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PERSPECTIVE

Sick for science: experimental endotoxemia as a translational tool to develop and test new therapies for inflammation-associated depression

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Abstract

Depression is one of the global leading causes of disability, but treatments remain limited and classical antidepressants were found to be ineffective in a substantial proportion of patients. Thus, novel effective therapies for the treatment of depression are urgently needed. Given the emerging role of inflammation in the etiology and pathophysiology of affective disorders, we herein illustrate how experimental endotoxemia, a translational model of systemic inflammation, could be used as a tool to develop and test new therapeutic options against depression. Our concept is based on the striking overlap of inflammatory, neural, and affective characteristics in patients with inflammation-associated depression and in endotoxin-challenged healthy subjects. Experimental administration of endotoxin in healthy volunteers is safe, well-tolerated, and without known long-term health risks. It offers a highly standardized translational approach to characterize potential targets of therapies against inflammation-associated depression, as well as to identify characteristics of patients that would benefit from these interventions, and, therefore, could contribute to improve personalization of treatment and to increase the overall rate of responders.

Introduction

Depression is a highly prevalent mental disorder and one of the leading causes of disability worldwide. Globally, an estimated 322 million people are affected by depression [1]. Although effective therapies are available, about one-third of patients with depression fail to respond to treatment with classical first-line antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) [2]. Consequently, there is a pressing need to identify new targets for the development of tailored therapies for those patients who exhibit resistance to the existing treatments.

During the last decade, an extensive body of experimental and clinical evidence has accumulated demonstrating that inflammation is an important factor in the etiology and pathophysiology of major depressive disorder (MDD), at least in a subgroup of patients [3–7]. Consistent with a view of depression as a multifactorial condition, it is thus now well accepted that inflammation contributes to so-called "inflammation-associated depression" [8, 9]. General population studies demonstrate that about 30% of the individuals who were taking antidepressants or who were hospitalized for depression had increased levels (i.e., >3 mg/L) of C-reactive protein (CRP), a clinical marker of inflammation [10, 11]. This subgroup of patients also exhibits increased systemic levels of pro-inflammatory cytokines compared to healthy individuals [12]. Given that patients suffering from inflammation-associated depression typically show resistance to classic antidepressants such as SSRIs [13, 14], this sub-population of patients represents a particular challenge to treat.

Herein, we propose to take advantage of experimental endotoxemia, a well-characterized model of experimental systemic inflammation, to support the development of

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therapies for this subgroup of patients. Employing this model in healthy volunteers has already provided valuable insights into the mechanisms underlying inflammation-associated depression and could, in the next step, be used to identify new therapeutic targets and to test new treatment strategies that are specifically directed against inflammation-associated depression.

Endotoxin-induced inflammation: effects on mood and behavior

Systemic inflammation can be experimentally elicited in both animals and healthy humans by administration of purified bacterial endotoxin (lipopolysaccharide [LPS]). LPS is a cell-wall component of Gram-negative bacteria and a prototypical pathogen-associated molecular pattern that activates the innate immune system through a Toll-like receptor 4-dependent pathway [15]. Intravenous endotoxin injection to healthy humans rapidly triggers a well-described inflammatory cascade, with increased blood and cerebrospinal fluid (CSF) concentrations of cytokines and acute phase proteins [16]. Importantly, a similar signature of inflammatory changes, including elevated blood levels of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and CRP, was also found in inflammation-associated depression [12, 17, 18]. Experimental studies in animals have identified several pathways by which peripheral cytokines can propagate their signal to the brain to induce behavioral and mood changes (Fig. 1a, see ref. [19] for

