Neuroinflammation and autism spectrum disorder: a review

How these two phenomena correlate according to physiology and external factors

Author: Silke Scheper
Supervisor: Robbert Havekes
Institute: Rijksuniversiteit Groningen
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university of groningen

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Abstract

Autism spectrum disorder (ASD) is a psychological disorder that affects 1-2 per 100 individuals. There is evidence that ASD patients display neuroinflammation. In this review, the link between ASD and neuroinflammation is highlighted. Several environmental factors are assessed, such as maternal inflammation, the amount in TNF-α in the ASD brain and functionality of the blood-brain barrier. We conclude that the maternal inflammation and autoimmune disease increase the risk of ASD, TNF-α is elevated in patients with ASD and the blood-brain barrier is dysfunctional. This implicates treatment of neuroinflammation in ASD patients rather than the original drug treatment. However, more research is needed to fully examine the neuroinflammation process in ASD patients.

Introduction

Autism spectrum disorder

Autism spectrum disorders (ASD) is the collective name of the psychological diseases characterized by reduced social behaviour, repetitive actions and limited and stereotypical interests (American Psychiatric Association, 1994). The prevalence of ASD is estimated to be around the 1-2 children per 100 individuals (Baron-Cohen et al., 2009). Determination of the disorders are limited to behavioural observations (Ozonoff et al, 2005).
Although ASD is mainly described as an heritable disorder, the interplay between genes and environment establishes a certain phenotype. A twin study from 2011 showed that the environmental portion with respect to the development of ASD is much higher than the genetic part, in contrast to what previously was reckoned (Hallmayer et al, 2011). Another study showed that risk genes only account for 10-20% in the development of ASD (Abrahams and Geschwind, 2008). Because of great impact of external compounds, focus has shifted towards the environmental influence on the development of ASD rather than the genetic impact.
Behavioural tests could be disadvantageous, because the observer is always subjective and can be biased in the determination of the diagnosis. Examination of a potential objective biomarker in individuals with ASD can be beneficial, since it seems more reliable and children can be diagnosed at a young age. This can make treatment more efficient and is proven to be more effective later in life (Sanchack et al, 2016). New treatment methods could thus be advantageous in the treatment of ASD.

Neuroinflammation

Different psychological disorders, like autism spectrum disorders all have a thing in common; inflammation of the brain, or so-called neuroinflammation (Kealy et al., 2018).
It is defined as inflammation in the central nervous system, following from injury and/or neurodegenerative diseases. Neuroinflammation can be seen in activated microglia, elevated levels of certain cytokines and chemokines and altered signaling pathways (Shastri et al., 2013). Next to neuroinflammation, patients with ASD also display overall peripheral inflammation (Zimmerman et al. 2005). Thus, neuroinflammation plays a role in patients with ASD. However, there is yet no agreement on how this neuroinflammation is established. Different physiological

and morphological structures can increase the degree of neuroinflammation, which are going to be examined in this review.
The link between peripheral and central inflammation, is the blood-brain barrier (BBB). Gaps can fall in this barrier, causing it to leak substances that cause harm into the brain, such as pro-inflammatory cytokines (Kealy et al., 2018). Since more unwanted substances can cross a dysfunctional BBB, this can accelerate the process of inflammation in the central nervous system. This leads to the question whether the BBB of ASD patients is dysfunctional and to what extent this dysfunctionality correlates with the prevalence of ASD.
There are also indications that maternal inflammation during the perinatal stage increases the chance of developing ASD in the child by 10 times. This result indicates that certain cytokines and chemokines can cross the placenta en alter the immune response in the embryonic brain. (Depino, 2012). It is not sure whether this is an autoimmune reaction, or a systemic inflammation (Li et al., 2009). It should be examined to what extend maternal inflammation and autoimmune disease influence the prevalence of ASD, because it is certain that maternal inflammation during the perinatal stage alters the brain.

Taking these research outcomes together leads to the question whether there is a link between neuroinflammation and the development of autism spectrum disorder. If so, how can this link be mapped using different approaches regarding neuroinflammation? In this review, the focus will be lying on a couple of different aspects and possibly causal factors of neuroinflammation in the brain of patients with ASD. In the conclusion the most important results will be highlighted, to create a clear overview regarding neuroinflammation in autism spectrum disorders.

What is the influence of maternal inflammation on the development of ASD?
Perinatal inflammation in the mother increases the risk of developing ASD in the child. A paper from 1995 even claimed that maternal viral infection is the most influential non-genetic risk factor in the development of autism in the child (Ciaranello and Ciaranello, 1995).

