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Research Article

Effect of Metformin in Acute Mice Models of Depression

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Abstract
There exists a controversy in the causality of depression and diabetes. Depression is known to cause physical illness like diabetes and vice versa. This controversy has also been extended to the therapeutic scope of metformin in improving depressive symptoms among diabetic patients. The reported claim on the potential antidepressant activity of metformin is yet to be validated. The aim of the study was to investigate the antidepressant activity of metformin in acute models of depression. The antidepressant activity of metformin (100, 200 and 400 mg/kg) was investigated using the tail suspension test (TST) and the forced swim test (FST) in mice. The effect of metformin on exploratory behaviour was assessed using open field test (OFT). Metformin did not significantly alter the immobility time of mice in both TST and FST. Sertraline significantly ($p \leq 0.05$ and $p \leq 0.01$) decreased IMT in both TST and FST respectively. Metformin non-significantly alter number of line cross (NLC) significantly ($p \leq 0.01$) decreased number of rearing (NR) only at 100 mg/kg. Diazepam significantly ($p \leq 0.01$) increased NLC and significantly ($p \leq 0.05$) decreased NR in OFT. Metformin does not possess antidepressant-like activity.

Keywords: depression; metformin; acute models, immobility time; exploration

1.0 INTRODUCTION

Depression is a mental disorder that is associated with a gradual and nearly unnoticeable withdrawal from an active way of life and enjoyment of living of an individual [1]. It is caused by a combination of genetic, psychological, environmental and biological factors [2]. A causal relationship exists between depression and physical illness. People that are physically unwell have an increased risk of developing depression [3,4]. Depression worsens or even initiates cardiovascular [5, 6], cancer [7], Parkinson disease and diabetes mellitus [8]. The pathophysiology underlying the inter-relationship between depression and diabetes is complex and poorly understood [9,10]. The psychological stress, pains, decreased quality of life, complexity of management may contribute to the increased incidence of depression in diabetes. People with adult onset diabetes have a 25% chance of having depression and depression also affects about 70% of patients with diabetic complications [11,12,13,14].

The association between depression and decreased adherence to oral hypoglycaemic agent and the reported increase in the therapeutic scope of metformin beyond its antihyperglycemic effect have become a relevant clinical issue. For example, metformin has been reported to reduce risk of cancer [15,16] improve cognitive function [17] and has

shown some therapeutic potential in Parkinson disease [18]. Long term use of metformin was found to remarkably decrease symptoms of depression in type 2 diabetic mellitus patients [19]. In spite of studies supporting the clinical efficacy of metformin in depression, there has been a considerable confusion between diabetes-related distress and depressive symptoms which stem from inadequate measurement that gives a clear distinction between clinical depression and nonpsychiatric emotional distress [20]. Based on literature report, metformin may possess antidepressant-like activity. This study therefore, aimed at investigating the antidepressant-like activity of metformin in acute models of depression.

2.0 MATERIALS AND METHODS

Drugs: Sertraline (Global Pharmaceuticals Ltd., England), metformin (Merck Pharmaceuticals Ltd., UK) diazepam (Valium^{R} Roche, Switzerland).

Animals

Swiss Albino mice of both sexes weighing 18-25g were obtained from the Animal House Facility of the Department of Pharmacology and Toxicology, Igbinedion University Okada. The mice were kept in a propylene cage, fed with standard animal feed and allowed free access to water. Animals were acclimatised for five days before experimentation and the experiment was carried out between the hours 8:00 to 6:00 hours. Experimental protocols were followed according to the International standard for care and use of laboratory animals.

Antidepressant Study

Tail suspension test

The method described by Sterul *et al* [21] was adopted for the study. Thirty mice were randomly divided into five groups of six animals each. Group 1 received 10 mL/kg distilled water, group 2 received 10 mg/kg sertraline while group 3, 4 and 5 received 100, 200 and 400 mg/kg metformin respectively per oral. One hour after drug administration each mouse was suspended on the edge of the shelf 68 cm above a table top by an adhesive tape placed approximately 1 cm from the tail end for a period of six minutes. The immobility time defined as the time the animal hang passively and completely motionless was taken and recorded [21].

Forced Swim Test

The method described by Alpermann *et al.,* [22] was adopted for the study. Thirty mice were randomly divided into five groups of six animals each. Group 1 received 10 mL/kg distilled water, group 2 received 10 mg/kg sertraline while group 3, 4 and 5 received 100, 200 and 400 mg/kg metformin respectively per oral. One hour after drug administration each mouse was placed in a plexiglass cylinder of 40 x 18 cm filled with water to the height of 15 cm at room temperature. Animals were allowed to swim for 5 minutes and immobility time defined as the time animal remains almost motionless with the head above the water was taken and recorded [22].