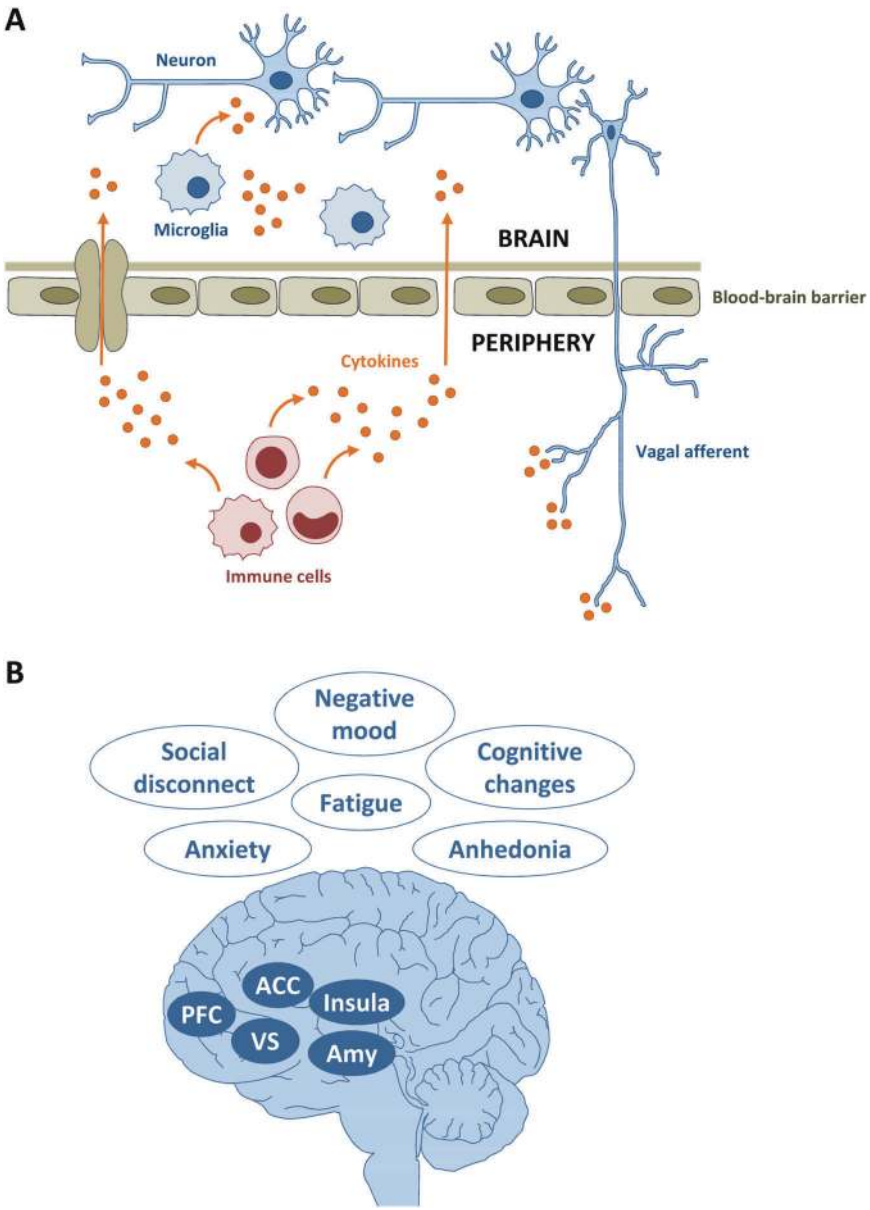

Fig. 1 Immune-to-brain communication pathways and cytokine-induced brain and behavioral changes. **a** Immune cells produce cytokines that circulate in the blood and signal the brain via multiple afferent pathways that can act in parallel. These routes comprise activation of vagal sensory neurons projecting to the brainstem, active transport of cytokines across the blood-brain barrier (BBB) via cytokine-specific saturable transporters, and passive diffusion of cytokines in brain areas with incomplete BBB (e.g., circumventricular organs and choroid plexus). The peripheral cytokine signal also activates microglia, which can, in turn, produce cytokines. **b** Cytokine signals reaching the brain trigger functional changes in brain areas involved in emotion processing and mood regulation, such as the insula, amygdala (Amy), ventral striatum (VS), anterior cingulate cortex (ACC), and prefrontal cortex (PFC). This leads to the behavioral reorganization of the individual and to affective changes. The figure was generated using images purchased from Motifolio Inc. (Ellicott City, MD, USA).

review). Engagement of these afferent pathways triggers inflammatory changes within the brain, affecting neural activity and neurotransmitter release in brain areas involved in emotion processing and mood regulation, such as limbic and cortical regions (Fig. 1b, see refs. [20–23] for reviews). This ultimately leads to the behavioral reorganization of the sick individual, who exhibits reduced locomotion, food consumption, and social exploration, commonly referred to as "sickness behavior" [24]. Interestingly, sick animals also exhibit depressive-like behaviors, such as increased immobility in the forced swim and the tail suspension tests [25], as well as reduced incentive motivation [26].