<u>Autoimmune deficits in the mother during the perinatal stage and ASD</u>
Pregnant women who display autoimmune diseases, have greater risk in giving birth to a child with ASD (Comi et al., 1999; Brimberg et al., 2013). This could be due to IgG anti-brain antibodies, affecting the development of the fetal brain. Perinatal IgG antibodies can cross the placenta during the perinatal stage of development (Saunders et al., 2012). Some mothers of patients with ASD display elevated levels of these IgG antibodies during pregnancy (Braunschweig et al., 2007). The maternal autoimmune disease effects on ASD are in line with work by Li et al, where the cytokine layout was examined in the cerebrospinal fluid (CSF) of patients with ASD, compared to control.
The CSF contained more cytokines specifically secreted by Th1 cells. The Th2 cytokines were unaffected, compared to the control subjects. In Figure 1, one can see that the ratio IFNγ/IL-10 is elevated in ASD patients. IFNγ is a cytokine secreted by Th1 cells, and the cytokine IL-10 is secreted by Th2 cells (Li et al., 2009). From this, the Th1/Th2 ratio is elevated in patients with ASD, a phenomenon that in the past has been seen in a couple of autoimmune diseases (Liblau et al., 1995). Therefore, it is not excluded that the expression of ASD can be affected by an autoimmune deficiency in the mother. Whether this is a causal effect of maternal autoimmune

deficiency, remains to be examined. Not every child with ASD has a mother with an autoimmune deficiency or infection during pregnancy, which makes it difficult to draw conclusions about the effect of autoimmune disorder on the development of ASD. Taking the maternal inflammation and the autoimmune response on the fetus together, it is certain that maternal inflammation is responsible for a higher prevalence of ASD.

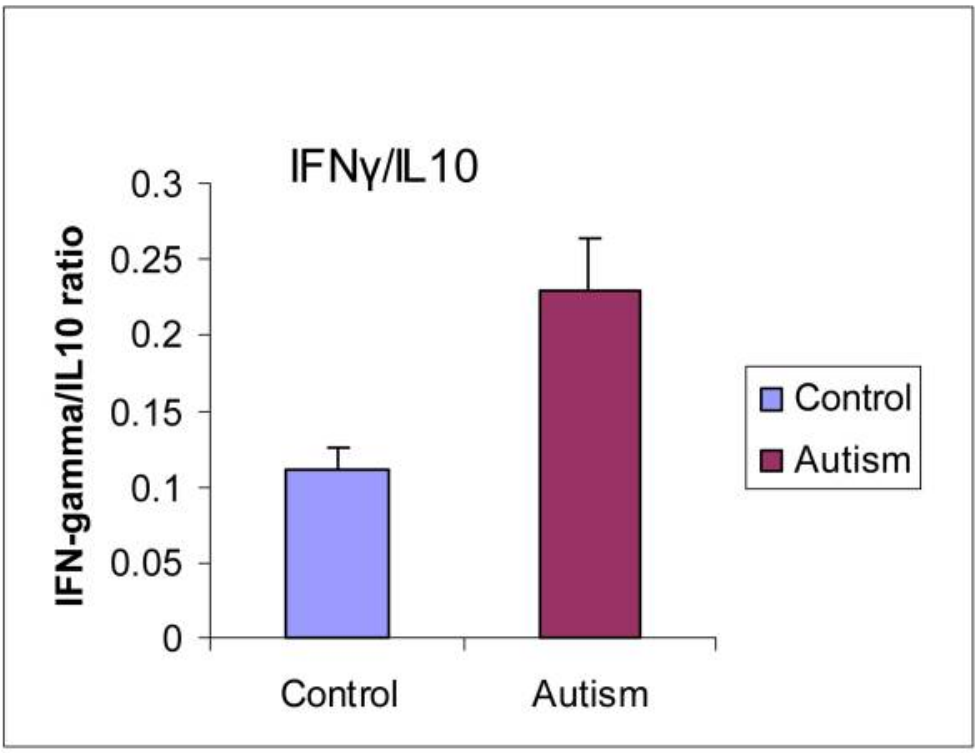

Figure 1: an elevated Th1/Th2 cytokine ratio in patients with autism, a phenomenon that also occurs in patients with autoimmune deficits.

Anti-brain IgG's in the mother during the perinatal stage and ASD

The question only remains whether inflammation follows the same IgG pathway as the autoimmune deficit. If this is the case, one can say quite confidently that IgG antibodies have a causal effect on the chance of developing ASD in the child, when these are administered in the perinatal period. In fact, a study using rhesus monkeys in which they administered purified anti-brain IgG from mothers which gave birth to 1 or more children with ASD, showed that the offspring of the rhesus monkeys with administration of this particular IgG's displayed stereotypical ASD behavior. Administration of IgG's from mothers without an ASD child showed no stereotypical behavior and more hyperactivity in the offspring (Martin et al., 2008). So, one can conclude that the IgG anti-brain antibodies are different between mothers with and without children that display ASD. Research in the rhesus monkeys showed that there's a causal relationship between IgG antibodies and the development of repetitive behavior and hyperactivity, stereotypical behavior for children with the diagnosis of ASD. A point of discussion is that not every mother injected with the IgG antibodies, gave birth to offspring with the behavior associated with ASD (Martin et al., 2008).

