Research report

TNF-alpha inhibition prevents cognitive decline and maintains hippocampal BDNF levels in the unpredictable chronic mild stress rat model of depression

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HIGHLIGHTS

Unpredictable chronic mild stress (UCMS) impairs learning and memory in MWM and PAT.
UCMS decreases expression of BDNF in CA1 and CA3 fields of hippocampus.
Chronic administration of Infliximab prevents stress-induced memory impairment.
Chronic administration of Infliximab prevents stress-induced reduction in hippocampal BDNF.

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ABSTRACT

Previous findings have shown that patients with depression express higher levels of proinflammatory cytokines such as TNF-α and IL-6. We have recently found that Infliximab (a TNF-α inhibitor) decreased anhedonia and despair-like behavior in the rat unpredictable chronic mild stress (UCMS) model of depression suggesting that inflammation might play an important role in depression. An increasing number of studies suggest that inflammation is also associated with cognitive impairments. The current study aimed to investigate the effect of UCMS on the cognitive performance of rats and their hippocampal BDNF levels and the effect of chronic Infliximab (5 mg/kg/weekly, i.p.) treatment on these measures. Rats were subjected to different types of stressors daily for a period of 56 days to induce depression-like state. The UCMS resulted in impairments in spatial and emotional memory acquisition and retention with no effect on the level of locomotor activity. These behavioral effects of UCMS were accompanied by reduction in the level of BDNF in the CA1 and CA3 regions of the hippocampus. Chronic Infliximab treatment prevented the UCMS-induced cognitive impairments as well as the reduction in the levels of hippocampal brain-derived neurotrophic factor (BDNF). These results suggest that Infliximab improves the spatial and emotional memory impairments induced by chronic stress in rats likely through its effects on hippocampal function by modulating inflammation.

1. Introduction

An increasing number of studies suggest that the overproduction of proinflammatory cytokines by the activation of immune-inflammatory process is related to the pathophysiology of depression [1]. Convergent lines of evidence have consistently supported this claim. For instance, in the clinic many depressed patients were found to have increased levels of proinflammatory cytokines such as TNF-α and IL-6 [2]. Furthermore, antidepressant
compounds have been found to have anti-inflammatory effects in both depressed patients [3] as well as animal models of depression [4,5] and anti-inflammatory drugs, which block the production or activity of proinflammatory cytokines have been reported to exert antidepressant effects in clinical studies [6]. The relation between inflammation and depression suggested by these findings has been recently supported by a study that reported the anti-depressant efficacy of Infliximab in the UCMS rat model of depression [7].

Chronic mild stress does not only lead to depression-like behaviors suggesting alteration in affective processes but also impaired cognitive performance as assessed in several learning and memory paradigms such as Morris water maze and object recognition test [8–10]. Among the multiple neurochemical changes that occur in response to stressors, excessive inflammation processes is thought to play a major role in resultant cognitive impairments [11]. Several studies have indeed reported that exposure to stressors increased the release of TNF-α in the plasma [9] and that there is a relationship between inflammatory cytokines and various types of learning and memory [11].

The current study aimed to investigate the effect of anti-inflammatory Infliximab on UCMS-induced memory acquisition and retention impairments in the rat using passive avoidance and Morris water maze tests. This study also aimed to relate the behavioral effects with neurobiological processes by investigating the effect of UCMS and Infliximab on the levels of brain-derived neurotrophic factor (BDNF) in the CA1 and CA3 fields of hippocampus.

2. Materials and methods

2.1. Animals and standard procedures

Adult male albino Wistar rats (Kocaeli University, Experimental Medical Research and Application Center, Kocaeli, Turkey) weighing 300–400 g were kept in an animal colony at a density of approximately 5–6 per cage for 2 weeks prior to experimentation. All experiments were conducted between 9:00 a.m. and 12:00 p.m. under standard laboratory conditions (22 ± 2 °C room temperature; 12-h light/dark cycle with lights on at 7:00 A.M.). Tap water and food pellets were provided ad libitum. All rats used in this study were naive to the experimental tests, and different groups of rats were used in each experiment. The experiments were conducted in accordance with the Regulation of Animal Research Ethics in Turkey. The ethical approval was granted by the Kocaeli University Animal Research Ethics Committee (Project number 2012/8, Kocaeli, Turkey).

