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Anti-inflammatory treatment for depression

Targeting pro-inflammatory cytokines

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Index

Summary

Depression is an enormous health problem worldwide, and is expected to be the second leading contributor to overall disease burden in 2020. Depression is a very complex and multifactorial disease, with many underlying causes. Current treatments consist of medication, including SSRIs, MAOIs, TCAs, anti-psychotics and lithium. However, these treatments do not have the desired effect in over half of the patients. This is why a new approach to depression is considered. Neuroinflammation is quite a new aspect of depression, and is expected to be one of the causes of depression. Depressed patients show all the hallmarks of neuroinflammation, including elevated cytokines and their receptors, elevated levels of acute phase proteins, chemokines, adhesion molecules and inflammatory mediators like prostaglandins.

Elevated levels of pro-inflammatory cytokines like IL-1β, IL-6 and TNF-α can lead to the development of depression by many pathways. They can activate the HPA-axis, stimulate serotonin reuptake and metabolism, induce glutamatergic excitotoxicity, downregulate BDNF and cause oxidative and nitrosative stress. The conventional antidepressants may inhibit inflammation, but their effects are limited and results seem inconsistent. This is why new therapies are directed at inhibiting pro-inflammatory cytokines. The new therapies inhibit cytokines with receptor antagonists, antibodies and anti-inflammatory cytokines. Until now, most of the research on these therapies is done in patients with other comorbid conditions, but in these patients they seem very effective in reducing the depression severity. To conclude, anti-inflammatory treatments have antidepressant effects, but before using them as new treatments for depression, a lot more research has to be done.

Introduction

Major depressive disorder is one of the most common mental disorders, affecting around 300 million people globally (World Health Organisation, 2018). Due to its high prevalence, high disability rate and heavy disease burden, it has become one of the biggest global health problems. Major depressive disorder (MDD) is expected to be the second leading contributor to overall disease burden by 2020 (Mathers et al, 2006). In a meta-analysis it was found that only 46% of all people receiving antidepressants responded to them (Khan et al, 2017). Even after two optimally delivered trials of antidepressant medications, more than 40% of patients with MDD did not achieve remission of their symptoms (Nierenberg et al, 2006). This would mean over half of the depressive patients worldwide, so over 150 million people, still do not have proper treatment. It is very important that a more efficient treatment is found. To find this, we should be looking at less traditional views of depression. For this reason, more research is conducted on neuroinflammation, a key player in the development of depression. One of the most important hallmarks of neuroinflammation is elevated levels of cytokines. In this thesis I will discuss depression and the effect of neuroinflammation, specifically pro-inflammatory cytokines. Lastly, I will try to find out that perhaps, a therapy targeting inflammation and pro-inflammatory cytokines could be more effective than conventional treatments of depression?

Depression

General

Major depressive disorder, unipolar depression or simply ‘depression’ affects approximately 1 in 6 people in the United States during their lifetime (Kessler et al, 2005), and over 300 million people worldwide (World Health Organisation, 2018). The prevalence is very dependent on how developed a country is; the lifetime prevalence in higher developed countries is 15%, while in the developing world it is 11%. Usually, the age of onset is between the ages 20 and 30. Females are affected about twice as much as males (Kessler et al, 2013).

Patients suffering from depression experience persistent feelings of sadness and hopelessness. Furthermore, they lose interest in activities they used to enjoy before the depression. Other symptoms include significant weight loss or weight gain without dieting, an increased or decreased appetite, a reduction of physical movement, lack of energy, feeling worthless and guilty, decreased ability to concentrate and indecisiveness. All these symptoms are described in DSM-V, a manual in which mental disorders are classified (American Psychiatric Association, 2013). However, depression is different for each individual and they all experience different combinations of symptoms. Probably the most serious symptom is recurrent thoughts of death. Suicide was the second leading cause of death among 15-29-year-olds globally in 2016 (World Health Organization, 2018). This implicates that depression is a very serious health problem, so treatment and prevention must be a high priority.

Causes

Although researching the mechanisms underlying depression, the exact cause is still unclear. It is believed that its cause is multifactorial, related to genetic, environmental and psychological factors. Risk factors include a family history of depression, major life changes, abuse, chronic illnesses, drugs and medication. Researchers worldwide have come up with different hypotheses that explain the possible mechanism that causes depression.

