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Pitolisant protects mice chronically treated with corticosterone from some behavioral but not metabolic changes in corticosterone-induced depression model

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ABSTRACT

Purpose: Histamine H_3 receptor ligands may have antidepressant and anxiolytic effects. They can also compensate for metabolic disorders, which affect glucose or triglyceride levels. In previous studies, we have shown that pitolisant, a histamine H_3 receptor antagonist/inverse agonist and σ1 receptor agonist, prevented the development of certain metabolic and depressive-like disorders in mice that have been treated chronically with olanzapine.

Methods: As a continuation of our previous experiments, this study aimed to investigate the antidepressant- and anxiolytic-like activity of pitolisant in mice using the corticosterone-induced depression model. The forced swim and the elevated plus maze tests were used as behavioral endpoints. We also studied the effect pitolisant had on the level of acetoacetic acid in the urine as well as the glucose tolerance and body weight of the mice that had been administered corticosterone.

Results: Pitolisant (10 mg/kg b.w.) did not prevent depressive-like behavior in mice during the chronic corticosterone administration but did counteract anxiety-like behavior, whilst fluoxetine (10 mg/kg) was shown to protect the mice from both of these behaviors. None of the treatments that were used in the study showed an effect on the locomotor activity of the mice. Pitolisant did not prevent an increase in acetoacetic acid levels in the urine, nor did it improve glucose tolerance in the tested mice.

Conclusion: Although literature data indicates that there is significant potential for finding an antidepressant and anti-diabetic drug among the histamine H_3 and σ1 receptor ligands, in our study, pitolisant was shown to only slightly compensate for corticosterone-induced abnormalities. However, further research will be required to study pitolisant's anxiolytic-like activity.

1. Introduction

Endogenous glucocorticoids are naturally occurring stress hormones that are secreted by the adrenal glands (Wong et al., 2016). As a response to stress, the hypothalamic–pituitary–adrenal axis (HPA axis) is activated, resulting in a cascade of neuroendocrine biochemical events. This cascade includes the release of corticotropin-releasing factor (CRF) from the hypothalamus, which, in turn, causes the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary. This ultimately results in the secretion of glucocorticoids from the adrenal glands into the circulatory system (in the form of cortisol in humans and corticosterone in rodents). Under normal conditions, the blood glucocorticoid level is tightly regulated by a negative feedback mechanism (Gong et al., 2016).

Depression and anxiety occur in over 50% of patients with Cushing's syndrome (Dimopoulou et al., 2013) and up to 20% of patients who receive exogenous glucocorticoids for immunosuppressive therapy (Kenna et al., 2011). Chronic glucocorticoid administration also promotes depressive-like and anxiety-like behaviors in animals (Sterner and Kalynchuk, 2010). Various compounds with antidepressant-like activity have been shown to significantly reverse the behavioral changes which are induced by corticosterone administration (Crupi

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et al., 2010; Huang et al., 2011; Mao et al., 2012).

Glucocorticoids also cause metabolic disturbances by acting directly on different tissues, e.g.: fat, liver, and kidneys. They promote gluconeogenesis in the liver and can cause hyperglycemia, insulin resistance and glucose intolerance; they can also stimulate the differentiation of pre-adipocytes into mature adipocytes, which increases lipolysis, in turn releasing free fatty acids (Ferris and Kahn, 2012; Fransson et al., 2013). Both endogenous and exogenous glucocorticoids have been used to induce metabolic syndrome in animal models (Wong et al., 2016).

