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Original Research Article

An experimental study on the influence of metformin on monosodium glutamate-treated depressed Wistar albino male rats

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ABSTRACT

Background: The current experiment aimed to determine the antidepressant-like properties of metformin in a monosodium glutamate- induced depression model in Wistar albino male rats.
Methods: The subjects were subjected to depression induced using oral intake of 500 mg/kg of MSG over a period of 21 days. The experimental period was between day 9 and day 21, during which metformin and an antidepressant drug, the standard dose of imipramine, were administered. The sacrifice of animals was conducted on day 23, and biochemical analyses were performed on the supernatants of hippocampal and amygdaloid tissues. Statistical analysis was done with a significance of $p<0.05$.
Results: MSG exposure led to a high level of interleukin-6 (IL-6) and a low level of brain-derived neurotrophic factor (BDNF). Metformin and imipramine treatment led to a significant decrease in IL-6 levels and a significant increase in BDNF concentrations compared with the MSG-treated group ($p<0.001$). The results of metformin were similar to the impact of a standard drug, imipramine.
Conclusions: The observed study results indicate that metformin has antidepressant-like properties in MSG-induced depressed rats, which could be due to the inhibition of neuroinflammation and the promotion of neurotrophic support.

Keywords: Monosodium glutamate, Metformin, Imipramine, Interleukin-6, Brain-derived neurotrophic factor

INTRODUCTION

Depression is a complicated mental condition that is marked by the chronic mood, behavior, and cognitive dysfunction, which causes serious disability in the quality of life.[1] Major depressive disorder is more prevalent in the women than in men around the world, the disorder is also commonly comorbid with the chronic diseases such as the diabetes mellitus, cardiovascular diseases, and malignancies, making it difficult to treat and raising the disease burden.[2] Depression can lead to serious consequences such as committing suicide, unless it is detected and treated in the early stages, which explains such a therapeutic approach.[3] Monosodium glutamate (MSG) is a common, widely used flavour-enhancing ingredient in processed foods. Although MSG is considered safe within the allowable dosage, experimental reports have shown that long-term exposure to increased doses of the substance can cause neurotoxicity.[4]

Excitotoxic neuronal damage, oxidative stress and induction of neuroinflammatory pathways are the main mediators of these effects, which result in behavioural and mood changes in laboratory animals.[5] The use of 500mg/kg MSG has been proven to be a valid experimental model of inducing depressive-like behavior in rodents and is commonly utilized in investigating the neurobiological basis of depression.[6] One of the newcomers in the oral antidiabetic agent first-line therapy is metformin, which has been reported to have pleiotropic effects in addition to glucose control.[7] According to the emerging evidence, metformin has neuroprotective and antidepressant-like effects caused by regulating the levels of inflammatory mediators and enhancing energy homeostasis of neurons.[8] The medication has been known to stimulate AMP-activated protein kinase (AMPK), which is a major cellular metabolic and synaptic plasticity controller.[9] Neuroinflammation is a central process in the pathophysiology of depression, and the participation of high levels of pro-inflammatory cytokines (interleukin-6 (IL-6) in particular) is repeatedly observed in clinical and experimental research. Metformin has been demonstrated to inhibit the synthesis of inflammatory cytokines, such as IL-6, and so it can suppress neuroinflammatory responses. Aiming at these observations, the current study was aimed at testing the antidepressant efficacy of metformin in an MSG-induced depressive model in Wistar albino male rats by measuring the alterations in the levels of BDNF and IL-6 in the hippocampus and amygdala.

METHODS

Study design and animals

This experimental study was conducted using healthy adult Wistar albino male rats (250-300 g). Animals were housed under standard laboratory conditions with controlled temperature, humidity, and a 12-hour light–dark cycle, with free access to standard pellet diet and water.

Ethical approval

The study protocol was approved by the Institutional Animal Ethics Committee of K.S. Hegde Medical Academy (Approval No. 115/1999) and conducted in accordance with CPCSEA guidelines.

Drugs and chemicals

Monosodium glutamate and metformin were procured from Sisco Research Laboratories Pvt. Ltd., India. Imipramine tablets were obtained from Novartis Pharmaceuticals Pvt. Ltd., India. ELISA kits for IL-6 and BDNF estimation were purchased from Sigma-Aldrich, India.

