tau structure and thereby promotes aggregation. It is yet unclear whether this mechanism is the same in all tauopathies. For now, it is known that this is at least roughly the mechanism of tau aggregation in tauopathy. However, since different tau protein folds can be found in different tauopathies, it is possible that this has an impact on how tau aggregates. This may contribute to the different characteristics of tauopathies.
As said, the balance of kinase and phosphatase is very important when it comes to tau hyperphosphorylation. Tau hyperphosphorylation by kinases results in destabilization of neurons. Different mechanisms of tau hyperphosphorylation were described, and all these mechanisms lead to pathology via either tau aggregation, dysfunction of synapses, avoidance of tau degradation or altered axonal transport. Since the tau protein isoforms, structures and folds differ in different tauopathies, as has been demonstrated in both Alzheimer's disease and Pick's disease, phosphorylation might be different in different tauopathies. Most of these hyperphosphorylation studies have been practiced in Alzheimer's disease, so investigating this in other tauopathies will give more insight in how hyperphosphorylation occurs in other diseases.
It is known that MAPT gene mutations are correlated with frontotemporal dementia with parkinsonism linked to chromosome 17. This was prove that tau dysfunction on its own was enough for causing neurodegeneration. It is unclear in which extent the MAPT gene mutations correlate with other tauopathies, but it is clear that MAPT gene mutations are the cause of altered tau physiology. There are different mutations that cause different changes in tau physiology: disruption of the paperclip-structure of tau, disruption of the interaction between tau and tubulin, higher rate of tau phosphorylation and dominant expression of either 3R tau or 4R tau. In Alzheimer's disease, both of

these isoforms are present and in Pick's disease only 3R tau is present. This may indicate that there are different mechanisms underlying the genetic tau pathology of Alzheimer's disease and Pick's disease.
Lastly, the prion-like properties of tau were discussed. Extracellular tau aggregates have the ability to transmit their misfolded state into the inside of a cell. The general mechanism of prion-like spreading of tau is clear, but I wanted to find an answer to the question whether there is a difference in spreading between different tauopathies which may cause the different characteristics of these diseases. Unfortunately, it is yet not clear why in some diseases, such as Alzheimer's disease, the tau aggregates affect the whole brain and in some diseases, such as Pick's disease, only certain areas of the brain are affected. It might be due to the different tau protein folds of these diseases, but this has not yet been studied.
Even though it is not yet clear what directly causes the different characteristics of different tauopathies, it is of importance to give an update on what the current therapeutic strategies are. That will give an answer to question (3): "Can this information lead to new therapeutic strategies?"
Currently, there are no treatments for neurodegenerative diseases, including tauopathies. However, there are some potential therapeutic strategies that not only give hope for treatment, but may also give more insight in these neurodegenerative diseases. As for tauopathies, there are several targets under investigation, the first one being inhibition of kinases. Tau is phosphorylated by kinases, and this affects the normal cellular distribution of tau in adult and developing neurons. As stated, inhibition of these kinases might solve this problem. Several kinase inhibitors have been under investigation, with success. Hopefully in the future, this may lead to a new therapeutic against tauopathy development.
The second therapeutic target are the microtubules, and to be precise the stabilization of these microtubules. This therapy is investigated mostly in Alzheimer's disease, since it blocks hyperphosphorylation of tau by beta-amyloid, but it may also have effect on general hyperphosphorylation of tau. However, the current studies addressing microtubule-stabilizing drugs do not discuss this.
Another therapeutic target is tau aggregation. The objective was to inhibit tau aggregation without disturbing the normal function of tau. In the studies discussed, they did find compounds that inhibit tau aggregation without affecting the normal function of tau. If this therapeutic strategy is successful, it can possibly be used in any tauopathy, since tau aggregation is a general pathological mechanism in all these diseases.
The most recent therapeutic strategy is developed to be more target specific. Numerous studies discussed tau immunotherapy, using either active or passive immunization. With tau immunization, tau antibodies are used to target pathological tau protein conformers. In these studies different tau protein conformers in different tauopathies were not yet discussed. Since more recently there have been more studies concerning tau protein conformers in different tauopathies, I can imagine that tau immunization can become very specific to target tau conformers unique for one certain tauopathy.

With all this taken together, some of the questions stated in the beginning can be answered. These answers however, are not all satisfying. Currently, there is not enough information available regarding the different tau mechanisms in different tauopathies. Taking that in consideration, it is fair to say that up until recently, all tauopathies were considered roughly the same. Although, this view is changing since there are some recent studies that address differences in, for example, the tau protein fold in Alzheimer's disease and Pick's disease. This is most likely the beginning of more research in this field, and in the future more tauopathies can and should be included in these studies. Hopefully this will lead to more insight in how different tauopathies, and maybe even other neurodegenerative diseases, develop and why this leads to the different characteristics of these diseases. And when these disease-specific characteristics and the development of these characteristics are clear, new, more specific and thereby better therapeutic strategies can be developed.

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