Antidepressant drugs can enhance glucocorticoid receptor-mediated inhibition of the HPA axis by increasing the expression of the glucocorticoid receptor (GR), this leads to a decrease in the level of cortisol/corticosterone (Budziszewska, 2002). Sigma-1 receptor (σ1R) deficiency causes down-regulation of the GR by reducing protein kinase C phosphorylation; this attenuates the GR-mediated feedback inhibition of the HPA axis and facilitates the stress response of the HPA axis, leading to the production of depressive-like behaviors (Di et al., 2017). σ1R is highly expressed in regions of the brain that are involved in emotion and neuropsychiatric disorders (Hayashi and Su, 2004), and σ1R agonists are a class of drugs used for the treatment of depression (Urani et al., 2001) and anxiety (Longone et al., 2011). The antidepressant-like activity of σ1R ligands can be directly connected with the GR function (Skuza et al., 2008). Furthermore, σ1R agonists enhance the functionality of the *N*-methyl-D-aspartate (NMDA) receptor, which controls various neuronal functions, including synaptic plasticity (Su et al., 2016), they can also increase dopaminergic neurotransmission in certain brain areas (Garcés-Ramírez et al., 2011). Activation of this receptor could also mitigate reactive oxygen species accumulation, possibly through the modulation of reactive oxygen species-neutralizing proteins (Nguyen et al., 2015). The properties mentioned above may be associated with the beneficial effects of σ1R agonists on behavioral disorders; therefore, stimulation of σ1R appears to be a good starting point in the search for new antidepressant drugs. Some studies demonstrate that σ1R agonists can modulate the activities of neurotransmitter systems, signaling pathways, and the brain regions implicated in the pathophysiology of depression (Fishback et al., 2010). σ1R agonists have also been shown to decrease the immobility time in both the tail suspension test and the forced swim test in mice (Ukai et al., 1998; Urani et al., 2001; Skuza and Rogóż, 2002).

Histamine plays a significant modulatory role in starting the neuroendocrine response to stress, for example, the release of several pituitary hormones such as ACTH (Kjaer et al., 1992). The histamine H_3 receptor (H3R) was identified pharmacologically as a presynaptic autoreceptor, which regulates the release of histamine from histaminergic neurons (Arrang et al., 1983). The released histamine decreases the further release of histamine, by affecting the presynaptic H_3 auto- or heteroreceptor and also inhibits the release of various other neurotransmitters (Singh and Jadhav, 2013). Several studies have demonstrated that activation or inactivation of the histamine receptors appear to exert a modulatory role in the regulation of the blood glucose level (Sim et al., 2014). H3R may regulate glucose levels directly through the release of insulin (Henry et al., 2011). This receptor is expressed in mouse beta cells (Nakamura et al., 2014) and is a potential target for the pharmacological treatment of glucose intolerance or diabetes (Henry et al., 2011).

Pitolisant is one of two currently available drugs (the other being betahistine) that works by acting on H3R - an antagonist (K_i = 1.0–2.4 nM)/inverse agonist (EC_{50} = 1.5 nM) (European Medicines Agency, 2015). Pitolisant was not specific for H3R over σ1R and σ2 receptors (σ2R). Pitolisant binds to the human σ1R with a subnanomolar Ki (Ki = 0.5 nM). It shows functional activity on σ1R-mediated calcium flux, demonstrating agonism with an EC_{50} of 402 nM. The in vitro assays showed that pitolisant binds to σ2R with a Ki of 6.5 nM and an IC_{50} of 8.55 nM. In a σ2R-mediated calcium flux functional assay, pitolisant did not elicit agonist activity but behaved as an antagonist since it decreased haloperidol-induced calcium release with an IC_{50} of 10 μM (European Medicines Agency, 2015). In our previous studies, we have shown that this drug may reduce depressive-like and metabolic disorders induced by the repeated administration of olanzapine (Dudek et al., 2016). Repeated administration of pitolisant has also been shown to improve glucose tolerance in obese mice (Kotańska et al., 2018). In this study, we aimed to examine whether pitolisant could reduce the behavioral and/or metabolic disorders caused by chronic corticosterone administration in mice.

2. Materials and methods

2.1. Animals

Adult male mice (CD-1, 18–21 g) were used for this experiment. The animals were purchased from the Animal House at the Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland. The mice were housed in a plastic cage maintained at room temperature (22 ± 2 °C), on a 12 h light/dark cycle (the lights came on at 7:00 a.m. and went off at 7:00 p.m.). During the habituation period, all mice had free access to their standard laboratory pellets and tap water. All behavioral procedures were performed between 9 a.m. and 2 p.m. Each experimental group consisted of 8 animals that had been randomly selected. After the experiment, the mice were killed by cervical dislocation. All experimental procedures were carried out under EU Directive 2010/63/EU and approved by the Local Ethics Committee for Experiments on Animals at the Jagiellonian University in Krakow, Poland (approval number: 45/2017).