One of the most well-known theories is the monoamine hypothesis. This hypothesis proposes that the underlying basis of depression is a deficiency of the monoamine neurotransmitters in the brain, mainly noradrenalin, serotonin and dopamine (Coppen, 1967). Serotonin has various functions in the central nervous system, including mood, appetite and sleep. Dopamine is involved in reward-motivated behavior and motor control. Noradrenalin increases arousal and alertness in the brain. In response to the monoamine theory, it was suggested that the enzyme monoamine oxidase A (MAO-A) may be overly active in depressed people. This enzyme metabolizes monoamines, which could cause the deficiency.

Despite the fact that the monoamine hypothesis is one of the cornerstones of depression, we should definitely take other systems and factors into account. Impaired corticosteroid receptor signaling and deregulation of the HPA-axis are other key mechanisms, which will be discussed in more detail later. Other disturbed endocrine factors that can contribute to depression are altered levels of growth hormone (GH) and thyroid hormones (Brigitta, 2002).

Furthermore, depression could also result from the brain's inability to appropriately adapt to stress (Duman et al, 1999). This inability to adapt could be caused by a deficit in brain-derived neurotropic factor (BDNF). BDNF is important for cell growth and changes in the synapses; it is responsible for synaptic plasticity. Serum levels of BDNF in depressive patients are abnormally low (Sen et al, 2008). To conclude with, understanding the causes of depression is still a challenging scientific problem.

Current treatment

In response to the monoamine theory, selective serotonin reuptake inhibitors (SSRIs) were developed. SSRIs block the reuptake of serotonin in neurons, and as a consequence the serotonin concentration is elevated in the synaptic cleft (Stahl, 1998). Other medications that build on the monoamine hypothesis are tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The majority of TCAs block the serotonin and noradrenalin transporter, similar to SSRIs. In addition, TCAs can act as an NMDA antagonist and a sodium, potassium and calcium channel blocker. MAOIS act by inhibiting the enzyme monoamine oxidase. This enzyme normally breaks down monoamine neurotransmitters, so when inhibited, these neurotransmitters increase in availability (Stahl, 1998).

Additionally, there are some new anti-depressant medications that do not involve the monoamine theory (Mathew et al, 2008). Among the new drugs that are currently under investigation are drugs that target corticotrophin-releasing hormone, dopamine and glutamate systems (Mathew et al, 2008). Other than that, there has also been interest in drugs targeting other neurotransmitters such as gamma-aminobutyric acid, melatonin and substance P (Mathew et al, 2008).

However, the most common way of treating depression is a non-pharmacological way, for example psychotherapy. This could be a helpful approach to help patients with a history of childhood adversity or recent stress (Nemeroff et al, 2003). Another approach is electroconvulsive therapy. Physical exercise has also been proven to have positive effects in depressive patients, improving their mood, energy and sleep (Zagorski, 2019).

Sadly, none of these means of treatment show the desired results, because they simply do not work for many people. To find a more efficient therapy, we must look at other aspects of depression.

Neuroinflammation

This other aspect of depression was first reported in 1991, when it was suggested that inflammation may have a crucial role in the pathophysiology of depression (Smith, 1991). This is not very surprising, as some inflammatory diseases like coronary artery diseases and rheumatoid arthritis are frequently co-morbidities with depression (Zellweger et al, 2004; Margaretten et al, 2011). The other way around, depression has been associated with an impaired immune function (Licinio et al, 1997).

It was long thought that the brain did not have an immune system, so inflammation would not have an effect here. However, in 1983 the first region of the blood-brain barrier (BBB) through which cytokines can cross was identified, which meant that inflammation could also reach the brain (Blatteis et al, 1983). Later it became clear that cytokines can cross not only that specific region, but all of the BBB (Banks, 2005). Moreover, it has even been found that endothelial cells in the BBB secrete cytokines (Verma et al, 2006). This means the central nervous system is susceptible to inflammation, called neuroinflammation.

Neuroinflammation is an inflammatory response within the brain or spinal cord. Under physiological conditions, this response protects the nervous system from infections. However, when the inflammation is chronic, it may cause damage to the neurons. Chronic neuroinflammation can be caused by toxic metabolites, autoimmunity, ageing, infection or traumatic injury. An important hallmark of neuroinflammation is a higher BBB permeability. This makes it possible for immune cells like macrophages, T cells and B cells to infiltrate the brain, which contributes to the chronic neuroinflammation. Another sign of neuroinflammation are activated microglia. Microglia are the macrophages of the central nervous system. Normally, they maintain and support neurons, they can recognize pathogens and activate T cells. When they are chronically activated, they can cause a significant increase in pro-inflammatory cytokines and neurotoxic substances like reactive oxygen species and nitric oxide (Singhal et al, 2017). This can result in neurodegeneration, subsequently leading to diseases like Alzheimer's and depression. It has already been proven that patients with major depression disorder exhibit all of the features of neuroinflammation mentioned above, including elevated cytokines and their receptors, elevated levels of acute phase proteins, chemokines, adhesion molecules and inflammatory mediators like prostaglandins (Raison et al, 2006).