Experimental design

The animals were randomly placed into six groups with six rats per group.

Group I (control): normal saline (1 ml, orally).

Group II (positive control): MSG (500 mg/kg, orally once daily) for 21 consecutive days.

Group III (metformin alone): Metformin was administered (500 mg/kg, orally) from day 9 to 21.

Group IV (imipramine alone): From day 9 to day 21 administered imipramine (15 mg/kg, orally).

Group V (MSG + metformin): MSG was administered for 21 days along with metformin from day 9 to 21.

Group VI (MSG + imipramine): MSG was administered for 21 days along with imipramine from day 9 to 21.

The treatment period from day 9 to 21 was selected to evaluate the therapeutic effect of metformin after the establishment of depressive-like changes. The medications were renewed and given orally after being diluted with normal saline. Metformin and imipramine doses were chosen on the basis of the human equivalent dose and using prior experimental investigations.[10]

Collection and preparation of tissues

The sacrifice of animals was carried out on the 23rd day of the experiment under proper anesthesia. The brain was promptly dissected, and the hippocampus and the amygdala were removed. The tissues were homogenized in ice-cold buffer, and the homogenates were centrifuged to extract the supernatant, which was stored at -20°C pending biochemical analysis.

Interleukin-6 (IL-6) estimation

The quantity of IL-6 in the hippocampal tissue was determined by a commercially available ELISA kit based on the instructions of the manufacturer. Tissue homogenates were made in the presence of a relevant buffer containing protease inhibitors to avoid protein degradation. A standard calibration curve was used to determine the concentration of IL-6, and was brought to the protein content.[11] The brain-derived neurotrophic factor (BDNF) is estimated. The amygdala BDNF was determined by a sandwich ELISA tool, utilizing monoclonal antibodies to BDNF. The Bradford method was used to determine the total protein concentration using bovine serum albumin as the reference. BDNF data have been represented as a result of division by overall protein content.[12]

Statistical analysis

The results were provided in the form of mean ± standard deviation (SD). Graphpad Prism software (version 5.0) was used to do a statistical analysis. To compare the difference between groups, one-way analysis of variance

(ANOVA) was used, followed by a Tukey post-hoc test. A p-value of below 0.05 was taken to be significant.

RESULTS

Impact on amygdala BDNF concentrations

The amount of amygdala brain-derived neurotrophic factor (BDNF) was found to be lowered in the positive control group exposed to monosodium glutamate (MSG) and was significantly lower in this group compared to the normal control group ($p<0.05$) (Figure 1), which shows that the neurotrophic support is impaired.

Treatments with metformin and imipramine, when administered to MSG treated animals, saw a significant rise in the level of BDNF relative to the positive control group ($p<0.001$). The metformin alone, the imipramine alone and no treatment with the normal control did not show any statistically significant change in animals.

Influence on hippocampal IL-6 concentrations

The levels of hippocampal interleukin-6 (IL-6) in the positive control group, MSG-treated, had significantly increased over the normal control group ($p<0.0001$) (Figure 2), indicating severe neuroinflammation. Metformin or imipramine in animals with MSG had a high reduction in the level of IL-6 in relation to the positive control ($p<0.05$). The animals treated with metformin alone or imipramine alone did not show any significant changes in the IL-6 levels.

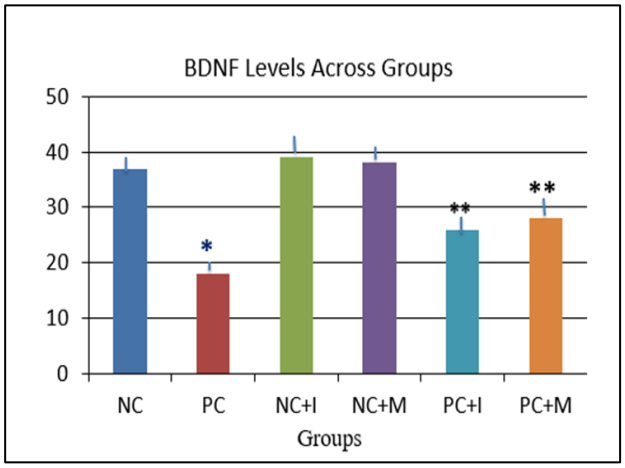

Figure 1: Effect of various treatments on amygdala brain-derived neurotrophic factor levels (*p<0.05 compared to control; **p<0.001 compared to positive control); n=6 in each group; data are represented as mean ± SD.