In humans, the endotoxin-induced inflammatory response is accompanied by negative affective and behavioral changes that resemble core symptoms of depression. Within two hours, individuals challenged with endotoxin typically develop depressive symptoms and negative mood, characterized by an increase in sadness, lassitude, anhedonia, and anxiety, which last for about 4–5 h [16, 27–31]. LPS-treated individuals additionally feel tired and sleepy, have reduced appetite, and engage less in social interactions [32–37]. Experimental endotoxemia also affects incentive motivation [38, 39], and alters the cognitive processing of negative information [40]. The magnitude of the inflammatory response in the circulation and CSF has been found to correlate with these affective changes [16, 27, 28, 34, 38]. Since LPS induces a well-described cascade of inflammatory changes together with behavioral and affective symptoms that are highly relevant for depression, experimental endotoxemia represents a unique model to investigate the role of inflammation in core symptoms of depression and their underlying mechanisms in humans [23, 41, 42].

Interestingly, such as with depression [43], there is some evidence for sex differences in the inflammatory and behavioral responses to experimental endotoxemia [44], but so far the findings are inconsistent. Some studies found a heighted pro-inflammatory response and more pronounced mood disturbances after LPS administration in women compared to men, while others did not [45–50]. It is possible that this heterogeneity is related to the hormonal status of the female volunteers, but this needs to be confirmed in future studies.

Endotoxin-induced inflammation and neuroimaging findings

Several studies have used experimental endotoxemia in healthy human volunteers to investigate the brain mechanisms underlying inflammation-induced behavioral and mood changes relevant for depression [22, 51]. These studies have analyzed, for example, alterations in the neural processing of social stimuli or rewards [30, 52–55], brain functional connectivity, glucose metabolism, and activation of glial cells [32, 33, 56, 57].

Regarding social and emotional functioning, a study investigated the neural correlates of inflammation-induced social disconnection and increased emotional responsiveness, and could show that the LPS-induced rise in circulating IL-6 levels was significantly positively correlated with the activity in the dorsal anterior cingulate cortex (dACC) and anterior insula during a social exclusion task in females (but not males) [53]. Furthermore, negative social feedback after endotoxin injection led to more pronounced BOLD responses in the amygdala, dACC, and the dorsomedial prefrontal cortex, although these changes were not reflected in behavioral measures [58]. On a related note, a functional magnetic resonance imaging (fMRI) study addressing neural responses to emotional stimuli during endotoxin-induced immune activation revealed increased activation of prefrontal regions, i.e., the inferior orbitofrontal, medial and superior prefrontal cortices, which are closely connected to the amygdala [55]. In another endotoxin study, increased amygdala responses were found in response to socially threatening stimuli such as fearful faces, with amygdala responses being related to feelings of social disconnection [59]. Altogether, endotoxin-induced inflammation seems to increase neural responses in the amygdala, ACC, and prefrontal regions during the processing of social and emotional information. These brain regions are—beside other functions—key contributors to emotion processing and regulation, and structural and functional alterations in these regions have been implicated in depression pathology. Indeed, amygdala responses to negative stimuli are more pronounced and longer lasting in depressed patients [60], which could be at least partially explained by altered inhibitory control from prefrontal regions [61]. In addition, increased ACC activation to emotional stimuli has been reported in depression [22, 62].