Cytokines

General

As mentioned before, neuroinflammation is associated with higher levels of cytokines, in both the circulation and the brain. Cytokines are multi-functional pleiotropic proteins. They are very important in cellular communication and activity. Even though they are quite large (15-25 kDa), they are still able to cross the BBB. Cytokines are a part of the innate immune system and they are produced by a broad range of different cells, including macrophages, monocytes, lymphocytes, mast cells and endothelial cells, in addition to microglia and astrocytes. In a situation where there is inflammation, cytokines are activated and their main goal is to repair damaged tissues and restore homeostasis (Woodroofe, 1995). Generally, cytokines are divided into two groups: pro-inflammatory and anti-inflammatory.

The most well-known and researched pro-inflammatory cytokines are interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and for that reason these three will be discussed in more detail later. Anti-inflammatory cytokines inhibit inflammatory responses, examples are interleukin-4 (IL-4) and interleukin-10 (IL-10). Under normal conditions, the concentration of cytokines in the blood is kept low (Pitossi et al, 1997). However, under chronic inflammation conditions, cytokine levels can increase 100-fold (Lee et al, 2002).

General pathways of cytokines in depression

To target neuroinflammation in depression, it is important to know how elevated levels of pro-inflammatory cytokines can contribute to the development of depression. Pro-inflammatory cytokines do this via several mechanisms, which will be explained in detail (Jeon et al, 2018). A summary can be found in Figure 1.

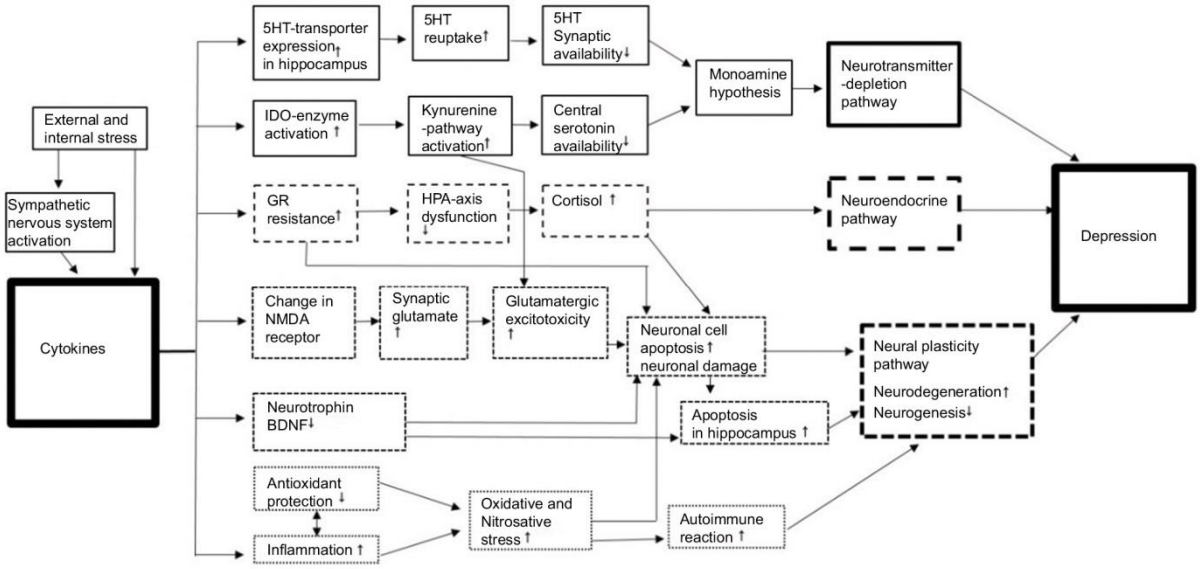

Figure 1: Summary of how cytokines contribute to the development of depression (Jeon et al, 2018).

The cytokine production is initially activated by stress and sympathetic nervous system activation.

First of all, elevated levels of pro-inflammatory cytokines increase the expression of the serotonin transporter in the hippocampus. This results in an increased amount of serotonin removed from the synapses, which makes serotonin less available. This depletion is, according to the monoamine hypothesis discussed before, the cause of depression (Jeon et al, 2018).