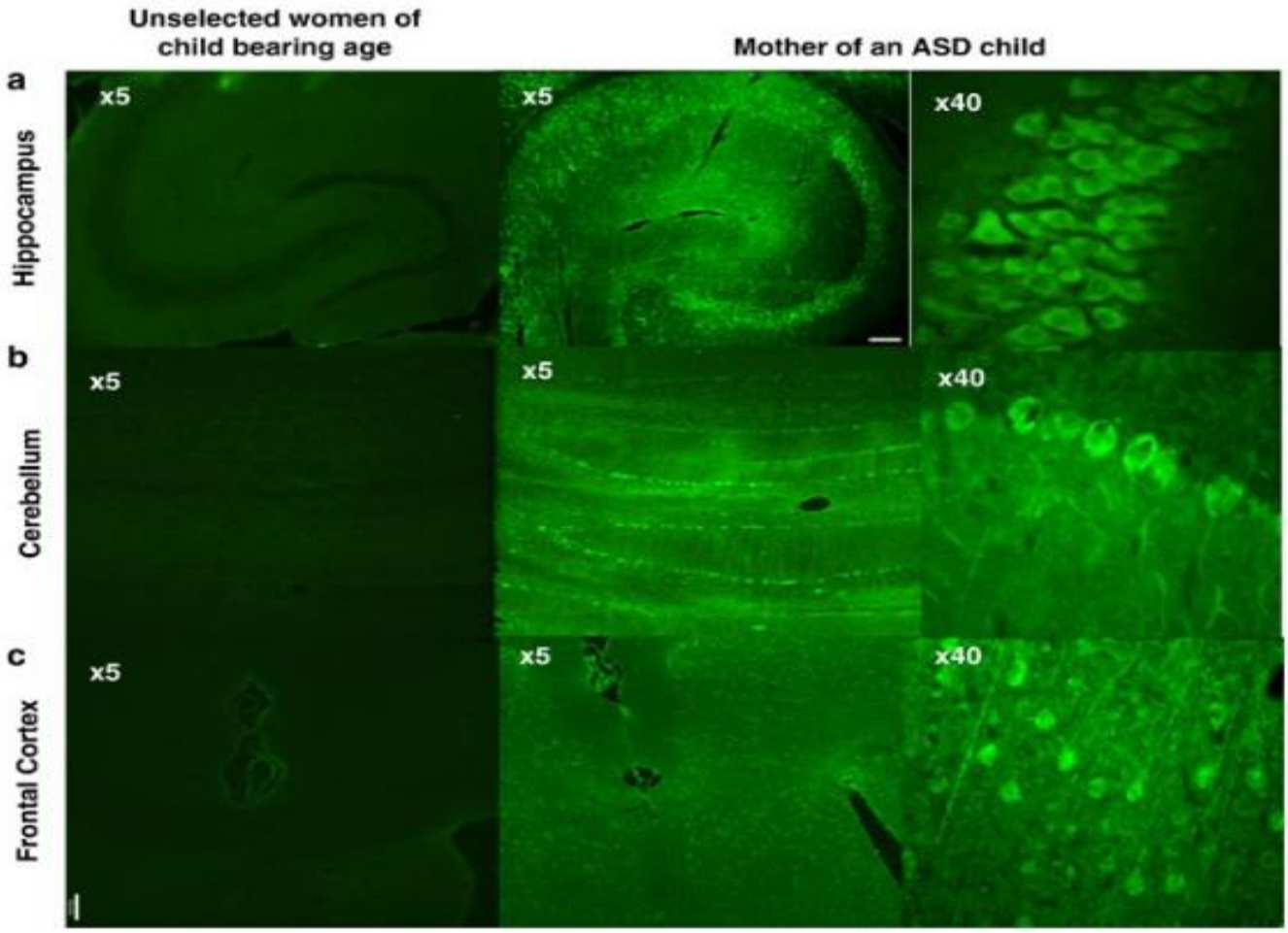

Figure 2: Anti-brain IgG staining in different regions of a mouse brain. Plasma of mothers with an ASD child was labeled and injected. Immunohistology was used to examine the difference in IgG activity between mothers with an ASD child and mothers with a normal developing child.

In a different set of studies, plasma of mothers that gave birth to a child with ASD was injected into the brain of an adult mouse, and with immunohistology the IgG binding was compared to control mothers. Mothers of an ASD child had significantly more anti-brain IgG than the mothers with a typical developing child. This is visible in Figure 2, where serum anti-brain IgG's were labeled with Green Fluorescent Protein (GFP). The amount of GFP labeled IgG was measured between serum coming from mothers with ASD children, comparing to serum from mothers that had typical developing children. Quantification of anti-brain IgG's was examined in three different brain areas.