Furthermore, significant reductions in ventral striatal activity to reward cues have been found during experimental endotoxemia [30], indicating that endotoxin-induced inflammatory activation alters the brain's sensitivity to rewards [30]. The clinical validity of such findings is indirectly supported by the observation that increased CRP levels were associated with reduced corticostriatal connectivity in patients with MDD [63]. In depression, increased sensitivity to negative feedback has been repeatedly observed [22], but its potential relationship to inflammation has so far only been experimentally explored in a model of typhoid vaccination, showing a shift in relative sensitivity to punishment as compared to reward [64]. If such effects could be also induced by endotoxin administration, this opens up possibilities to manipulate a core feature of depression and to use neuroimaging to study its neural signatures. As early changes in reward sensitivity

predict treatment outcomes [65], and because inflammation is indicative of treatment-resistant depression [14], a model to better understand this shift would be valuable.

Recently, a number of studies have shown that experimental inflammation results in rapid modulation of interoceptive pathways, including the insular and cingulate cortices [56, 57, 66, 67]. Importantly, altered functioning in these pathways is also a central feature in major depression [68, 69], and is believed to represent neural substrates of psychological states common to depression and sickness, such as fatigue, malaise, and social disconnect [70]. These fMRI findings were supported by the results of a positron emission tomography (PET) study, in which changes in glucose metabolism in the insula (and to some extent also in the cingulate) were correlated with increased depressive symptoms after endotoxin injection [33].

PET imaging also has recently been used to measure microglia activity by selectively targeting the 18 kDa mitochondrial translocator protein (TSPO), which is upregulated in activated microglia. A series of studies have shown increases in TSPO binding after immune provocation and in MDD patients [32, 71–74]. Building on an initial study in baboons [75], a PET study in healthy humans using the radioligand [^{11}C]PBR28 observed increased TSPO binding throughout the brain together with more pronounced sickness symptoms after endotoxin injection [32]. This TSPO binding pattern was similar to those in patients with MDD, for which a meta-analysis reported increased TSPO expression in ACC, frontal lobe, prefrontal and temporal cortices, insula, and hippocampus when compared to healthy controls [71]. Interestingly, a recent study showed that higher TPSO values in patients with treatment-resistant depression predicted better treatment response to Celecoxib [76]. However, these findings need to be interpreted with caution, as results of TSPO PET studies in neuroinflammatory conditions or states have shown inconsistent results [77], challenging the general assumption that altered TSPO expression or binding unequivocally mirrors neuroinflammation [78, 79]. In line with this, no changes in TSPO binding were found after IFN-α immune challenge in healthy human volunteers [80], or in patients with rheumatoid arthritis [81], or severe seasonal allergy [82].

Taken together, neuroimaging techniques can provide important insights into the neural pathways and physiological processes involved in behavioral and mood-related symptoms during endotoxin-induced inflammation. The above findings suggest that these symptoms are at least partially mediated by functional changes in subcortical and prefrontal brain regions. Importantly, the activation of these regions show a striking overlap to neural changes found in inflammation-associated depression, suggesting that the chronic alteration of these pathways by inflammation leads to the development of clinical depression [22, 51]. While there is some support for specific neural substrates of inflammation-associated depression, including alterations of ACC activity while processing negative affective stimuli, and inhibited activity of the ventral striatum during reward tasks (as outlined in ref. [83]), future imaging studies implementing identical experimental tasks and techniques to compare behavioral and brain responses between healthy endotoxin-treated individuals, and patients with inflammation-associated and "typical" depression are suggested.

Experimental endotoxemia as a tool to develop and test therapies for inflammation-associated depression

Thus far, experimental endotoxemia has been used in animals and humans to mainly identify the afferent (immune-to-brain) communication pathways and to characterize inflammation-induced behavioral and neural changes. Given the overlap of inflammatory, neural, and affective characteristics in patients with inflammation-associated depression and in endotoxin-challenged healthy subjects, we herein emphasize that experimental endotoxemia constitutes a useful translational model for the development of therapies for inflammation-associated depression (Fig. 2), as previously suggested for inflammatory diseases [84]. Furthermore, we propose that this model could also serve as a tool to define the characteristics of populations of patients that would benefit most from therapies targeting inflammation-associated depression.