Secondly, cytokines increase the activity of indoleomine-2,3-dioxygenase (IDO). This enzyme metabolizes the serotonin precursor tryptophan into kynurenine and quinolinate. With the precursor being less available, serotonin will be produced less, and therefore will be less available. This again, will lead to depression according to the monoamine hypothesis (Raison et al, 2009).

Additionally, cytokines affect the HPA-axis. Normally, the hypothalamus makes corticotropin-releasing hormone (CRH), which causes the pituitary to make adrenocorticotropic hormone (ACTH). This activates the adrenal glands, which then make cortisol. The glucocorticoid receptor (GR) detects increased levels of cortisol, and inhibits the hypothalamus via a negative feedback loop. However, pro-inflammatory cytokines can cause blunted GR sensitivity, also called increased GR resistance. This will lead to hyperactivity of the HPA-axis and elevated levels of cortisol in the plasma, urine and cerebrospinal fluid (Pariante et al, 2008). Animal studies have suggested that high cortisol levels result in hippocampal neuron loss (Clark et al, 1995). Furthermore, elevated levels of cortisol reduce adult hippocampal neurogenesis in rodents (David et al, 2009). These results are confirmed in a study by Brummelte and Galea, showing that high levels of cortisol reduced neuronal cell proliferation in female rats and reduced cell survival in both male and female rats (Brummelte and Galeo, 2010). Less proliferation and more cell death leads to a loss of neural plasticity, which is a cause for depression (Liu et al, 2017).

Moreover, cytokines cause a change in the NMDA receptor, which results in increased levels of synaptic glutamate (Kim et al, 2016). Glutamate can overactivate the NMDA and AMPA receptors, causing neuronal cell death by excitotoxicity. Quinolinate, a serotonin metabolite which is also increased by cytokines as mentioned before, contributes to this excitotoxicity (Ting et al, 2009). This also causes a loss of neural plasticity.

Furthermore, pro-inflammatory cytokines decrease the level of brain-derived neurotropic factor (BDNF). BDNF supports the survival of existing neurons and is a growth factor for new neurons. It also encourages differentiation of neurons and synapses. A decrease in BDNF will cause neuronal cell death and less survival, also causing a loss of neural plasticity (Lotrich et al, 2012).

Lastly, cytokines obviously cause systemic inflammation, a chronic activation of the immune system. The immune system, mainly phagocytes, can produce both reactive oxygen species and reactive nitrogen species (Nathan and Shiloh, 2000). They are produced as a mechanism of killing pathogens. When the inflammation is chronic, like in depression, it causes higher levels of oxidative and nitrosative stress to the neurons and can cause autoimmune reactions, leading to loss of neural plasticity (Maes, 2008).

We will now be looking at how the three most investigated pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) are connected to and involved in depression.

IL-1β in depression

First of all, some evidence that IL-1β is connected to depression will be discussed. The first evidence of IL-1β involvement in depression goes back to 1991, when they found increased IL-1β production in depressed patients (Maes et al, 1991). Compared to healthy people, patients with MDD have significantly higher levels of IL-1β circulating in their blood. There is a linear correlation between the level of IL-1β and the severity of depression, measured by the Hamilton Depression Rating Scale (HAMD) (Zou et al, 2018). Moreover, it was found that the IL-1 receptor has a higher expression level in depressed patients (Howren et al, 2009). In elderly depressed patients, IL-1β concentrations were higher when the depression onset was earlier (Diniz et al, 2010). In women with post-partum depression, increased levels of IL-1β were found in the urine (Corwin et al, 2008). Higher serum levels of IL-1β are correlated with the number of depressive episode a patient has had (Maes et al, 2012). To summarize these results, depressed patients have elevated levels of IL-1β.

More proof can be found by administering IL-1β in animal models. Administration of IL-1β causes a significant reduction of neurogenesis in the hippocampus in humans (Borsini et al, 2017). This effect was also seen in rats. The decrease in neurogenesis was stopped by an IL-1 receptor antagonist. This antagonist also stopped depressive like behavior caused by unpredictable stress (Koo et al, 2008). When IL-1β is administered to mice, combined with IL-6, they show depressive-like behavior and a loss of body weight (Kurosawa et al, 2015).