Animals were divided into three groups (n = 12 per group): Control, UCMS and UCMS+Infliximab. The Control and UCMS groups received physiological saline (intraperitoneally) and UCMS+Infliximab group received Infliximab (intraperitoneally, 5 mg/kg) weekly during 8 weeks of chronic mild stress treatment. The selected Infliximab dose was chosen based on previously reported studies. [7,12,13]. Behavioral tests started three days after the final injection and they were conducted on consecutive days in the following order: locomotor activity test, passive avoidance test, and Morris water maze test.

2.2. Drugs

Infliximab (Schering-Plough) was dissolved in physiologic saline. Drugs were prepared immediately prior to use and administered intraperitoneally (i.p.) to the rats in a volume of 0.1 ml per 100 g body weight.

2.3. Unpredictable chronic mild stress procedure

Unpredictable chronic mild stress (UCMS) has been widely used as an experimental animal model of depression-like disorders, and it is regarded to have resemblances to the unavoidable stressors of everyday life in humans [14]. UCMS was applied as previously described by Yazir et al. [15]. Briefly, both UCMS groups were subjected to different types of stressors: restraint for 4 h, cage tilting for 24 h, wet bedding for 24 h, swimming in 4 °C cold water for 5 min, swimming in 45 °C hot water for 5 min, pairing with another stressed animal for 48 h, level shaking for 10 min, nip tail for 1 min, and inversion of the light/dark cycle for 24 h. These nine stressors were randomly applied over 56 days, and each stressor was applied 4–5 times during this time period. Rats received one of these stressors per week day and the same stressor was not applied for two days in order to minimize the predictability of the occurrence of each stimulation. The stress procedure did not involve any food or water deprivation. The rats in the control group were not exposed to any of the stressors and had free access to food and water.

2.4. Locomotor activity test

Locomotor activity was assessed using a fully-automated animal activity monitoring system (Commat Ltd., Ankara, Turkey) composed of a Plexiglas chamber, a computer, and open field activity software. The Plexiglas chamber (42 cm × 42 cm × 30 cm) was equipped with 15 pairs of infrared photo-beams and detectors were mounted horizontally every 2.5 cm (bottom) and vertically every 4.5 cm (upper). Interruptions of photocell beams were detected and recorded by the software. The total locomotor activity was measured as the sum of stereotypic, ambulatory, and vertical activities. The activity was monitored continuously for 10 min following acclimation to the test room for a period of an hour.

2.5. Passive avoidance test

A one-trial, light-dark passive avoidance apparatus (Ugo Basile model 7551, Italy) was used for evaluating emotional memory based on contextual fear conditioning paradigm [16]. In this task, the animal learns to avoid the compartment associated with an aversive stimulus. The latency to cross between compartments was used as an index of learning. The apparatus had two compartments (dimensions of each compartment were 22 × 21 × 22 cm). The illuminated white box was connected to the dark box. The dark box was equipped with an electrifiable grid floor that was used to deliver an inescapable electrical shock via a shock generator. A flat-box partition including an automatically operated sliding door at the floor level separated the two boxes.

A training trial was conducted as described by Monleón et al. [17]. On the first day of training (preacquisition trial), rats were placed individually into the light compartment and they were allowed to explore the boxes. The animal could move freely into the dark compartment after the door between the two boxes was opened (after 30 s). Fifteen minutes after the preacquisition trial, an acquisition (training) trial was performed. Rats were again placed in the light compartment of the passive avoidance apparatus. After 30 s of familiarization with the apparatus, the door between the compartments was opened. When the animal entered the dark compartment completely, the sliding door between the chambers was closed, followed by the delivery of an electric foot-shock (0.5 mA) for 3 s through the grid floor. The time taken to enter the dark compartment was noted as the training latency. The animals were then removed from the dark box and put back in their home cages. If the animal did not cross over to the dark compartment within 300 s, it was excluded from the experiment. In order to
remove any confounding olfactory cues, both compartments of the box were cleaned thoroughly between each training session.

Twenty-four hours after the acquisition trial, the retention test was conducted. The retention was tested by measuring the latency of the rats to enter the dark compartment (four paws in) after they were returned to the light compartment. The foot shock was omitted during this test trial. A cross-over latency of 300 s was recorded if the animal did not enter the dark compartment within 300 s. This latency was used as a measure of the retention of the passive avoidance response.

2.6. Morris water maze test

The Morris water maze was a circular pool (150 cm diameter) that was filled with water (25 °C). The pool was kept in a soundproof dimly lit test room that contained a number of extra-maze visual cues: a white–black colored poster on the wall, a camera, and the experimenter. The maze was divided into four quadrants and three equally spaced points around the edge of the pool were used as starting positions. We systematically varied the order of the release positions throughout the experiment. Small black plastic pieces were placed on the surface of the water in order to make the platform invisible [18].