Ever since the role of inflammation in the pathophysiology of depression gained interest, various potential pharmacological targets have been identified for the treatment of inflammation-associated depression (see refs. [4, 85, 86] for reviews). Such targets include molecules involved in immune-to-brain communication such as pro-inflammatory cytokines and prostaglandins [87]. In this regard, the prostaglandin synthesis inhibitors celecoxib (cyclooxygenase [COX]-2 inhibitor) and aspirin (COX-1 and COX-2 inhibitor) have been found to enhance the therapeutic efficacy of classical antidepressants [88, 89]. Furthermore, depressed patients with signs of inflammation showed better improvement in depressive symptoms when treated with selective cytokine antagonists, such as the TNF-inhibitors etanercept and infliximab, compared to patients receiving placebo [90, 91]. Two meta-analyses also indicate potential beneficial effects of anti-inflammatory treatments on depressive symptoms [92, 93], although the number of studies included in these meta-analyses was limited (less than 20). Other studies have suggested to directly targeting neuroinflammatory processes by drugs that inhibit microglia activation such as the tetracycline antibiotic minocycline [5, 94, 95].

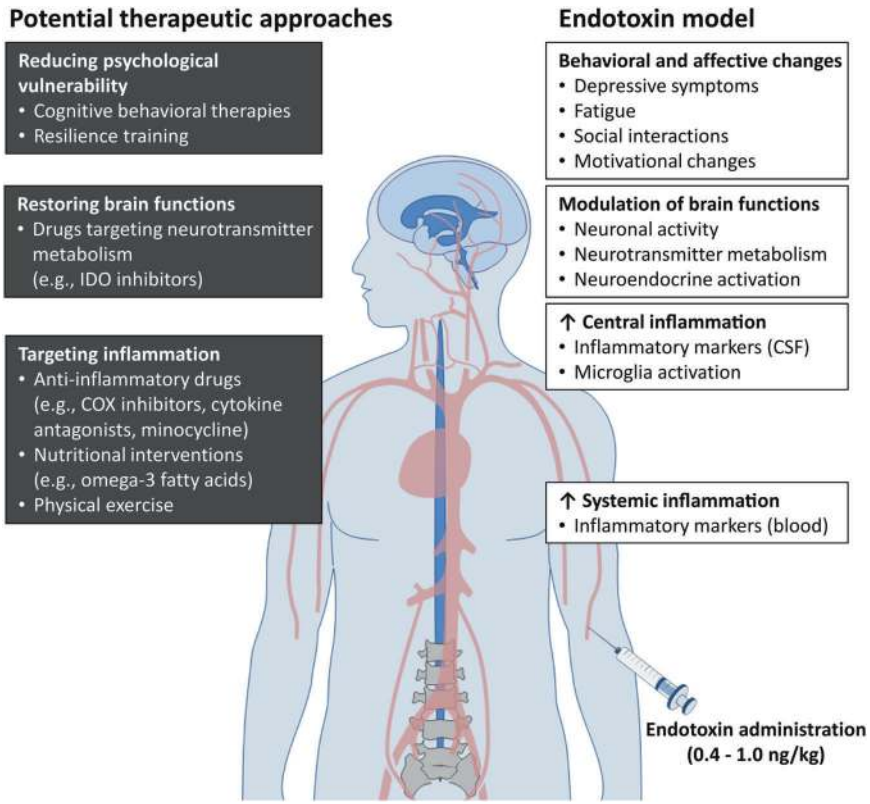

Fig. 2 Potential treatment targets and therapeutic approaches that can be studied and tested using human experimental endotoxemia. Administration of endotoxin leads to a cascade of inflammatory, neural, and affective changes that are highly relevant for depression and that can be measured and treated at different levels. Potential treatment options include pharmacological and non-pharmacological therapies targeting the peripheral and central inflammatory responses, neurotransmitter metabolism, or the behavioral/psychological vulnerability. The figure was generated using images purchased from Motifolio Inc. (Ellicott City, MD, USA).

