single 50 mg/kg dose of intravenous streptozotocin administration. The experimental protocol was approved by the Anadolu University Animal Experiments Local Ethics Committee. Effects of 7 and 14 days agomelatine (40 and 80 mg/kg) administration on hyperglycemia were assessed by measuring fasting blood glucose levels and conducting oral glucose tolerance tests (OGTT). Changes in metabolic parameters such as food and water consumption and excretion of urine and feces were monitored using metabolic cages. Weekly changes in the body weights of animals were recorded as well. The effect of agomelatine treatment on hyperalgesia occurring due to peripheral diabetic neuropathy was examined using Randall-Selitto (mechanical noxious stimulus), Hargreaves (thermal nociceptive stimulus), and cold-plate (4°C, thermal nociceptive stimulus) tests. The dynamic plantar aesthesiometer, which measures the threshold values for mechanical stimuli, was used for allodynia studies; in addition, thermal allostynia was evaluated using warm-plate (38°C) test. Agomelatine administration was initiated 4 weeks after the induction of diabetes to permit development of nociceptive perception deficits in rats.

**Results:** Subacute administration of agomelatine did not cause any alterations in the blood glucose levels or metabolic parameters of diabetic rats with respect to the untreated diabetic animals. Moreover, body weights of diabetic rats were not affected by the agomelatine treatment. In contrast, subacute administration of agomelatine caused a significant increase in the reduced paw-withdrawal threshold, decreased paw-withdrawal latency and shortened reaction period of diabetic rats. Data obtained from OGTT, as well as blood glucose and metabolic cage measurements, suggest that agomelatine treatment does not induce a significant anti-hyperglycemic effect. On the other hand, findings of neuropathy tests indicated that subacute administration of agomelatine at doses of 40 and 80 mg/kg restored hyperalgesia and allodynia responses of the diabetic rats to the levels of normoglycemic control animals. Anti-hyperalgesic and anti-allodynic effects of this new antidepressant were comparable to the reference drug pregabalin (10 mg/kg).

**Conclusion:** Considering its antidepressant, anxiolytic and antinociceptive effects, it seems that agomelatine may propose clinical advantages for providing an ability to avoid polypharmacy in treatment of painful diabetic neuropathy and diabetes-induced affective disorders such as depression and anxiety.

**Keywords:** diabetes mellitus, agomelatine, neuropathy

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**Objective:** The aim of this study was investigating the potential effect of subacute mianserin administration on diabetes-induced chronic hyperglycemia and metabolic alterations.

**Methods:** Male Wistar rats of the same age (weight: 250-300 g) were used for the experiments. Diabetes was induced by a single 50 mg/kg dose of intravenous streptozotocin (STZ) administration. Effects of 14 days mianserin (30 and 45 mg/kg) administration on hyperglycemia arising in 6-week diabetic rats were assessed by conducting oral glucose tolerance tests (OGTT) and by measuring glycated hemoglobin (HbA1c) levels. Changes in metabolic parameters such as food and water consumption and urine and feces excretion were observed using metabolic cages. Body weights of the animals were recorded weekly. Possible effect of mianserin treatment on Ins1 mRNA expression of diabetic rats was evaluated by real-time polymerase chain reaction (PCR) method. The experimental protocol was approved by the Anadolu University Animal Experiments Local Ethics Committee.

**Results:** Fourteen-days subacute administration of mianserin did not alter the OGTT results or HbA1c levels of normoglycemic animals. Similarly, mianserin caused significant alterations neither in the measured metabolic parameters nor in the body weights of normoglycemic rats. On the other hand, subacute administration of this drug to the diabetic animals significantly reduced the augmented HbA1c levels with respect to the untreated diabetic groups. Further, mianserin treatment caused significant reduction in the increased urine discharge, fecal output, water, and food consumption characteristic of diabetic animals. Weight loss of diabetic animals was also improved. With regard to the anti-hyperglycemic effect, mianserin administrated at a dose of 30 mg/kg was found to be as effective as the reference drug metformin (dose, 1g/kg). Moreover, our real-time PCR results indicated that Ins1 mRNA expression levels of diabetic rats significantly decreased with respect to the normoglycemic rats, as expected. Mianserin administration significantly increased the reduced
levels of Ins1 gene expression in diabetic animals. Our data obtained from this study indicated that subacute administration of mianserin has a remarkable anti-hyperglycemic effect on STZ-induced long-term hyperglycemia. Further, this drug has a notable beneficial effect on chronic hyperglycemia-induced polydipsia, polyuria, polyphagia and weight loss. The observed anti-hyperglycemic effect of mianserin in this study seems to be mediated by an increase in insulin synthesis. Nevertheless, additional studies, such as examining the alterations in expressions of other related genes or measuring the levels of synthesized insulin by Western-blot method, are needed to verify this idea.