2.2. Drugs

Pitolisant was synthesized in the Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland. Pitolisant or fluoxetine (Sigma, Germany) were dissolved in 1% Tween 80 and administered intraperitoneally (i.p.) at a volume of 10 ml/kg. The doses of pitolisant (10 mg/kg b.w./day) and fluoxetine (10 mg/kg b.w./day) were chosen based on previous experiments carried out in our laboratory (Dudek et al., 2016; Pytka et al., 2015). Corticosterone (Sigma, Germany) was dissolved in 1% dimethylsulfoxide (DMSO) and administered subcutaneously at a dose of 20 mg/kg b.w./day, at a volume of 10 ml/kg.

2.3. Experimental design

Mice were subjected to the chronic stress-like procedure by the subcutaneous administration of corticosterone suspended in 0.1% DMSO at a dose of 20 mg/kg for 21 days (Fig. 1) (Pytka et al., 2018). These mice received an additional intraperitoneal injection of 1% Tween 80 (the vehicle of the compounds). The control group was subcutaneously injected with the corticosterone's vehicle, composed of 0.1% DMSO; they were also administered 1% Tween 80 i.p. Simultaneously, certain groups of mice received corticosterone subcutaneously and pitolisant (10 mg/kg/day) or fluoxetine (10 mg/kg/day) i.p. Furthermore, some mice received only pitolisant (10 mg/kg/day) chronically. On the 20th day, animals were placed into metabolic cages for 24 h in order to collect their urine. On consecutive days, we conducted the locomotor activity test (LA), FST, elevated plus maze test (EPM) and finally, the glucose tolerance test (GTT) – which was carried out after removing the diet for 20 h. Urine collection and the locomotor activity test were carried out prior to the next administration of corticosterone and the studied drugs.

2.4. Locomotor activity

The locomotor activity test was performed as previously described (Pytkaa et al., 2016). Briefly, locomotor activity was recorded individually for each animal using specially designed activity cages which

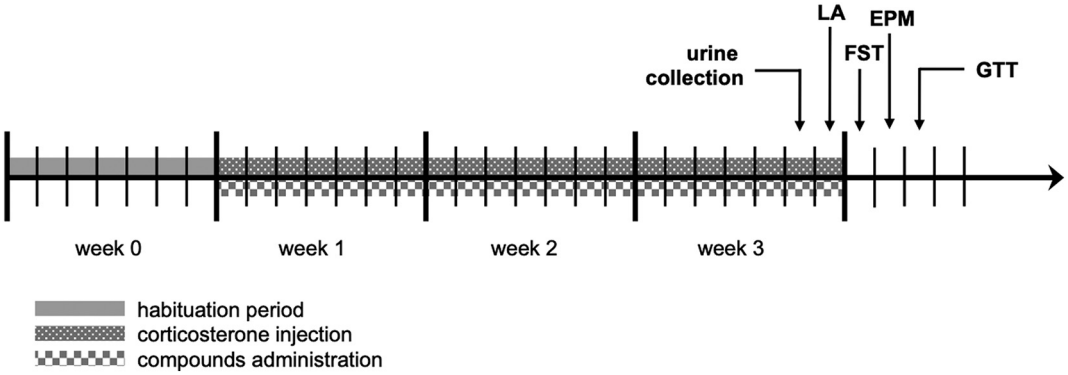

Fig. 1. Scheme of experiment.
EPM – elevated plus maze, FST – forced swim test, GTT – glucose tolerance test, LA – locomotor activity.

were made from clear Perspex (40 cm × 40 cm × 31 cm, Activity Cage 7441, Ugo Basile, Italy). The cages came supplied with infrared (I.R.) horizontal beam emitters connected to a counter which recorded the light-beam interruptions. Each mouse was placed in a cage for a 30-minute habituation period. After that time, the number of breaks in the photobeams was measured for 6 min. For analysis, we used the time slots from the 1st to the 5th min and from the 2nd to the 6th min, which corresponded with the observation periods used in the elevated plus maze and forced swim test, respectively. The cages were disinfected with 70% ethanol after use by each mouse.