This shows that serum of mothers with an ASD child contains more anti-brain IgG than mothers that gave birth to typical developing children. Also, autoimmune diseases are more common in mothers of ASD children (Brimberg et al., 2013).
Increased levels of IgG due to autoimmunity or an infection does not lead to alterations in the brain of the mother. IgG antibodies cannot cross the blood-brain barrier when it's fully

developed. The reason that it can cause modifications in the fetal brain, is that the BBB is not completely developed, leading to a less protective function (Braunschweiger er al., 2012). These results taken together, it is clear that maternal inflammation increases the risk of developing ASD. Autoimmune antibodies like IgG seem to cross the BBB of the fetus and alter the development of the brain, leading to an increased risk on ASD.

The role of the TNF-α pathway in the autistic brain

Several studies show that cytokines with different origins and function are elevated in the autistic brain (Li et al., 2009, Yang et al., 2015). However, it remains unclear which cytokine is the most reliable predictor for the development of ASD. Xie et al. show in a study in 2017 that Tumor Necrosis Factor Alpha (TNF-α) is the only cytokine that holds a positive correlation with the severity of ASD. The severity of ASD is assessed using the Autism Behavior Checklist, see figure 3. That is why we in this paper asses the role of the TNF-α pathway.

TNF-α, along with other proinflammatory cytokines, is crucial for the activation of the immune response (Hashimoto et al., 1991). A study from 2009 showed that TNF-α concentrations, along with other pro-inflammatory cytokines, were elevated in the brains and periphery of autistic patients (Li et al., 2009).

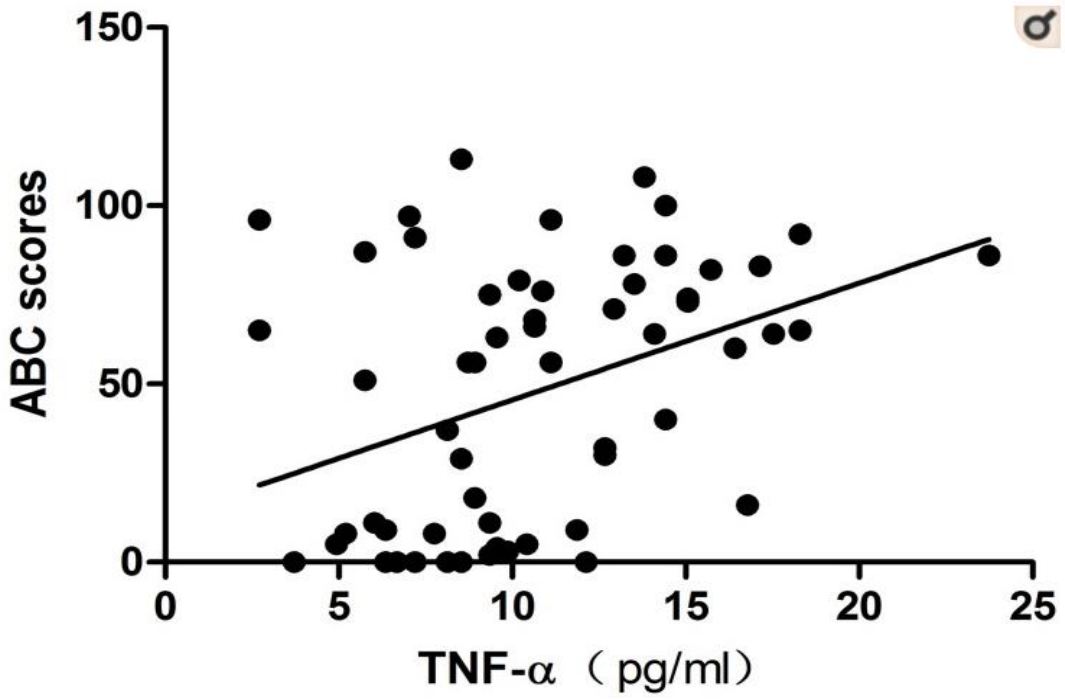

Figure 3: a significant correlation between the Autism Behavior Checklist (ABC) and the amount of TNF-α in the serum of autistic patients.