The rats were trained in the Morris water maze over five daily sessions performed between 9:00 and 12:00 h (familiarization session, S1, S2, S3, S4). During the acquisition phase of the experiments, each rat was given three trials each day [19]. An escape platform (6 cm in diameter and 12 cm high) was located in one of the quadrants 1 cm above the water surface during the familiarization session. During the consecutive four sessions, the platform was in a fixed position 1 cm below the water surface so that it was not visible from water level.

In each daily trial, the rat was taken from its home cage and placed into the water maze from one of three randomly picked locations with its head facing to the center of the water maze. The trial time started when a rat was released into the maze. When the rat had found and climbed onto the hidden platform (diameter 6 cm), the trial was terminated and the escape latency was noted for that trial. The maximum trial length was 60 s. If the rat had not climbed onto the platform within 60 s, the trial ended and the experimenter guided the rat by hand to the platform. In these cases, an escape latency of 60 s was recorded for that trial.

The inter-trial interval (ITI) was 60 s. During the ITI the rat was kept on the escape platform before the next trial was initiated. After the inter-trial interval had elapsed, the rat was placed in the pool again from a different location, which initiated the next trial. In the end of the third trial, the rat was returned to its home cage.

Twenty-four hours following the last acquisition session, a ‘probe trial’ was commenced to assess the rat's retention of the location of the hidden platform based on the spatial memory established during previous trials. During the probe trial, the escape platform was removed from the maze and the rat was allowed to search the pool for the platform for 60 s. During this period, due to the spatial memory of the platform location, animals are expected to spend more time searching the quadrant that previously contained the hidden platform compared to each of the other three quadrants.

2.7. Immunohistochemistry

Paraffin sections were prepared from rat brains that were fixed with 10% neutral buffered formalin. Sections were deparaffinized in xylene, rehydrated through a graded alcohol series and they were washed with PBS. Following these procedures, an antigen retrieval procedure was performed by treating the samples in 10 mM citrate buffer (pH 6.0) in a microwave oven at 600 W for 5 min two times. The samples were allowed to cool for 20 min at room temperature and incubated in 3% H2O2 for 15 min. In order to block nonspecific bindings, the sections were then incubated in a blocking serum (Histostain-Plus Kit, Broad Spectrum, Invitrogen, Carlsbad, CA, USA) for 10 min at room temperature. The primary rabbit polyclonal anti-BDNF antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA) was applied overnight at a 1:100 dilution at room temperature. Also anti-cFOS antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA) was applied overnight at a 1:150 dilution at room temperature. The negative control samples were prepared by replacing the primary antibody with the antibody diluent solution (Ab-diluent reagent solution, Invitrogen, Carlsbad, CA, USA) at the same concentration. After a number of washes, the slides were incubated with a biotinylated secondary antibody (Histostain-Plus Kit, Broad Spectrum, Invitrogen, Carlsbad, CA, USA) for 20 min at room temperature, and diaminobenzidine (DAB) (DAB Substrate Kit, Invitrogen, Carlsbad, CA, USA) was applied for visualization. The sections were briefly counterstained with Mayer's hematoxylin (Invitrogen, Carlsbad, CA, USA) and they were mounted with ClearMount (Invitrogen, Carlsbad, CA, USA) on glass slides. The slides were examined under a light microscope (Olympus BX 50, Tokyo, Japan), and photomicrographs were taken with a Leica DM 100 system (Leica DFC 290HD, Wetzlar, Hessen, Germany). The same protocol was used to treat all the samples. The staining intensity was graded using a semiquantitative scale ranging from no (−), very weak (+), moderate (++), strong (+++) and very strong (++++) expression.

2.8. Statistical analysis

All results were expressed as mean ± SEM. The total locomotor activity scores and the time spent in the correct quadrant in MWM were compared between groups by one-way ANOVA. Significant overall differences were followed by post-hoc Tukey test. Escape latencies in MWM and Passive Avoidance performance were analyzed by mixed-design two-way ANOVA and the significant interactions were followed by simple effects analysis. When appropriate, the Holm-Bonferroni method was used to correct for multiple comparisons. Immunoreactivity scores were analyzed by Kruskal–Wallis test. Alpha level of 0.05 was used for all statistical tests.