2.5. Forced swim test

The forced swim test was performed according to the method which we previously described (Pytkab et al., 2016). Mice were placed individually into a glass cylinder (height 25 cm, diameter 10 cm) containing water (23–25 °C) at a depth of 10 cm for 6 min. After a two-minute habituation period, the immobility time was recorded for the next 4 min. The experiments were recorded and scored using the aLab.io software operated by a trained observer who was blind to the treatments.

2.6. Elevated plus maze

The elevated plus maze was performed according to the method described by Sałat et al. (2015). The elevated plus maze used was specifically designed for mice, it consisted of two opposing open arms (30 cm × 5 cm) and two opposing enclosed arms (30 cm × 5 cm × 25 cm), which were connected by a central platform that formed the shape of a plus sign (+). The open and closed arms were connected with a central field (5 cm × 5 cm). Each mouse was individually placed in the central field of the apparatus with the head pointing toward one of the closed arms. The animals' behavior was then observed for 5 min. The device was disinfected with 70% ethanol after each mouse completed the test. The number of entries into the open and closed arms and the time spent in these open and closed arms were recorded. The experiments were again recorded and scored using the aLab.io software operated by a trained observer who was blind to the treatments.

2.7. Glucose tolerance test

This test was performed on the 25th day of the experiment. After which each mouse had been administered twenty-one doses of the test compound. Food was removed for 20 h prior to the glucose tolerance of the mice being tested. Glucose (1 g/kg b.w.) was administered i.p. (Kotańska et al., 2018; Kotańska et al., 2019). Blood samples were taken from the tail vein at several time points, the first of which started prior to glucose administration (0 min) and then samples were taken at 30-minute intervals after administration, up until the 120-minute time point (30-, 60-, 90-, and 120-minute time points). Glucose levels were measured with a glucometer (ContourTS, Bayer, Germany, test stripes: ContourTS, Ascensia Diabetes care Poland Sp. z o.o., Poland, REF: 84239666).

2.8. Urine collection and determination of ketone bodies

This test was performed on the 20th day of the experiment after twenty administrations of the test compound. Animals were subcutaneously administered 2 ml of 0.9% saline and placed into the metabolic cage. Urine was collected for 24 h. Some ketone bodies such as acetoacetic acid were produced during disturbed carbohydrate and fat metabolism and were labeled with stripes (Keto-Diastix REF 2883, Bayer).

2.9. Body weight changes

Mouse body weight was measured every day throughout the chronic procedure (before the administration of compounds) using specially designed scales (WPT 1c, RADWAG).

2.10. Data analysis

Results are presented as means ± SEM. With exception of the results from the body weight changes and the GTT, all other comparisons between experimental and control groups were performed by one-way ANOVA, followed by Newman-Keuls post hoc (GraphPad Prism Version 6.00 software). The body weight changes and GTT were assessed using two-way ANOVA with repeated measures, followed by Bonferroni post hoc. A value of $p < 0.05$ was considered to be significant.

3. Results

3.1. Pitolisant's influence on depressive-like behavior in corticosterone-treated mice

Chronic administration of corticosterone increased the immobility in the test compound group of mice by 15.9% when compared to the non-corticosterone-treated control groups (Fig. 2A). Pitolisant (10 mg/kg/day) co-administered for 21 days did not prevent the increase in immobility induced by corticosterone. However, the administration of fluoxetine did prevent the negative behavioral changes, i.e., the reference drug decreased the immobility time by 25.7% as opposed to the corticosterone-treated control mice ($F(3,26) = 16.320$, $p < 0.001$). Pitolisant did not show any influence on the measured parameter (data not shown).