TNF-α, NFκb and ASD

TNF-α is a proinflammatory cytokine, produced by activated macrophages, monocytes and T-helper cells (Awad et al., 2015). It binds the TNF receptor in the periphery and in regions in the brain. It alters the activation of NFκb, which is called 'the master switch' in regulating gene expression (Banks et al., 2014). However, this is one pathway known to be activated by TNF-α. For a good review, I will only discuss this pathway regarding autism. A study by Naik et al. performed in 2011 shows that the amount of folds in NFκb was much higher in children with ASD, compared to controls. More folds in NFκb predicts more DNA binding, since the DNA binding site is exposed to the external environment and tends to bind the DNA. Also, they assessed the fold intensities of 3 children who has recovered from autism. These children had the least fold intensity of all groups, which can indicate that ASD is recoverable. Recovery from ASD might have something to do with the fold intensity of NFκb, which is altered by TNF-α.
An explanation for elevated levels of TNF-α could be maternal infection. TNF-α is mostly secreted by macrophages, which are activated by infection. TNF-α can cross the placenta during pregnancy, indicating that this could trigger alterations in the brain during development (Xie et al., 2017). The development of ASD in children can be caused by this phenomenon. However, not every woman with a child that expresses ASD had an infection during pregnancy or suffered from autoimmune disease.

Systemic inflammation and ASD

It could be that children with ASD have systemic inflammation, and therefore elevated levels of TNF-α secreted by macrophages. This TNF-α crosses the blood-brain barrier to possibly alter the connectivity of neurons and brain regions (Gutierrez et al., 1993). This is in line with a study from 2018, where Eftekharian et al. show a significant correlation between TNF-α and other cytokines, such as IL-6, IL-17 and IFNɣ. These cytokines are known to be proinflammatory cytokines, and can cause systemic inflammation. It is remarkable that this correlation only applies to males, not to females. The cause of these non-consistent finding is that regulation of cytokines is reported to differ between sexes (Klein et al., 2012). Elevated mRNA expression of proinflammatory cytokines is known to cause systemic inflammation in the periphery, and systemic inflammation can be the cause of neuroinflammation. Also, higher expression of TNF-α can alter the permeability of the blood-brain barrier and can therefore modify development of neurons and connections in the brain since more pathogens and other substances that don't belong in the brain can enter more easily (Banks et al., 2014).
TNF-α is overexpressed in autistic children, but only in the cerebrospinal fluid (CSF). The ratio CSF versus serum TNF-α was much higher in ASD children, which indicates that this elevation is a local reaction in the brain (Chez et al., 2007).
This local reaction can be due to a dysfunction blood-brain barrier, which will be discussed later in this review.

The results of the papers above are promising and offer a new perspective on the etiology of ASD. TNF-α can be seen as an important substance for the development of ASD, because it is the only known cytokine that is correlated with the severity of symptoms regarding ASD. Elevated levels of TNF-α in patients with ASD can cause activation of NFκb, which alters gene

expression. This can lead to systemic inflammation and upregulation of proinflammatory cytokines. These peripheral cytokines can also trigger the expression of cytokines in the brain and alter the permeability of the blood-brain barrier, causing neuroinflammation. There is evidence that the elevated TNF-α levels are a local reaction, in line with a dysfunctional blood-brain barrier. Whether elevated TNF-α concentrations are the cause or consequence of ASD, is yet unknown and should be examined more thoroughly in the future.

The role of the blood-brain barrier in the autistic brain

The blood-brain barrier (BBB) is a network of pericytes, astrocytes, macrophages from the capillaries, endothelial cells and a basal lamina (Bradbury, 1985). This complex network functions as the first line of defense regarding homeostasis of the brain environment. It separates the peripheral blood circulation from the brain, essential for brain homeostasis (De Vries et al., 1997). In figure 4, a schematic representation is drawn and the differences between peripheral and central capillaries can be seen.

Because of the morphological differences between systemic and neural capillaries, deposition of substances are tightly regulated in the BBB. Problems may occur when the endothelial cells of the BBB are not tightly linked. Several substances can alter the permeability of the BBB, such as cytokines, free radicals, adhesion molecules and eicosanoids (De Vries et al., 1997).

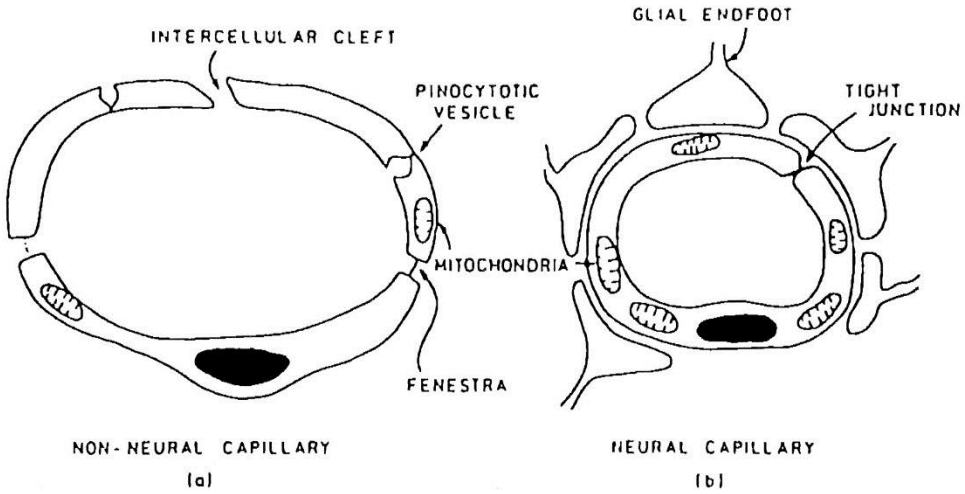

Figure 4: A schematic representation of the differences between systemic capillaries and capillaries surrounding the brain. Tight junctions are present between the endothelial cells in the BBB, while in the peripheral capillaries these are absent.