3. Results

3.1. Effects of UCMS and infliximab on locomotor activity:

One-way ANOVA did not reveal any significant differences between the three treatment groups in terms of locomotor activity levels, $F(2,33) = 1.34$, $p = .28$, $\eta^2_p = .08$ Fig. 1.

3.2. Effects of UCMS and infliximab on the passive-avoidance test:

Mixed-design repeated measures ANOVA revealed a significant effect of training, $F(1,33) = 109.41$, $p < .001$, $\eta^2_p = .77$. There was also a significant overall difference between the three treatment groups, $F(2,33) = 20.88$, $p < .001$, $\eta^2_p = .56$. As expected the effect of training in Passive Avoidance test interacted significantly with the treatment groups, $F(2,33) = 18.90$, $p < .001$, $\eta^2_p = .53$. The significant interaction between training and test groups was followed by simple effects analysis. The simple effects analysis revealed a significant difference between control vs. UCMS and UCMS + Infliximab vs. UCMS groups (both $p < .001$) but not between control and UCMS + Infliximab groups ($p = .07$) during Day 2. The same results held after Holm-Bonferroni correction for multiple comparisons (separately for different training days) as well as the separate one-way ANOVA comparison of the performance observed in Day 2.
3.3. Effects of UCMS and infliximab on the morris water maze test:

The mixed design ANOVA analysis showed that escape latencies decreased significantly over four days of testing \(F(2,31, 76.26) = 31.16, p < .001 (\eta^2_p = .49)\). The between group comparisons also revealed a significant overall difference between different treatment groups, \(F(2,33) = 10.11, p < .001 (\eta^2_p = .38)\). As in the case of Passive Avoidance results, the effect of training on escape latency interacted with treatment groups, \(F(4,62, 76.26) = 3.46, p < .01 (\eta^2_p = .17)\). The simple effects analysis of the significant training day by treatment group interaction revealed a significant difference between chronic stress (UCMS) vs. control, and UCMS vs. UCMS + Infliximab groups for the last three days of testing (all \(p < .01\)). The same results held after Holm-Bonferonni correction for multiple comparisons (separately for different training days).

There was no difference between the control and UCMS + Infliximab during these training days. There were no other differences (all \(p > .41\)). There was no difference between any treatment groups during the first day of testing (all \(p > .14\)). Separate repeated measures one-way ANOVA comparisons of escape latencies between different training days revealed a significant effect for the control group \(F(3,33) = 13.69, p < .001 \eta^2_p = .55\), UCMS + Infliximab group \(F(3,33) = 27.40, p < .001 \eta^2_p = .71\) but not for the UCMS group \(F(1.66, 18.23) = 1.54, p = .24 \eta^2_p = .12\).

There was a significant overall difference between the three treatment groups in terms of the percentage of time spent in the correct quadrant in the probe trial \(F(2,33) = 30.20, p < .001, \eta^2_p = .65\). The post-hoc Tukey comparisons revealed significant differences between the control vs. UCMS and UCMS + Infliximab vs. UCMS groups (both \(p < .001\)) but not between control vs. UCMS + Infliximab groups \((p = .94)\). The percentage of time spent in the correct quadrant was then compared to the chance level of 25% separately for each group. This value was significantly higher than the chance level for both control group \((t(11) = 9.59, p < .001)\) and UCMS + Infliximab group \((t(11) = 9.33, p < .001)\) but not for the UCMS group \((t(11) = -.33, p = .75)\) Fig. 3.

3.4. Effects of UCMS, and infliximab on BDNF protein expression

The Kruskal–Wallis test showed that the BDNF levels differed significantly between the three groups both in CA1 region \(\chi^2(2, N = 24) = 14.04, p < .001\) and CA3 region of hippocampus \(\chi^2(2, N = 24) = 13.77, p < .01\). We then followed these significant overall effects with pairwise comparisons. The Mann–Whitney tests showed a significant difference between all three pairs in CA1 region, and control vs. UCMS and UCMS vs. UCMS + Infliximab groups in CA3 region (all \(p < .05\)). The same results held after Holm–Bonferonni correction for multiple comparisons Table 1 (separately for CA1 and CA3 regions) Fig. 4.