Alternative potential targets for therapies against inflammation-associated depression could be neurotransmitter metabolism pathways that are demonstrably affected by inflammation, as extensively reviewed previously [3, 96]. For instance, activation of the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan into kynurenine (KYN) to the detriment of serotonin synthesis, appears to be one key mechanism for inflammation-induced changes in depressive symptoms [21]. Activated microglia converts kynurenine (KYN) into quinolinic acid (QUIN), a highly potent N-methyl-D-aspartate (NMDA) receptor agonist that triggers the release of the excitatory neurotransmitter glutamate. Increased brain glutamate, notably in the basal ganglia and dACC, has recently been shown in inflammation-associated depression [97]. The current use of low-dose ketamine as antidepressant therapy in patients with treatment-resistant depression is based on ketamine-blocking effects on NMDA-mediated glutamate transmission. Interestingly, particularly patients with elevated levels of inflammatory markers seem to benefit from low-dose ketamine treatment [98, 99], which is in line with the findings from rodent studies showing that ketamine prevents LPS-induced depressive-like behavior [100–102].

Potential therapies for inflammation-associated depression are not restricted to pharmacological therapies. Nutritional interventions such as supplementation with anti-inflammatory omega-3 polyunsaturated fatty acids can improve inflammatory states/conditions [103], or favor a good gut microbiota balance [104]. This, in turn, is likely to modulate mood symptoms [105, 106]. In the same way, exercise interventions have anti-inflammatory effects [107] and could, thus, improve inflammation-associated depressive symptoms [108]. Furthermore, non-pharmacological therapies can target the behavioral changes associated with inflammation rather than inflammation per se. Such therapies would focus on improving psychological factors that could confer vulnerability to inflammation-induced mood changes, such as sleep disturbances [46], pre-existent anxiety [31] and depressive symptoms [109], trait sensitivity to social disconnection [110], and negative affectivity [111]. Importantly, psychological and mind-body therapies appear to also have positive impact on the inflammatory state [112, 113], and therefore arise as an interesting tool for inflammation-associated depression.

Altogether, the challenge to treat inflammation-associated depression does not seem to come from a lack of possible targets (Fig. 2), but rather from the difficulty to determine the efficacy of such therapies. In particular, clinical trials are highly challenging with respect to time, achievability, as well as financing. Furthermore, clinical trials addressing inflammation-associated depression might lead to false-negative results, as only a sub-population of depressed patients would benefit from these therapies, and

positive effects might be diluted in the overall group of depressed patients. Thus, we believe that experimental endotoxemia could be an important tool to countervail these issues. The model might be particularly useful in the preclinical phase to test whether a particular drug/treatment is effective in preventing affective and behavioral changes in endotoxin-challenged healthy humans. This would nicely complement animal studies (e.g., [100–102, 114–116]), by developing tailored therapies for patients with inflammation-associated depression, and testing them in a human population free of comorbidities and in a limited period of time.

Two previous studies have tested whether a pretreatment with an SSRI or with bupropion prevents mood alterations induced by endotoxin [29, 117], with limited effects, in line with the notion that inflammation-associated depression is resistant to classic antidepressant therapies [13]. Future studies will need to investigate the potential usefulness of the therapies described above against inflammation-associated depression.

Characterization of the patient target population

Although the above therapeutic options might be to some extent promising for the treatment of inflammation-associated depression, the success of such therapies largely depends on the proper identification of patients that benefit from this kind of interventions. One of the biomarkers that have gained strong interest in the quest for selecting depressed patients with inflammation is CRP [118]. Measuring circulating CRP concentrations has already been suggested as a marker to identify depressed patients that would benefit most from anti-inflammatory treatments [91]. A major advantage of CRP is that it is highly standardized and relatively easy to measure in the blood (when following recommendations [119]). However, CRP has two isoforms, one that is not soluble in plasma, with pro-inflammatory properties (mCRP), and one highly soluble and possessing *anti*-inflammatory properties (pCRP). The standard CRP assays measure both CRP isoforms [120]. Consequently, although clinically high levels of CRP (>10 mg/L) probably relate to increased production of mCRP, it is less clear when only a slight elevation in CRP is observed [120]. Thus, it remains unclear whether moderate increases in CRP levels can indicate with confidence a risk for inflammation-associated depression.