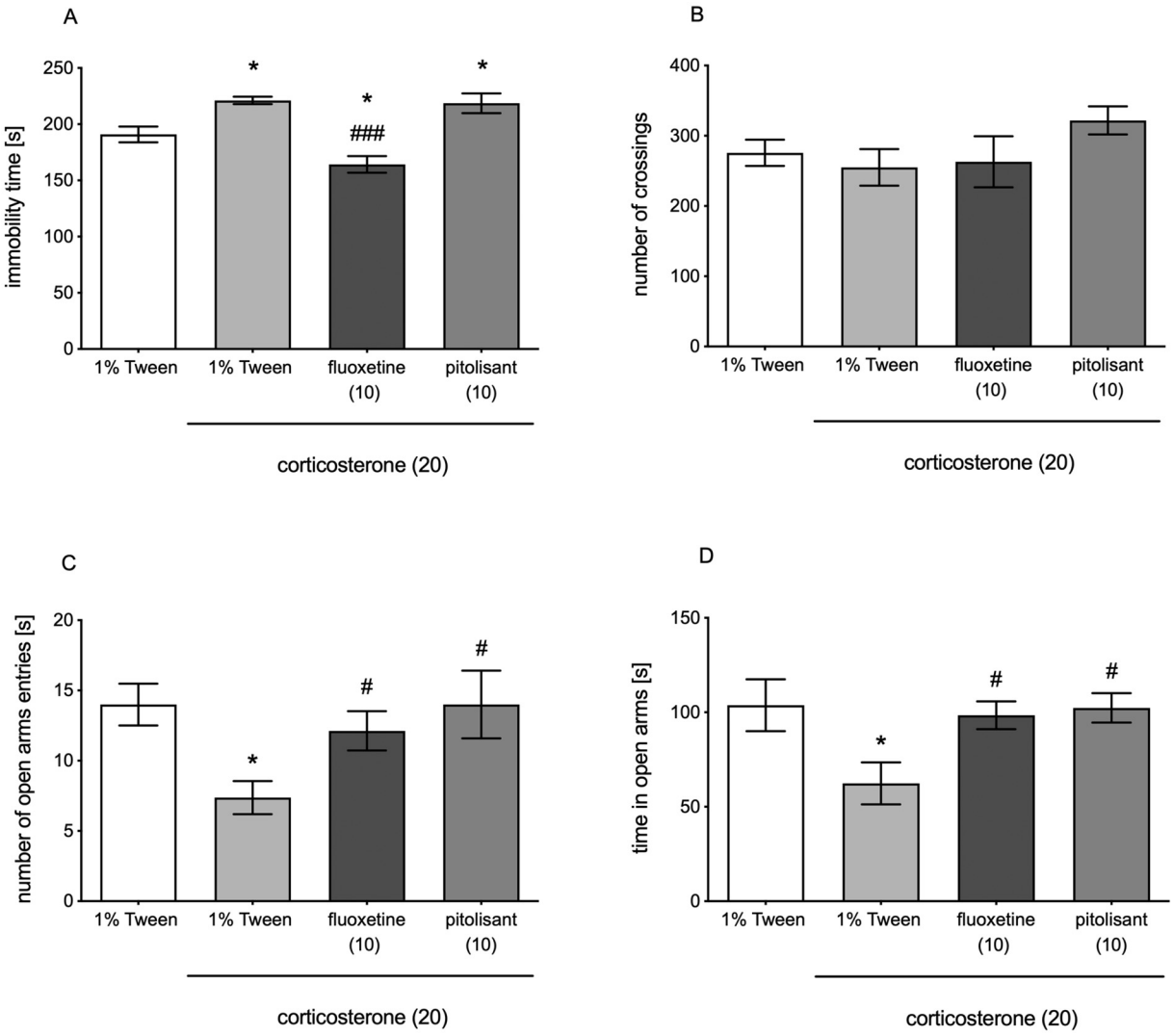

Fig. 2. Effect of pitolisant and fluoxetine on the behavior of mice chronically treated with corticosterone.
A. Forced swim test. B. Locomotor activity. C, D. Elevated plus maze test. Statistical analysis: one-way ANOVA (Newman-Keuls post hoc); *$p < 0.05$ vs control (vehicle + vehicle); $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ vs corticosterone control (vehicle + corticosterone); mean ± SEM, n = 8.

3.2. Pitolisant's influence on locomotor activity of the corticosterone-treated mice

There were no significant changes in locomotor activity between the non-corticosterone- and corticosterone- treated groups (Fig. 2B). When administered for 20 days, neither pitolisant (at the dose 10 mg/kg) nor fluoxetine (at the dose 10 mg/kg) showed an influence on locomotor activity during a 4-minute session in the corticosterone-treated mice ($F(3,26) = 1.051$, $p = 0.387$).