Permissive BBB's are correlated with numerous neurological diseases, such as multiple sclerosis Alzheimer's disease and epilepsy (Moor et al., 1996; Bell et al., 2009; Weissberg et al., 2011). However, little is known about the BBB integrity regarding protection from the systemic blood flow and ASD.

Tight junction functionality and ASD

In 2016, a study performed by Fiorentina et al., showed that there are differences between healthy subjects and patients with ASD regarding the BBB. ASD patients have higher expression of pore-forming tight junction (TJ) proteins (claudin-12), which make the endothelial cells more permeable. The ASD subjects also display lower levels of at least one barrier forming TJ protein. This can indicate that the BBB in ASD is more permeable compared to control. They also found a correlation between a dysfunctional BBB and leakage in the intestinal epithelial barrier. In ASD patients, intestinal problems are common and well documented (Luna et al., 2016; Luna et al., 2017). One can conclude that the same processes apply to both the BBB and intestine epithelial dysfunction, although this should be researched more thoroughly.
Matrix metalloprotease (MMP)-9 is also upregulated in the cortex of ASD compared to control. This protein is correlated with an impaired BBB and involved in several neuroinflammatory diseases, such as autoimmune encephalomyelitis, eosinophilic meningoencephalitis and multiple sclerosis (Kandagaddala et al., 2012; Chiu et al., 2014; Yong et al, 2007). Also, translocator protein 18 kDa (TSPO) is overexpressed in the ASD brain. Surplus of TSPO is associated with neuroinflammation (Chen et al., 2008; Karlstetter et al., 2014). These results clearly indicate a flaw in the BBB of patients with ASD, since these barriers contain more space between the endothelial cells resulting in greater permeability caused by dysfunctional tight junctions.

Amino acid transport, endothelial autoantibodies and ASD

A study from 2016 showed that not the permeability, but impaired transport of branched-chain amino acid (BCAA's) is the cause of developing autism (Tărlungeanu et al., 2016). Deletion of the Large Neutral Amino Acid Transporter 1 (LAT1) gene *SLC7A5* resulted in display of behaviour typical for ASD. However, direct administration of the BCAA's normalized behaviour. The SLC7A5 gene is absent in a certain ASD cases, but it is not yet examined whether BCAA administration in
ASD patients normalize their stereotypical behaviour. Overall, these results indicate that impaired BCAA transport is the cause of ASD, which can be normalized in experimental animals. In table 1 is the expression of genes displayed that are known to be altered in patients with ASD.

Gene	**Up- or downregulated in ASD**	**Association with this altered gene expression**
MMP-9	↑	Impaired BBB, neuroinflammatory diseases
TSPO, only on protein level	↑	Neuroinflammation
SLC7A5	↓	Stereotypical ASD behavior due to impaired BCAA transport

Table 1: an overview of altered gene expression in ASD patients and the correlation of these altered gene expression with several disease markers.

A subgroup of children with ASD have higher levels of autoantibodies against endothelial cells in their neurons compared to control children (27% vs. 2%). This indicates a disruption in the integrity of the BBB. Also, this implicates that a subset of ASD patients may have difficulties with homeostasis of their autoimmune reaction (Connolly et al., 1999). Subsequently, two studies found increased levels of S100β, one in serum (Al-Ayadhi et al., 2012) and one in plasma (Guloksuz et al., 2017). The latter found also a correlation with TNF-α, indicating a neuroinflammatory response in ASD patients. This mean that endothelial cells in the BBB of ASD patients can be altered by autoantibodies.

The blood-brain barrier and neuroinflammation

Because neuroinflammation and an impaired BBB is observed in patients diagnosed with ASD, we're now going to zoom in to the link between neuroinflammation and a dysfunctional BBB. Neuroinflammation is tightly correlated with a dysfunctional BBB, present in several neurological disease like Alzheimer's Disease (AD) (Takeda et al., 2014) and Schizophrenia (Pasternak et al., 2015). This shows that BBB dysfunctionality and neuroinflammation are paired in several neuropsychological disorders. However, this evidence is contradictory. There is no significant increase in the expression level of proinflammatory cytokines in patients with autism. Although there was no elevation of TSPO on the genetic level, they found increased levels of TSPO on protein level in the brains of ASD patients. In the same study, the integrity of the BBB was assessed, concluding that neuroinflammation and a dysfunctional BBB are both present in the autistic brain lamina of BBB, resulted in an more permeable layer of endothelial cells. This permeability was accompanied, and may be caused, by changes in the morphology of the actin filaments. (Fiorentino et al., 2016). In 1995, Deli et al. demonstrated that administration of TNF-a to the BBB, more specifically to the basal