Experimental endotoxemia could help identifying the characteristics of patients that would benefit from therapies targeting inflammation-associated depression. Arguably, these patients would exhibit an increased inflammatory state, but also higher target cell sensitivity to the effects of cytokines, and thus would show a stronger behavioral response to endotoxin [44, 121]. Using experimental models of inflammation, recent studies have provided clues regarding variables possibly associated with higher emotional and behavioral response to cytokines, such as baseline psychological state (e.g., state anxiety, negative affectivity, perceived stress) [31, 40, 111, 121], sleep disturbances [46], and baseline activity of some transcription factors [122]. Identifying further the characteristics that predict a higher and/or prolonged emotional response to inflammation would help determining which subgroup of patients would benefit the most from therapies for inflammation-associated depression.

Demarcation from other models of inflammation-associated depression

In addition to experimental endotoxemia, two other models have provided valuable insights into inflammation-associated depression: the IFN-α model and the typhoid vaccination model. IFN-α treatment has been clinically used, and about half of the patients develop depressive symptoms within 8–12 weeks after the onset of IFN-α treatment [123]. Studies in IFN-α-treated patients have greatly expanded knowledge on the role of inflammation in depression [96]. Interestingly, chronic IFN-α treatment in hepatitis C patients [124] induced a comparable pattern of CSF cytokine changes as in endotoxin-treated healthy subjects [16]. Moreover, both acute LPS administration and chronic IFN-α administration induced similar changes in brain function, including reduced activation of ventral striatum in response to reward [125], increased glutamate in the ACC [126], and reduced functional connectivity [127]. In addition, changes in basal ganglia were observed acutely (4 h) after the administration of IFN-α, and predicted the long-term development of fatigue [128, 129]. Although the model of chronic IFN-α administration allows assessing the long-term effects of inflammatory activation, IFN-α cannot be applied chronically to healthy volunteers for ethical reasons.

Administration of typhoid vaccine can be safely used in healthy subjects, and triggers a mild immune activation and very subtle changes in mood in a small proportion of subjects [130, 131]. Changes in brain functions have been also observed after typhoid vaccination, such as increased activation of the ACC during emotional face processing [130], increased activity in the amygdala and in the insula [132], and reduced activity in the ventral striatum in response to reward [64], in line with those observed during experimental endotoxemia. However, because of the response being very mild and not as reproducible as in experimental endotoxemia, this model seems less useful as a tool for the

development and testing of new treatments against inflammation-associated depression.

Advantages and limitations of the experimental endotoxemia model

The model of experimental endotoxemia offers many advantages. First, because of the transient nature of the endotoxin-induced inflammatory and behavioral responses, the efficacy of a potential therapeutic intervention can be assessed within a relatively short period of time. Second, dose-effect relationships can be easily obtained by modulating the dose of endotoxin [28, 133, 134]. For example, a dose of 0.4 ng/kg body weight (bw) induces very slight behavioral changes that are imperceptible to participants, while a dose of 2.0 ng/kg bw triggers very strong sickness symptoms and emotional distress in the majority of participants. Note that the majority of studies assessing LPS-induced changes in mood and negative affect used doses between 0.4–1.0 ng/kg bw, while higher doses (2.0–4.0 ng/kg bw) are mainly used in studies focusing on sepsis-related symptoms. Third, since the response to LPS is highly conserved across vertebrate species, the model allows forward and reverse translation of the findings from animals to humans [135]. Using experimental endotoxemia in humans additionally provides an evident benefit of assessing feeling states, which are not necessarily reflected in objective behavioral changes (e.g., a feeling of fatigue does not necessarily translate into lower physical activities) [135]. Even though this model is not a model of depression per se (see below), the model of experimental endotoxemia provides crucial information about inflammation-induced affective changes and the underlying mechanisms.