When mice are exposed to chronic mild stress, they exhibit depressive like-symptoms and with that also elevated IL-1β. However, when this is done to mice with deletion of the IL-1 receptor (IL-1rKO), there were no depressive-like symptoms. The same effect was seen in mice with transgenic, brain-restricted overexpression of an IL-1 receptor antagonist (Goshen et al, 2007). Another factor that can induce depressive-like behavior is administration of LPS. However, inhibition of IL-1β activity will stop this effect, it will protect neuroinflammatory an oxidative responses (Li et al, 2017). To conclude, inhibiting IL-1β will stop depressive-like symptoms, meaning IL-1β is definitely connected to depression.

IL-1β is involved in a lot of the mechanisms discussed in the previous paragraph. First of all, IL-1β activates the HPA-axis by stimulating CRH, ACTH and cortisol secretion (Dunn, 2000). In addition, IL-1β inhibits the translocation of the GR from the cytoplasm to the nucleus. It also inhibits GR-mediated gene transcription. This means IL-1β directly induces GR resistance, an important mechanism of depression (Pariente et al, 1999).

Besides activating the HPA-axis, IL-1β is also involved in serotonin and other monoamines. Peripheral injection of IL-1β in rats cause elevated levels of 5-HIAA, a serotonin metabolite. This implies that IL-1β induces serotonin breakdown (Clement et al, 1997). This could be explained by the fact that IL-1β increases the activity of IDO, an enzyme mentioned before (Raison et al, 2009). Similarly, injections of IL-1β cause increased noradrenaline, serotonin and dopamine turnover, so these monoamines are metabolized faster (Zalcman et al, 1994). What's more, is that IL-1β acts on serotonin transporters to increase serotonin reuptake, causing a decrease in serotonin availability, an important cause of depression according to the monoamine hypothesis (Kim et al, 2016).

Lastly, IL-1β can precipitate elevations in extracellular glutamate and with that, cause excitotoxicity in nervous tissue (Rothwell et al, 2000). This leads to loss of neuronal plasticity, leading to depression, as mentioned before. Neuronal plasticity is also disrupted by the inhibition of BDNF by IL-1β (Tong et al, 2012).

IL-6 in depression

Not only IL-1β, but also IL-6 is associated with depression. A recent meta-analysis of 16 studies shows that IL-6 concentrations were significantly higher in depressed subjects compared with control subjects (Dowlati et al, 2010). Moreover, serum levels of IL-6 are significantly higher in women with post-partum depression than in women with no complications after pregnancy (Liu et al, 2016). Another meta-analysis concluded that blood levels of IL-6 in suicidal depressive patients were significantly higher than those of depressive patients who were not suicidal and healthy control subjects, suggesting that peripheral IL-6 may be associated with suicidal ideation, a core symptom of depression (Black et al, 2015). Not only the serum levels, but also the cerebrospinal fluid levels of IL-6 are higher in MDD patients (Sasayama et al, 2013). Also, the production of the soluble receptor for IL-6 (sIL-6R) is upregulated in depressive patients (Maes et al, 1995). The severity of the depression, according to the Beck Depression Inventory, is positively correlated with higher levels of IL-6 (Bob et al, 2010).

In addition, IL-6 knockout mice show reduced despair when they are forced to swim and in the tail suspension test. They also show enhanced hedonic behavior, a behavior that is impaired in depressive patients. Moreover, IL-6 knockout mice showed resistance to helplessness and stress (Chourbaji et al, 2006). These results can be confirmed by the fact that a polymorphism in the IL-6 gene, the 'low IL-6' synthesizing genotype, is associated with significantly fewer symptoms of depression (Bull et al, 2008). As mentioned earlier, IL-6 administration, combined with IL-1β, induces depressive like behavior and weight loss in mice (Kurosawa et al, 2015). Taken together, the previous data suggest that IL-6 plays an important role in the pathogenesis of depression.

An important mechanism by which IL-6 influences depression is via activation of IDO, the enzyme that metabolizes tryptophan. Like discussed earlier, the depletion of tryptophan may contribute to the deficiency of central serotonin. In MDD, lower plasma tryptophan levels are negatively correlated with IL-6 production (Maes et al, 1993). Peripheral injections of IL-6 enhance the turnover of serotonin and dopamine in the hippocampus and prefrontal cortex, also causing a serotonin deficit (Zalcman et al, 1994). The serotonin deficit will contribute to the development of depression.