Concluding, a dysfunctional BBB is present in ASD patients, due to destabilized tight junctions between the endothelial cells. Undesired molecules from the periphery can enter the brain more easily, resulting in impaired brain environment homeostasis. This non-integer BBB is possibly caused by neuroinflammation, which alters the gene expression of tight junction proteins. Disruption of the BBB by neuroinflammation can trigger a positive feedback loop, since more unwanted substances can enter the brain and therefore generate even more neuroinflammation.

Possible treatment alterations

Nowadays, autism spectrum disorder is treated mainly by targeting behavioral difficulties that patients face on a day to day basis. This is done through coaching and intensive training, usually starting at a young age to reach maximum effect. ASD itself is seldom the only problem patients experience, since ASD patients often have co-occurring illnesses, such as sleep problems and gastrointestinal problems (Lai et al., 2014). Treatment for these side effects is also necessary, since quality of life is heavily improved when those do not occur anymore. We however don't yet know whether the co-occurring diseases improve when ASD is treated with drugs, next to intensive cognitive training.

Current drug treatment of ASD

A couple of drugs are known to reduce the amount of repetitive behaviour in children with ASD, such a serotonin reuptake inhibitors (SSRIs) and antipsychotic drugs, although findings are not always consistent per research. The risk of creating adverse effects is always present, which make these drugs difficult to administer properly to the patients (McPheeters et al., 2011). These drugs only relate to the reduction of repetitive behaviour, not to the other stereotypical behaviour often displayed by patients with ASD. Also, a lot of the co-occurring diseases are not treated by these drugs, which makes additional medication necessary. A combination of different drugs is often dangerous and the separate effects could cancel each other out, making them non-efficient.

Possible new drug treatment of ASD

The new insights regarding inflammation in the autistic brain offer new opportunities regarding treatment and possibly even prevent the development of ASD in a fetus.

Tight junctions between the endothelial cells should be preserved under inflammatory conditions, to limit neuroinflammation and secure the integrity of the BBB. Netrin-1 is a protein that is associated with cell-cell adhesion and cell proliferation. When netrin-1 is administered, tight junctions in the endothelial layer when and inflammatory condition was present is normalized. Knockout *netrin-1* mice displayed disorganized tight junctions and a leaky BBB. Netrin-1 can thus be seen as an important regulator of the integrity of the BBB, which also protects the brain against neuroinflammation (Podjaski et al., 2015).

Because TNF-α is one of the most important cytokines to induce an inflammatory response and neuroinflammation is clearly present in patients ASD, one can take a look at TNF-α inhibitors to reduce neuroinflammation. A recent study showed that Ginsenoside Rb1 is a potent inhibitor of TNF-α, by inhibiting the NFκb pathway. Administration of Rb1 resulted in less apoptosis and normalization of injury on endothelial cells, which is perfect for the misbalanced endothelial cells in the blood-brain barrier, see figure 5 (Zhou et al., 2017). However, this study was done in patients with arteriosclerosis, not in patients with ASD. We need further research to examine whether Ginsenoside Rb1 is a suitable drug to treat neuroinflammation and repairing damage on the endothelial cells of the BBB. Rb1 could also be given orally to mothers who have an autoimmune disease, to examine whether this drug can reduce or even prevent the development of ASD. The only problem is that we don't know whether or not Rb1 can cross the BBB and penetrate the brain to attenuate the neuroinflammatory response. If this is not the case, only peripheral TNF-α is inhibited, but this also has advantages. Systemic inflammation in the periphery can cause neuroinflammation and a dysfunctional BBB, pathogens entering the brain are not necessary for the neuroinflammatory response. Suppression of the systemic inflammation can therefore reduce neuroinflammation, but they didn't examined this hypothesis thoroughly yet.