**Conclusion:** To the best of our knowledge, this is the first study to show that the anti-hyperglycemic effect of mianserin, an atypical antidepressant, in the experimental diabetes model was comparable to those of the reference drugs metformin. Considering that mianserin simultaneously exhibits antidepressant and anti-hyperglycemic effects, it seems that this drug could have an additional advantage for diabetic patients for treating the mood disorders caused by diabetes.

**Keywords:** anti-hyperglycemic, Ins1 mRNA expression, mianserin

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[Abstract:0681] **Biological psychiatry and neuroscience**

**Antidepressant-like effects of quercetin in mice: evidence for the involvement of monoaminergic mechanisms**

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**Objective:** Recent evidence suggests that quercetin, which has the structure 3,3',4',5,7-pentahydroxyflavone, exhibits several central nervous system (CNS)-related activities like antinociception and cognitive enhancements as well as antidepressant-like and anxiolytic-like effects etc. In this study, we aimed to investigate the possible mechanism underlying the antidepressant-like effect of quercetin.

**Methods:** Adult BALB/c female mice, weighing 30–35 g, were used for the experiments. The animals were housed in a room with a controlled temperature (25±1°C) and photoperiod (12-h light/dark cycle, with lights being switched on at 08.00 AM). Temperature, sound levels, and light conditions were not altered during the course of the experiments. The antidepressant-like activity of quercetin (100 mg/kg, intraperitoneally) was evaluated by modified forced swimming and tail suspension tests, which are widely used behavioral despair models for anti-depressant drug screening studies. Additionally, the spontaneous locomotor activities of the mice were assessed using the activity cage apparatus. To determine the mechanisms underlying the antidepressant-like effect of quercetin, mice were treated with different pharmacological agents. A possible participation of the serotonergic system in the pharmacological effect of quercetin was investigated using p-chlorophenylalanine methyl ester (inhibitor of serotonin synthesis, PCPA), and the probable contribution of the catecholaminergic system was examined using α-methyl-para-tyrosine methyl ester (inhibitor of catecholamine synthesis, AMPT). Statistical analyses were performed using GraphPad Prism 6.01 software (GraphPad Software, San Diego, CA, USA). Comparisons between the experimental groups were performed either by one-way ANOVA followed by Tukey's test or two-way ANOVA followed by the Bonferroni post hoc test. The experimental protocol was approved by the Local Ethical Committee on Animal Experimentation of Anadolu University, Eskisehir, Turkey.

**Results:** In both modified forced swimming and tail suspension tests, immobility time of the mice was significantly reduced by quercetin administrations (100 mg/kg i.p.), indicating the antidepressant-like activity of this phenolic compound. In the activity cage tests, quercetin administration did not change the total number of horizontal or vertical activities indicating that the observed antidepressant-like effect was not affected by probable changes in the locomotor activity.

Data obtained from the mechanistic studies showed that the anti-immobility effect of quercetin in the tail suspension test was reversed with both AMPT and PCPA administrations. This finding provides evidence that the anti-depressant-like effect of the compound is related with an increase in the serotonin and catecholamine levels in the CNS.

**Conclusion:** To the best of our knowledge, this is the first study to show the underlying mechanisms of the anti-depressant-like effect of quercetin. Although our results are preliminary, further studies with specific receptor antagonists are expected to clarify possible involvement of other receptors in the antidepressant-like effect of quercetin.

**Keywords:** modified forced swimming test, quercetin, tail suspension

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