Exploratory Study

Open Field Test

The method described by Kalueff *et al.,* [23] was adopted for the assessment of spontaneous locomotor (horizontal) and exploratory (vertical) activity. It consisted of plywood (72 x 72 x 36 x 36 cm), one of the walls is a clean transparent plexiglass for visibility. The base was divided into 16 squares (18 x 18 cm) with blue marker and covered with transparent plexiglass [24].

Thirty mice were randomly divided into five groups of six animals each. Group 1 received 10 mL/kg distil water, group 2 received 1.5 mg/kg diazepam while group 3, 4 and 5 received 100, 200 and 400 mg/kg metformin respectively per oral. One hour after drug administration each mouse was placed at the centre of the open field arena and allowed to explore for five minutes. The number of lines crossed and number of rearing were observed and recorded.

Statistical Analysis

Data were collected and analysed using One-way analysis of variance followed by Dunnett's post-hoc test in statistical package for social sciences (SPSS).

3.0 RESULTS

Tail Suspension Test (TST)

Metformin at all doses tested did not significantly alter the immobility time of mice compared to the distilled water group in the tail suspension test. Sertraline significantly ($p \leq 0.01$) decreased immobility time (figure 1).

Forced Swim Test

Metformin at all doses tested did not alter the immobility time of mice while sertraline significantly ($p \leq 0.01$) decreased immobility time compared to the

distilled water group (figure 2).

Open Field Test

Metformin did not significantly alter the number of lines crossed at all doses tested. Number of rearing was significantly ($p \leq 0.05$) decreased only at 100 mg/kg. Diazepam significantly ($p \leq 0.01$) increased number of lines crossed and significantly ($p \leq 0.05$) decreased number of rearing in the open field test (Table 1).

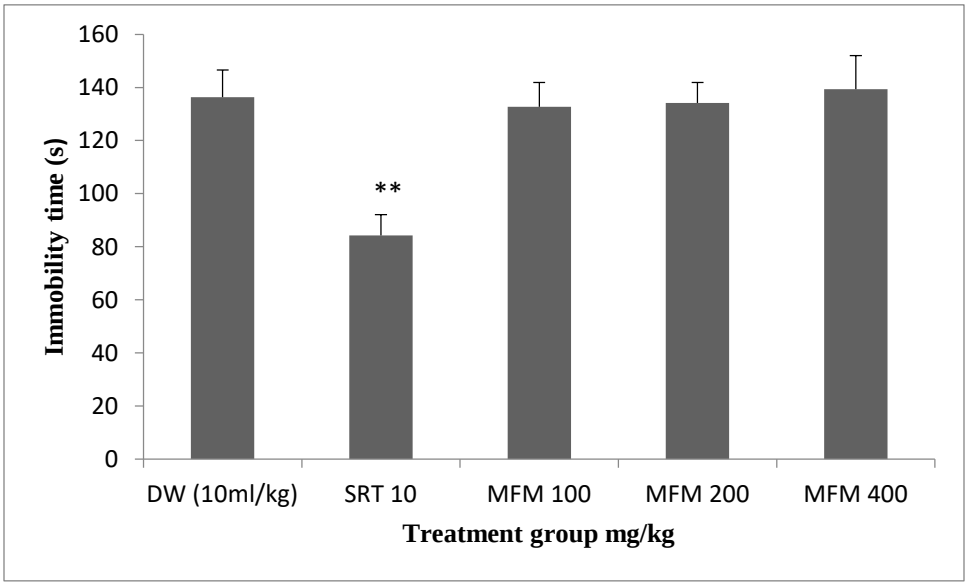

Figure 1: Effect of Metformin on Immobility Time of Mice in Forced Swim Test

Data presented as mean ± S.E.M; n=6; one-way ANOVA; ***p ≤0.01* compared to distilled water followed by Dunnett's post hoc test. DW = distilled water; SRT= sertraline; MFM = metformin