3.3. Pitolisant's influence on anxiety-like behavior in corticosterone-treated mice

Corticosterone treatment caused a decrease in the number of open arm entries (Fig. 2C) and the time spent in the open arms (Fig. 2D) by 47% and 39.9%, respectively. Both fluoxetine (10 mg/kg/day) and pitolisant (10 mg/kg/day), administered for 23 days, reversed these negative changes by increasing the time spent in the open arms by 57.8% and 64.2% ($F(3,26) = 3.521$, $p < 0.05$) respectively and increased the open arm entries by 64.5% and 89.8% ($F(3,26) = 4.025$, $p < 0.05$), respectively.

3.4. Pitolisant's influence on glucose tolerance

Fasting glucose concentrations were measured after 20 h of food deprivation and prior to the glucose load test. Blood glucose levels of both groups treated with corticosterone (corticosterone alone and pitolisant + corticosterone) did not differ significantly at the same time points and only at the 120 minute time point (after glucose load) was it significantly higher than when compared with the glucose level of the control mice. In the group treated with only pitolisant (without corticosterone), we observed a significantly lower glucose level compared with the control mice (treated with 1% Tween) at the 90 min after glucose loading time point. However, 120 min after glucose loading, the glucose level normalised and did not differ significantly between the groups treated with either only pitolisant or only 1% Tween 80. At these two time points, glucose levels in both the groups which received pitolisant were significantly different. Therefore, pitolisant did not prevent higher glucose levels 120 min after glucose loading in the corticosterone-treated mice. Pitolisant alone however, had a positive effect on the post-load glucose level. Fig. 3A shows these results.

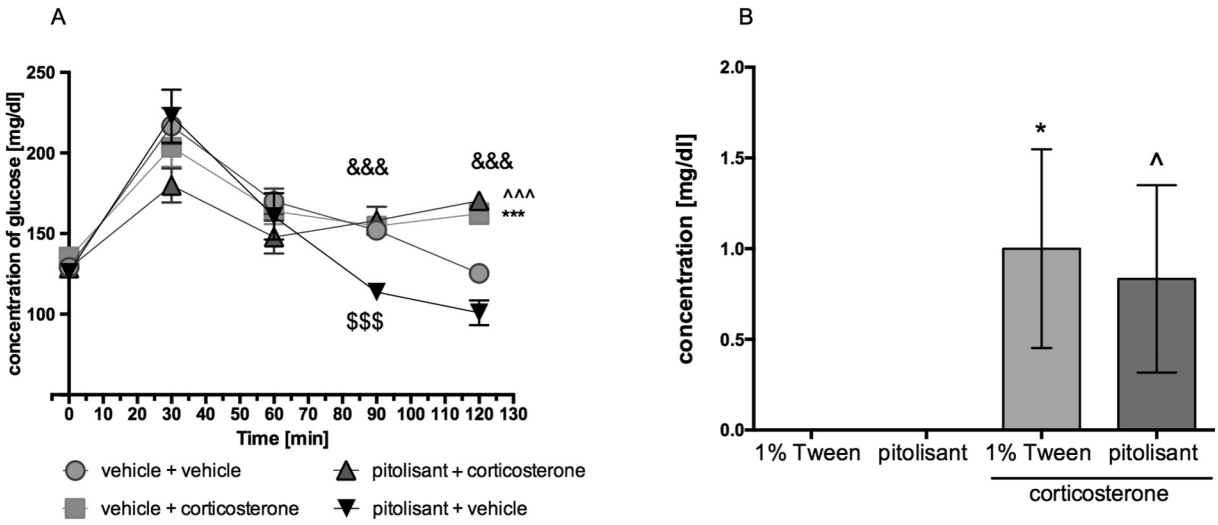

Fig. 3. Effect of pitolisant on glucose tolerance or level of urine acetoacetic acid in mice under chronic administration of corticosterone.
A. Glucose level curve over time (GTT test), B. Urine acetoacetic acid.
Statistical analysis: two-way ANOVA (Bonferroni post hoc) (A) or one-way ANOVA (Dunnett post hoc) (B); *$p < 0.05$, ***$p < 0.001$ corticosterone control (vehicle + corticosterone) vs control (vehicle + vehicle); $^{\hat{}}p < 0.05$, $^{\hat{}\hat{}\hat{}}p < 0.001$ pitolisant (pitolisant + corticosterone) vs corticosterone control (vehicle + corticosterone); $^{\$\$\$}p < 0.001$ pitolisant (pitolisant + vehicle) vs control (vehicle + vehicle); $^{\&\&\&}p < 0.001$ pitolisant (pitolisant + vehicle) vs corticosterone control (vehicle + corticosterone); mean ± SEM, n = 8.