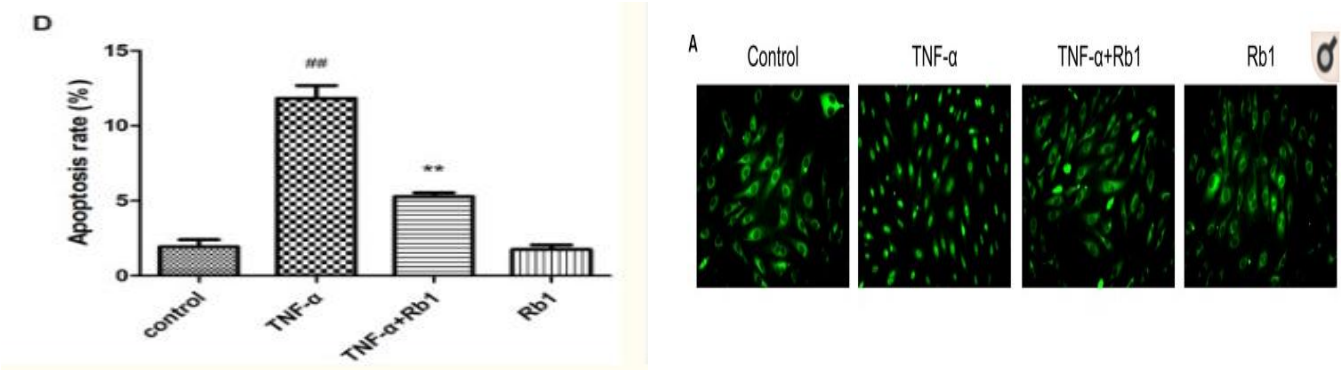

Figure 5: Ginsenoside Rb1 normalized the apoptosis rate of injured endothelial cells in patients with arteriosclerosis (Zhou et al., 2017).

To make sure that TNF-α is inhibited directly in the brain, a molecule that can penetrate the BBB is required. Biologic TNF-α inhibitors (TNFIs) are potent, but cannot cross the blood-brain barrier. A BBB-crossing TNFI was engineered, and administered to mice suffering of Alzheimer's disease (AD). It dramatically reduced the formation of amyloid-beta plaques, BBB dysfunctionality, neuroinflammation and novel memory was improved compared to mice with AD and without the BBB-crossing TFNI (Chang et al., 2017). This makes it very interesting to test on mice who display characteristics of patients with ASD, to look at the effects it has on behaviour, neuroinflammation and the integrity of the BBB. It also should reduce systemic inflammation, because it reduces the induction of an inflammatory response.
TNF-α inhibitors seem useful to treat neuroinflammation, but the question still remains whether this reduction in inflammation can alter behaviour displayed by the patient. If so, one can conclude that these stereotypical behaviours are a product of neuroinflammation, but this seems unlikely. A decrease in neuroinflammation could have positive effects on the co-occurring diseases that are frequently observed in patients with ASD.
However, since not a single drug that potentially treats ASD without behavioral intervention works, the stereotypical behavior cannot be normalized without cognitive therapy. Also, it is important to note when and how the drugs should be administered, because this early intervention is necessary to have the best effect.

Discussion

Maternal anti-brain IgG's can cross the blood-brain barrier of the fetus because it is not fully developed. Therefore, it is important to take a look at these IgG's in children with ASD when they have a dysfunctional BBB caused by inflammatory conditions. If administration of anti-brain IgG's to experimental animals without an ASD phenotype, but with a non-integer BBB lead to ASD behaviour, one can conclude that anti-brain IgG's combined with a damaged BBB can lead to autism. The brain-crossing TNFI discussed above also decreases the parenchymal IgG's, this is also a marker for disruption of the BBB. In schizophrenia, they found a very robust correlation between TNF-α and anti-gliadin IgG, indicating peripheral inflammation has a link with IgG's (Kelly et al., 2018). However, we yet don't know much about the link between TNF-α and

specific anti-brain IgG's. Further research is needed to link these two molecules together, to see how they influence each other and maybe find a causal relationship to chronologically map the processes of neuroinflammation in the autistic brain. This can help with the treatment of ASD, so one can make sure that the treatment is not only symptom management.
Finding a drug that can help the patient with neuroinflammation and the dysfunctional BBB is now the next step. We need more research about neuroinflammation inhibition and ASD. However, since not a single drug that potentially treats ASD without behavioral intervention works, the stereotypical behavior cannot be normalized without cognitive therapy. Also, it is important to note when and how the drugs should be administered, because this early intervention is necessary to have the best effect. Such a research can take years of practice, and often costs a lot of money.
This is also one of the reasons why it is useful to have an objective and reliable marker for the development of ASD later in life, but this is not an easy task. Neuroinflammation and disruption of the BBB is observed in several disorders, such as Alzheimer's disease, Schizophrenia and Multiple Sclerosis. Therefore it could be that an interplay between different molecules can actually predict whether a baby develops ASD. Determination of one or multiple markers of ASD makes the diagnosis easier, earlier, and faster, which is beneficial for the intervention, treatment, and the costs of ASD.

Conclusion

In conclusion, neuroinflammation is present in patients with ASD, potentially due to systemic inflammation in the periphery, maternal inflammation during the perinatal stage and a dysfunctional BBB. Whether neuroinflammation is a cause or consequence of ASD pathology remains a question for further research, in line with the chronology of altered processes in the autistic brain. Also, current treatment could be altered with anti-inflammatory drugs.

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