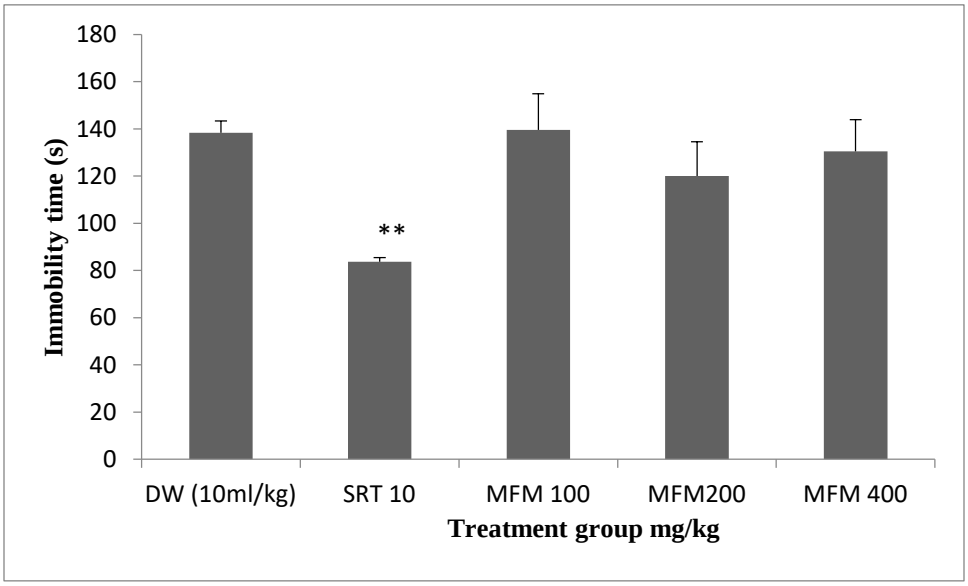

Figure 2: Effect of Metformin on Immobility Time of Mice in Tail Suspension Test

Data presented as mean ± S.E.M; n=6; one-way ANOVA; ***p ≤ 0.01* compared to distil water followed by Dunnett's post hoc test. DW = distilled water; SRT= sertraline; MFM = metformin

Table 1: **Effect of Metformin on Number of Lines Crossed and Rearings of Mice in an Open Field Test**

Groups (mg/kg)	NLC	NR
DW (10 mL/kg)	42.67 ±4.54	21.00 ±1.86
DZP 1.5	78.33* ±8.73	8.5* ±1.31
MFM 100	43.00 ±6.44	13.00* ±2.93
MFM 200	33.33 ±1.87	17.67 ±1.78
MFM 400	44.67 ±3.89	22.33 ±2.04

Data presented as mean ± S.E.M; n=6; One-way ANOVA; *$p<0.05$, compared to distil group water followed by Dunnett's post hoc test. DW = distilled water; SRT = sertraline; MFM = metformin; NLC = number of lines crossed; NR = number of rearings

4.0 Discussion

The inter-relationship between depression and diabetes is well reported. However, the pathophysiology underlying this inter-relationship is poorly understood [25, 26]. This has led to a considerable confusion between diabetes-related emotional distress and depressive symptoms which also extend to metformin improving depressive symptoms among diabetic patients [19, 14]. The proposed antidepressant-like effect of metformin is yet to be validated thus necessitates this study.

In the forced swim test and tail suspension test metformin could not decrease the immobility time compared to the control which implies the lack of antidepressant activity. Sertraline significantly decreased the immobility time in tail suspension test and forced swim test. The tail suspension and forced swim tests are acute behavior despair model of depression, employed in rodents to predict antidepressant potential of drugs by decreasing immobility time [27]. Immobility time of mice subjected to an inescapable stress in tail suspension and forced swim test represent a state of despair or hopelessness typical of depressive symptom in human [28,29]. Antidepressants and newer compounds with potential antidepressant activity decrease the immobility time in these tests. This can be correlated to an improvement in the state of despair in clinical depression.

The lack of antidepressant-like activity of metformin in the acute models of depression may suggest need for clear distinction between depressive symptoms and nonpsychiatric emotional distress in diabetes. This may have led to the claim of metformin improving depressive symptoms among diabetic patients. It is therefore possible that the improvement in depressive symptoms among diabetic patients using metformin may result from proper diabetic control that consequently improved diabetic emotional distress. Almost all available antidepressant act through the monoamine neurotransmission and are able to decrease immobility time in tail suspension and forced swim test [30]. This may also imply that the acute models of depression is more specific for screening agents acting through monoaminergic system despite involvement of other pathways in the pathophysiology of depression and its causal relationship with diabetes. The dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is hypothesised to be a biological association between depression and diabetes [30]. The HPA is activated by a wide variety of stressful stimuli with resultant increase in cortisol level, autonomic activity and activation of the proinflammatory cytokines. These all lead to diabetes mellitus and depression through alteration in the normal physiological processes [31].

Drugs with psychostimulants and central nervous system depressants activity can affect the immobility time thereby creating a false positive or negative effect. The open field test was employed to rule out this effect. In the open field test, metformin could not significantly alter the number of lines crossed which implies lack of stimulating or sedating effect. Diazepam significantly increased the number of lines crossed due to its anxiolytic effect. Metformin could not significantly alter the number of rearings except at 100 where it significantly decreased the number of rearings. The inability of metformin to alter the number of rearings may be due to lack of central nervous depressant activity. Diazepam significantly decreased the number of rearings due to its anxiolytic effect.

Conclusion

Metformin possesses no antidepressant-like activity in acute models of depression suggesting that it may not be acting through monoaminergic neurotransmission. The reported clinical improvement in depressive symptoms may result from an improvement in diabetic control possibly via other mechanism.

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Conflict of Interest

There is no conflict of interest

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