4. Discussion

Depression is a neuropsychiatric disorder primarily characterized by altered (negative) affective state. Importantly, the negative affective symptoms of depression are also coupled with pronounced cognitive deficits in the clinic [20]. In fact, due to the high coexistence of depression and cognitive deficits, the latter symptoms have been referred to as pseudo-dementia [21]. In addition to the cognitive deficits observed in depression where the symptoms are reversible with antidepressant treatment [22], depressive symptoms are also observed in Alzheimer’s disease (AD) [21], which is associated with progressive cognitive deficits. The strong coupling between the cognitive and affective symptoms of these disorders suggests commonalities in the neuroanatomical and neurochemical bases of cognitive and affective functions.
Earlier studies have revealed an important role of hippocampal formation in major depression (MD) [23,24]. Hippocampus is also one of the brain areas that is most affected by chronic stress [25], a common trigger/risk factor for disorders associated with emotional and cognitive deficits [25,26]. Consistently, experimental models have shown that chronic stress or stress hormones lead to cellular, molecular, and functional alterations in the hippocampus [25, CMS, 27 (UCMS)]. These findings in turn suggest that hippocampus might also be the primary structure that mediates the cognitive deficits observed in unpredictable chronic mild stress (UCMS) animal model of depression.

Our findings support the view that in the UCMS model, inflammation leads to reduction in the neurotrophic factors in the hippocampus and memory impairments and that these alterations can be prevented by the anti-TNF treatment. Specifically, our results showed that Wistar rats exposed to eight week-long UCMS treatment had (1) reduced memory performance in the Morris Water Maze and Passive Avoidance tests, (2) they had reduced BDNF expression in the CA1 and CA3 fields of hippocampus and (3) that systematic chronic Infliximab treatment rescued cognitive deficits as well as the reduction in BDNF expression induced by the UCMS. The first two sets of findings have been consistently supported by earlier studies. On the other hand, the therapeutic effects of chronic peripheral TNF inhibition (by a TNF-alpha blocker) on the behavioral and molecular alterations induced by the chronic stress constitute a novel finding.

The chronic mild stress models of depression captures the cardinal helplessness/despair and anhedonic symptoms of depression with high face, predictive, and etiological validity [28]. On the other hand, more recent approaches to the models of depression include the memory function deficits in addition to the typical affective alterations. Consistent with the known effects of stress on the hippocampus-dependent memory functions, animal studies that utilized spatial memory tests in the stress models of depression have shown that the acquisition and/or retention of spatial memories were negatively affected by the stress-manipulations [8,10,29–34]. These results are consistent with the findings of the current study regarding the MWM test.

Different from the MWM test, the Passive Avoidance learning was shown to involve hippocampal in addition to the amygdala function because of having contextual features in addition to fear-related factors [35–37]. Relatively few studies have used Passive Avoidance Test in the chronic mild stress models. One of these studies has shown that the PAT performance was not affected by the CMS or anhedonic behaviors [38]. On the other hand, other studies have shown that the disruption of PAT performance can exhibit strain-dependent differences [39-CMS], that the reduction in PAT performance was more pronounced in the ischemia-induced compared to the UCMS model of depression [40], and that alterations in PAT performance constitute a pronounced effect, that are reversible by various treatments [41-UCMS, 42-CMS]. In any case, the effects of stress on emotional memory function are not as clear as its known effects on spatial memory function. It was argued that stress might affect the fear memory at different stages of the memory function. For instance, even though stress enhances the consolidation of fear memories, it can block the retrieval processes [43]. Although, the PAT is a suitable test for evaluating the acquisition, consolidation, and retention of emotional memories, one cannot conclude which stage of memory function in this task is affected by the chronic treatments in our study.

The antidepressant effects of many agents and manipulations are correlated with the brain-derived neurotrophic factor (BDNF) in the hippocampus [44]. In the current study, the memory deficits of rats in the UCMS group were accompanied by the reduction in the level of BDNF expression in the CA1 and CA3 subfields of hippocampus. CA1 and CA3 subfields were chosen due their known

**Table 1**

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No expression (0), slight (1+), moderate (2+), strong (3+), very strong (4+) expression.
Fig. 4. Representative images illustrating BDNF expression (arrows) in the hippocampal formation. Control (a), UCMS (b) and UCMS + Infliximab (c) groups in CA1 region, and control (d), UCMS (e) and UCMS + Infliximab (f) groups in CA3 region. BDNF expression was decreased in UCMS in the both CA1 and CA3 regions of the hippocampus, whereas in UCMS + Infliximab group, BDNF expression was similar to those in the control group in the both regions. Scale bars: 50 μm.

involvement with the specific tasks utilized in the current study [35,45,46]. Studies that contained behavioral assessments have demonstrated (although not always linear) a relationship between the hippocampal BDNF levels and depression and/or memory scores [9,10,40,47] and a correlation between effectiveness of treatments and BDNF in the hippocampus [10,41,47]. For instance, Song et al. [47] showed that CMS as well as learned helplessness models of depression led to learning and memory deficits as assessed in Morris water maze and these deficits were accompanied by increased concentrations of the plasma corticosterone and lower levels of BDNF and CREB mRNA levels in the hippocampus. In the same study, repeated treatment with imipramine and fluoxetine ameliorated these cognitive deficits, and reduced the concentration of plasma corticosterone and increased the BDNF and CREB levels. The BDNF, one of the main determinants of neuroplasticity, has been argued to be regulated by various factors such stress hormones, monoamines, glutamatergic system, and inflammatory cytokines [48–50].