Furthermore, IL-6 shares the HPA-activating activity with IL-1β, although it is less potent and effective (Dunn, 2000). This is in correspondence with a study by Lenczowski et al, where rat IL-6 was administered intracerebroventricular. This administration leads to the activation of the HPA-axis (Lenczowski et al, 1999). That the HPA-axis is activated by IL-6, is proven by the fact that IL-6 correlates with elevated levels of serum cortisol (Boss et al, 2000). This eventually leads to loss of neural plasticity, a cause for depression.

Lastly, higher levels of IL-6 are associated with lower levels of BDNF, another cause of depression mentioned before (Jehn et al, 2015).

TNF-α in depression

Compared to healthy people, patients with MDD have significantly higher levels of TNF-α circulating in their blood. There is a linear correlation between the level of TNF-α and the severity of depression, measured by the Hamilton Depression Rating Scale (HAMD) (Zou et al, 2018). These results correspond to the findings in a meta-analysis of 13 studies, finding that TNF-α had significantly higher concentrations in depressed subjects than in control subjects (Dowlati et al, 2010). Not only TNF-α itself, but also its soluble receptors sTNF-R p55 and sTNF-R p75 are elevated in depressive patients, compared to the normal population (Himmerich et al, 2008).

A polymorphism in the gene for TNF-α was found to significantly increase the risk for a suicide attempt, which also proves TNF-α must play an important role in the development and eventually suicide (Kim et al, 2013).

More evidence of TNF-α connected to depression was found by Kaster et al. TNF-α administration to mice can produce depressive-like behavior including anhedonia. This effect could be stopped by either an anti-TNF-α antibody or inhibiting the synthesis of TNF-α. Moreover, TNF-α receptor 1 (TNFR1) knockout mice were protected against depression (Kaster et al, 2012). All these data suggest that TNF-α and the development of depression are connected to each other.

TNF-α activates the HPA-axis just like IL-1β and IL-6, with around the same efficacy as IL-6, so less efficient and potent than IL-1β (Dunn, 2000). The activation happens at the hypothalamic, pituitary and adrenal level, resulting in an increase of cortisol. High cortisol levels can eventually lead to neuronal cell death.

Just like IL-1, TNF-α activates the serotonin transporters, causing faster reuptake and less serotonin availability in the synapse (Zhu et al, 2006). Furthermore, peripheral administration of TNF-α results in elevated levels of 5-HIAA, which implies that TNF-α induces serotonin breakdown (Clement et al, 1997). The availability of serotonin becomes even less, because TNF-α also activated IDO, which leads to a depletion of tryptophan, the precursor for serotonin (Heyes et al, 1992). Moreover, the activation of IDO leads to the production of quinolinate, a glutamatergic agonist which can cause excitotoxicity, causing neuronal cell death.

In addition, BDNF also seems to in involved in the effect of TNF-α in depression. Unpredictable chronic mild stress in rats causes anhedonia and depressive-like behavior, as well as a decrease in the level of BDNF in the hippocampus. Inhibiting TNF-α with Infliximab prevents the depressive-like behavior, as well as the BDNF reduction. This suggests that TNF-α causes a reduction in BDNF, which leads to loss of neural plasticity and depression (Sahin et al, 2015).

We must take the synergistic effect and interaction of cytokines into account when looking at all the previously discussed results of the different cytokines. A synergistic effect is seen when more cytokines are present together, and they show greater effects than the individual cytokines can produce alone (Brebner et al, 2000). The cytokines cooperate, so to say. For example, it appears that a combination of IL-1β and TNF-α synergistically influence consumption of food and the plasma corticosterone plasma concentrations in mice (Brebner et al, 2000). Moreover, the cytokines can influence each other's production. IL-1β can induce IL-6 production, and IL-6 and TNF-α can induce IL-1β production (Panzer et al, 1993).

Treatment

Current antidepressants, effect on inflammation

Stress can induce oversecretion of pro-inflammatory cytokines, which can result in depressive symptoms. Current antidepressants may reduce this stress in patients, and therefore also reduce the level of pro-inflammatory cytokines. The different kinds of antidepressants have varying capacities to downregulate the production of cytokines. In a meta-analysis, it was found that treatment with antidepressants reduced the IL-1β levels significantly in depressed patients. This effect was not found on TNF-α levels, and the effect on IL-6 was questionable. However, when divided into subgroups, it was found that SSRIs could reduce TNF-α and IL-6 as well. Other antidepressants did not have an effect on cytokine levels (Hannestad et al, 2011).