Some limitations of the human experimental endotoxemia model as a model of depression need to be considered as well. The main limitation lies in the discrepancy of the severity and chronicity of the LPS-induced emotional symptoms compared to the symptoms of MDD. While emotional symptoms in MDD last for at least two weeks, the behavioral and emotional changes induced by endotoxin are acute and subside completely 6–8 h after endotoxin injection. Repeated or chronic administration of very low doses of endotoxin have been attempted to extend the LPS-induced behavioral and physiological symptoms [136], but these approaches were hampered by endotoxin tolerance. One critical question is whether the acute changes observed during experimental endotoxemia would turn into clinical depression if inflammation and activation of the immune-to-brain pathways would persist for a longer period of time. Despite similarities in the emotional and neural changes observed under acute experimental inflammation and in inflammation-associated depression [22, 23, 41, 42, 51], one can only speculate if such changes would become chronic with ongoing inflammation, as the acute LPS-induced mood effects last only for a few hours. However, findings from IFN-α treatment studies suggest that this indeed might be the case, by demonstrating that acute IFN-α-induced changes predicted the later development of neuropsychiatric symptoms [128, 129, 137]. An important research question to investigate would be to which extent the emotional and neural responses to LPS predict the later development of depression. In any case, phase-I studies to determine the potential usefulness and safety of a therapy do not require having a model that reflects precisely the disease. Given the characteristics and advantages of the model of experimental endotoxemia described above, phase-I studies of therapies against inflammation-associated depression would benefit from using this model.

Another limitation is that experimental endotoxemia has only been used in very healthy subjects, without physiological diseases, medications, or mood, sleep, and stress disorders, apart from one recent study in obese but metabolically healthy individuals [138]. Thus, endotoxin-induced neural and behavioral changes in populations that are at higher risk at developing depression, for instance individuals suffering from diabetes, chronic pain, or cancer [139], and in depressed individuals, remain unknown and need to be investigated.

Methodological considerations

Although experimental endotoxemia is a safe model of systemic inflammation when performed under controlled conditions, some technical recommendations need to be considered. As endotoxin-induced systemic inflammation leads to increases in heart rate and body temperature, and can (depending on the dose) induce nausea, headache, as well as dizziness and acute drop in blood pressure, medical supervision is necessary. Furthermore, only low doses of LPS can be used when studying neural mechanisms using brain imaging, to limit shivering and nausea in the scanner. In addition, individuals should be monitored until the sickness response has subsided (i.e., until 6–8 h after endotoxin injection) before being discharged after a medical examination to insure their safety.

Various research groups have used the model of experimental endotoxemia in humans, with variations in experimental procedures. Although it is unclear how each parameter of the procedure affects the response to endotoxin, some parameters are likely to modulate the immune and/or brain outcomes, such as time of injection [140], individuals' expectations [134], and fasting state [141]. Furthermore, various tools have been used to measure the depressive response, including semi-structured interviews

(e.g., Montgomery-Åsberg Depression Inventory MADRS) and self-administered questionnaires (e.g., Profile of Mood States POMS). Lassitude and fatigue have rarely been assessed specifically [142], but rather as subscale from the MADRS or POMS. State anxiety seems as the only symptom that was measured across studies consistently with the State-Trait Anxiety Scale (STAI). While it is difficult to advise on the choice of specific scales, we recommend to compile scales designed to assess specific symptoms, to have an overview of the inflammation-induced specific neuropsychiatric changes and how they relate to a general state of sickness [143]. Furthermore, it can be useful to assess objective behavioral aspects, such as objective motivational [38, 39] and appetite [37] changes, as they provide additional information on the specific mechanisms underlying the development of affective symptoms [135]. Such procedures might overcome the limitation of sickness as a generalized behavioral response to the inflammatory stimulus, and increase precision and specificity for depression-relevant behavioral changes. We also urge to report protocol details when using human experimental endotoxemia, and call for a standardization of the procedure to make the best use of this model for the proposed purpose.

Conclusion

Experimental administration of endotoxin to healthy volunteers offers a highly standardized translational model of systemic inflammation that has been successfully used to investigate the mechanisms underlying inflammation-associated behavioral and mood changes. It has been proven to be safe, well-tolerated, and without any known long-term health risks. The overlap of inflammatory, neural and affective characteristics in endotoxin-challenged healthy subjects and patients suffering from inflammation-associated depression emphasizes that human experimental endotoxemia might serve as a suitable tool in the quest to develop personalized and thereby more effective therapies for major depression.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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