When evaluated within the framework of inflammatory hypothesis of depression, cognitive deficits associated with this disorder might be underlain by the effect of enhanced proinflammatory cytokines on the hippocampal function. Among the multiple neurochemical changes that occur in response to stress, excessive inflammation processes is thought to play a major role in stress-induced cognitive impairments. Several studies have reported that exposure to stress increased the hippocampal [9,34,51] and plasma TNF-α levels [52]. Accumulating evidence indeed supports a relationship between inflammatory cytokines and various types of learning and memory. For instance, Li et al. [9] observed that CMS procedure decreased the performance in the object recognition and object location tests, which was accompanied by increased plasma levels of proinflammatory cytokines (i.e., IL-1β, IL-6, and
TNF-α) in addition to higher plasma levels of HPA hormones [9]. The CMS procedure also decreased the bromodeoxyuridine (BrdU) positive cells and the expression of BDNF in dentate gyrus. In another study, Belarbi et al. [51] showed that the chronic infusion of lipopolysaccharide increased the gene expression of TNF-α and IL-1β in the hippocampus and the resultant chronic neuroinflammation impaired spatial learning and memory (including the MWM performance) but not hippocampus-independent novel object recognition performance. These spatial learning and memory deficits were reversed with the chronic administration of lipopolipidic TNF-alpha synthesis inhibitor (3,6-dithiothalidamide, DT), which brought TNF-α levels back to normal (but not IL-1β levels). DT administration further normalized the fraction of hippocampal neurons that expressed Arc, a plasticity-related immediate-early gene. These findings provide convergent evidence regarding the important role of proinflammatory cytokines in mediating the relation between depression and cognitive deficits via their detrimental effects on the hippocampus. Overall, these studies suggest that depression-related cognitive and memory deficits may represent the potential clinical correlates of increased cytokine production.

The most novel finding of this study is that chronic Infliximab treatment prevented the UCMS-induced memory disruption as well as the reduction in the expression of BDNF in the hippocampus. Importantly, these findings show that peripheral administration of an anti-TNF agent that in theory cannot enter the central nervous system, exhibited central nervous system-related responses in terms of molecular and behavioral end-points. A similar response profile was observed in our earlier studies that investigated the anti-depressant efficacy of the systematic anti-TNF alpha agents. However, the contemporary approaches do not conceptualize the central nervous system as isolated from the peripheral immune system. Although there is lack of clear understanding regarding its mechanisms of action, systematic inflammation has been consistently shown to be associated with the central nervous system, exhibited central nervous system-related responses in terms of molecular and behavioral end-points. A similar response profile was observed in our earlier studies that investigated the anti-depressant efficacy of the systematic anti-TNF alpha agents.

5. Conclusions

There are three major views regarding the etiopathogenesis of depression and these approaches might also explain the cognitive deficits associated with depression [50]. One of the traditional views is the monoamine hypothesis, which constitutes the basis of many contemporary therapists. The other two views that have been primarily developed based on animal studies, are the neurotrophin/neurogenesis and cytokine/inflammation hypotheses. The current study have shown that one of the inflammatory markers TNF-alpha is directly related to the hippocampal BDNF that is associated with neurogenesis as well as memory functions. These findings suggest that different approaches to depression should be evaluated within an overarching framework that encompasses the key assumptions of different views. The mechanistic understanding of such integration requires future studies.

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[25] C.D. Conrad, Chronic stress-induced hippocampal vulnerability: the role of estrogen and neurotrophin/neurogenesis and cytokine/inflammation hypotheses. The current study have shown that one of the inflammatory markers TNF-alpha is directly related to the hippocampal BDNF that is associated with neurogenesis as well as memory functions. These findings suggest that different approaches to depression should be evaluated within an overarching framework that encompasses the key assumptions of different views. The mechanistic understanding of such integration requires future studies.