However, it was found that anti-psychotics, commonly used to treat depression, can cause a decrease in several pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, IL-2 and IFN-γ (Pollmacher et al, 2000). Moreover, they can increase the production of the anti-inflammatory cytokine IL-10 (Pollmacher et al, 2000). Another popular anti-depressant, lithium, also inhibits the production of pro-inflammatory cytokines, as well as the hyper activation of the HPA-axis (Rybakowski, 2000). Lithium has a response rate of 56%, but does not have an FDA approved indication for augmentation in MDD (Geier, 2012). Ketamine also inhibits the up-regulated production of IL-1β, IL-6 and TNFα. Furthermore, ketamine also inhibits the activation of IDO in depression (Wang et al, 2015). The response to ketamine is quite high (up to 70%), but it is not a treatment of first choice, as there are concerns of cognitive decline, neuronal injury and physical dependence of ketamine (Lener et al, 2017).

In addition, antidepressants like desipramine stimulate GR translocation from the cytoplasm to the nucleus and increase GR-mediated gene transcription, meaning the GR sensitivity will be restored and the negative feedback to the HPA-axis will be functional again. This will prevent the excessive levels of cortisol found in depression, caused by cytokines (Pariente et al, 1997). Other antidepressants include Riluzole and ketamine, which are glutamatergic modulators. These treatments can prevent the excitotoxicity by glutamate and can moducate NMDA receptors, preventing the loss of neural plasticity (Zarate et al, 2010).

Although these effects look very promising, anti-inflammatory effects of antidepressants are inconsistent. Some studies mentioned above only found SSRIs to be effective to inhibit inflammation, but in lots of other studies, other antidepressants were also found to be effective. There is even more inconsistency in this field, as in some studies no significant differences were found (Jazayeri et al, 2010; Ranjbar et al, 2013), or sometimes even elevated levels of cytokines after antidepressant treatment (Fluitman et al, 2011; Vogelzangs et al, 2012)

Anti-inflammatory treatment of depression

As discussed above, current antidepressants can already have a positive effect in reducing inflammation. However, these results don't seem too promising, because they seem very inconsistent. It would make a lot more sense if we addressed the problem of depression with this new approach of neuroinflammation. This means developing specific medicine that inhibits inflammation to prevent depression, instead of the current therapies that *might* in some cases reduce inflammation as a side effect.

Non-steroid anti-inflammatory drugs (NSAIDs) are drugs that inhibit COX, leading to a decrease in production of prostaglandins, important inflammatory markers. NSAIDs are the most commonly used anti-inflammatory drugs. A meta-analysis reports that an NSAID called celecoxib can reduce depression severity, and they found higher remission and response rates, compared to the control (Na et al, 2014). When celecoxib is added to the normal SSRI antidepressant treatment, greater reductions in both serum IL-6 levels and depression scored are measured, compared to the SSRI-only group (Abassi et al, 2012).

Because cytokines play such an important role in pathophysiology of depression, eventually cytokine-inhibitors may improve depressive symptoms. The inhibitions of the most important cytokines, IL-1β, IL-6 and TNF-α, which are discussed before, will be discussed as a possible treatment below.

An example for such a treatment is an IL-1 receptor antagonist (IL-1ra). There are a number of drugs that use this mechanism, including Anakinra, Canakinumab and Rilonacept. The antagonist can block fear and helplessness effects of a stressor (Maier et al, 1995). Moreover, it is observed that it can stop the neurodegeneration and the depressive-like behavior in depression (Koo et al, 2008). However, there are some reports of patients receiving exogenous administration of IL-1ra (Anakinra) that exhibit depressive-like symptoms as a result of this treatment (Jonville-Bera et al, 2011).

Patients receiving the IL-6 receptor antagonist tocilizumab had significantly higher depression scores, as well as more anxiety, more severe pain and worse sleep. These results are very undesirable, as it was expected that an IL-6 antagonist would improve depression symptoms (Knight et al, 2019). A possible IL-6 antibody has been found, called Sirukumab. In patients with Cutaneous Lupus Erythematosus (CLE) Sirikumab improves the quality of life due to the improvement in their mood (Szepietowski et al, 2013). Whether this antibody is useful in the treatment in depression still has to be explored. So, although it seems logical when looking at the mechanisms of IL-6, there is still no evidence of efficacy of blocking IL-6 in the treatment of depression (Shariq et al, 2018).