Effect of metformin and imipramine in comparative effect

The treatment with metformin led to a considerable reduction in IL-6 and a considerable rise in BDNF levels in MSG-induced depressed rats, and the responses to the metformin were similar to those of the antidepressant drug imipramine.

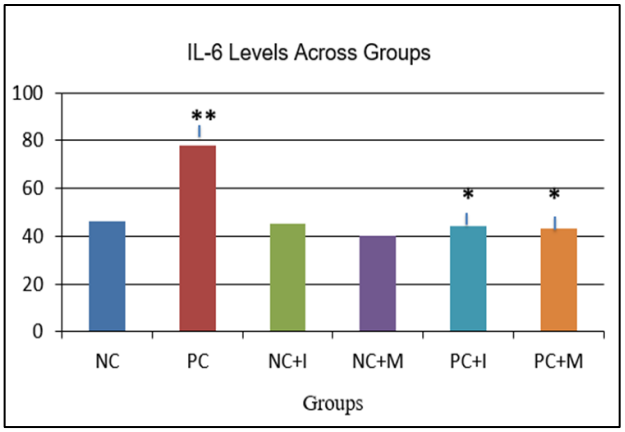

Figure 2: Effect of various treatments on hippocampus IL-6 levels (*p<0.0001 compared to control; **p<0.05 compared to positive control); n=6 in each group; data are represented as mean ± SD.**

DISCUSSION

Chronic diseases such as obesity, diabetes, hypothyroidism and cancer have been attributed to depression. Because depressed patients have a high risk of committing suicide, safe and effective antidepressant treatment should be established. The MSG-induced depression model was evaluated by estimating IL-6 levels in the hippocampus and BDNF levels in the amygdala following metformin treatment. The neurotrophic factors include BDNF, which is associated with neuronal plasticity and recovery from depression. The sluggish clinical profile is linked to the reality that numerous antidepressants elevate the BDNF within the duration of one week of treatment. Metformin can also enhance BDNF expression via the AMPK-CREB pathway and histone acetylation of BDNF promoters and has been suggested to mediate a neurotrophic effect triggering synaptic plasticity and neuronal survival.[13]

Neuroinflammation is another major cause of depression, and the quantity of IL-6 is never low whenever depression is involved. Metformin has been reported to exert significant anti-inflammatory effects: the drug inhibited central and systemic IL-6 synthesis in LPS-induced models and reduced oxidative stress and sickness-like behaviour caused by the activation of the AMPK.[14] It also inhibits the NLRP3 inflammasome and IL-1b release in chronic stress models, which favours its anti-inflammatory antidepressant effects.[15]

Metformin also has other protective effects on the brain besides reducing inflammation. It inhibits the depressive-like behaviour through the TRPV1/NLRP3 pathway and the microglial response in the allergic rhinitis models, indicating that it can inhibit the central immune responses.[16] The AMPK stimulation also has an extra role

in metabolic control, neuronal viability, and CREB phosphorylation, as well as BDNF transcription. Besides, the action of metformin in suppressing IL-6 and TNF-alpha is AMPK-dependent, and it is executed by suppressing NF-κB signaling by ATF-3.[17]

Metformin demonstrated significant antidepressant-like activity in MSG-induced depressed Wistar albino male rats by reducing neuroinflammation and enhancing neurotrophic support. Further studies involving behavioral assessments and clinical evaluation are warranted to establish its therapeutic potential in depression.

CONCLUSION

The present study demonstrates that metformin exhibits significant antidepressant-like activity in monosodium glutamate-induced depression in Wistar albino male rats. This effect is likely mediated through reduction of neuroinflammation (decreased IL-6 levels) and enhancement of neurotrophic support (increased BDNF levels). The findings suggest that metformin may have potential as an adjunct therapeutic agent in the management of depression. However, further clinical studies are required to validate these results in humans.

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