Infliximab is a TNF-α antibody, which can decrease anhedonia and despair-like behavior in the rat unpredictable chronic mild stress (UCMS) model of depression (Sahin et al, 2015). This drug is also tested in humans, and improved depression and its symptoms in patients with ankylosing spondylitis, a type of inflammatory arthritis, and patients with Crohn's disease (Ertenli et al, 2010; Guloksuz et al, 2013). The effect of other anti-TNF-α agents, etanercept, adalimumab and golimumab was investigated for the treatment of depression in individuals with comorbid psoriasis. The prevalence rate of depression in these patients decreased within 3 months of treatment, and then steadily decreased during the next 24 months, making them very effective (Wu et al, 2016).

Another possible therapeutic strategy can be the administration of anti-inflammatory cytokines. IL-4, an important anti-inflammatory cytokine, has been found to reduce IL-1β-induced depressive-like behavior (Park et al, 2015). Higher levels of IL-10, another anti-inflammatory cytokine, also reduce depressive-like behavior (Mesquita et al, 2008).

Lastly, there are non-pharmacological means of inhibiting inflammation to treat depression. Physical activity and exercise are critical to health, not only to the body but also to the brain. Exercise improves the mood in many people (Johnson and Castle, 2015). Long-term exercise can improve cognitive function, and these improvements are correlated with a decrease in IL-1β and an increase in the level of IL-10, an anti-inflammatory cytokine (Piao et al, 2013). Another study has also found reductions in IL-6 and TNF-α as a result of physical activity. This implies that exercise can protect the brain against neuroinflammation, and can be effective against depression (Funk et al, 2011). This can be confirmed by a study in mice with stress-induced depression. A long-term swimming exercise intervention completely abolished their depressive behavior. The reduction of the depression was correlated with an increase in serotonin a decrease in pro-inflammatory cytokines (Liu et al, 2013). Exercise intervention in humans found that exercise can induce improvements in the symptoms of depression, which is correlated with a significant decline in the concentration of IL-1β (Rethorst et al, 2012). So, the efficacy of exercise in the treatment of depression is likely for a part due to its anti-inflammatory effects.

Discussion

Accumulating evidence supports that neuroinflammation plays a big role in the development of depression, and specifically cytokines play an important role. Pro-inflammatory cytokines can contribute to the development of depression via multiple pathways, including activating the HPA-axis, stimulating serotonin reuptake and metabolism, inducing glutamatergic excitotoxicity, downregulating BDNF and causing oxidative and nitrosative stress. Current antidepressants can inhibit inflammation, but these results seem quite inconsistent. Moreover, they only work about half of all the patients with depression. This is why new research into anti-inflammatory therapy for depression is needed.

At the moment, there are a lot of anti-inflammatory treatments under investigation, to see if they also have antidepressant effects. NSAIDs seem to be quite effective to prevent depression, but findings are controversial whether NSAIDs can be used safely in combination with antidepressants (Warner-Schmidt et al, 2011; Uher et al, 2014). This has to do with the levels of p11, a small protein that regulates the serotonin receptor. P11 knockout mice show a depressive-like phenotype (Svenningsson et al, 2006). Antidepressants increase p11, but NSAID treatment abolishes this effect (Warner-Schmidt et al, 2011). Furthermore, NSAIDs increase the risk of cardiovascular events (Schjerning Olsen et al, 2011). However, NSAIDs have the advantage of being easily available and inexpensive.

Blocking the pro-inflammatory cytokines or administering anti-inflammatory cytokines seem to inhibit the development of depression, even though also some negative results have been found. However, the evidence of their antidepressant efficacy came mainly from studies that evaluated reduction in depressive symptom severity as a secondary outcome. In these studies, TNF-α, IL-1β and IL-6 were inhibited by receptor antagonists or antibodies, primarily to target another condition, like arthritis, lupus or psoriasis. There were only very few studies that were specifically designed to investigate the efficacy and safety of the inhibition of these cytokines in depressed patients without other comorbidities. Nevertheless, the evidence found in these studies support possibilities for the future. The therapies must be tested in patients with only depression, to see whether they can be used as conventional treatment. Moreover, more research must be done on their dosage, treatment length, side effects and safety. It has already been found that cytokine-inhibitors increase the risk of infection (Toussi et al, 2013). Physical activity also seems to have very beneficial effects on neuroinflammation in depression, making it an interesting topic to investigate more in the future.

For the future, perhaps a more personalized approach would be the most effective, and have the highest remission rate in patients with MDD. New research is needed to determine which specific cytokine blockers or other anti-inflammatory medication is beneficial for which specific subgroup of patients. The risk of side effects is important to be considered for the individual patient. Moreover, exercise should be prescribed to depressed patients, in combination with these medications, to improve their mood. All in all, this approach seems very promising as a future treatment for depression.

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