3.5. Pitolisant's influence on corticosterone-induced disturbed combustion of energy material (level of urine acetoacetic acid – some ketones bodies)

In both groups treated with corticosterone (corticosterone alone and pitolisant + corticosterone), acetoacetic acid was found in the urine. This result confirms that corticosterone disrupts energy metabolism and shows that, unfortunately, pitolisant is not able to reverse this effect when it is administered for 20 days. The results can be seen in Fig. 3B.

3.6. Influence of pitolisant on body weight changes in mice treated with corticosterone

Fig. 4A shows the effects seen on the body weight of the mice on individual days of the experiment. The body weight was significantly reduced by 50% in the first week, 33% in the second and 50% in the third week in the group of mice that were chronically treated with corticosterone and receiving 1% Tween 80 compared with the non-corticosterone-treated controls (Fig. 4B). Body weights in the groups treated with pitolisant together with corticosterone (both given at a dose of 10 mg/kg b.w./day), were only reduced by 12.5% in the first week of administration, then by 33% in the second week and by 75% in the third week. Interestingly, in the mice from the group treated with pitolisant plus corticosterone, it was only during the third week that body weight was significantly lower than in the control group. Weight loss in this group was also lower than in the corticosterone group.

4. Discussion

In our study, in order to examine whether pitolisant can, at least in part, prevent the occurrence of the central nervous system and metabolic disorders induced by chronic corticosterone administration, we assessed the effect of the parallel administration of both drugs on the animals' behavior (i.e., depression- or anxiety-like behaviors) and the metabolic changes seen (i.e., glucose intolerance, ketone bodies in urine, body weight change). Considering that glucocorticosteroids are often used for the treatment of autoimmune, inflammatory and allergic diseases and that their chronic use causes many unacceptable side effects, including obesity, diabetes or panic, anxiety and depression disorders (Ceccarelli et al., 2018; Poznańska et al., 2019; Sullivan et al., 2018; Sakimura et al., 2018; Wichmann et al., 2017; Fischer et al., 2018), the search for a therapeutic solution for this problem is critical from both a social and an economic point of view.

Earlier studies using mice have also shown that pitolisant shows an antidepressant-like effect in the tail suspension test at a dose of 10 mg/kg, i.p., which may be associated with the effect of this drug on σ1R (Ki = 0.5 nM) (European Medicines Agency, 2015). Besides, when the drug was administered jointly with olanzapine for 14 days, it significantly prevented the development of depressive-like behaviors as well as some metabolic disorders which were induced by this atypical antipsychotic in mice (Dudek et al., 2016). In the present study, pitolisant was unable to prevent the development of corticosterone-induced depressive-like behaviors, however, it did show an anxiolytic-like effect. Therefore, we plan to conduct further research into this area.

In our study, we chose a model in which the induction of depressive-like and anxiety-like behaviors occurred within three weeks of corticosterone administration. During this time, the first metabolic disorders develop, i.e., reduced glucose tolerance and weight change (Shibata et al., 2015; Sawamoto et al., 2016), as well as ketone bodies being present in the urine. Accordingly, we observed similar disorders in our research. We assumed that pitolisant, as a ligand for the H3R and σ receptors, could not only compensate for some behavioral disorders but also contribute to reducing the development of metabolic disorders in the tested mice. Finally, in the initial period of administration, when using the two drugs together, the weight changes of the mice were similar to the control group, which would indicate that the induction of metabolic disorders in these animals was at least partially inhibited. However, after the first week, the mice treated with pitolisant and corticosterone began to gain less weight and developed metabolic disorders similar to the group that received only corticosterone; this was indicated by the presence of ketone bodies and the similar influence that was seen on the glucose tolerance of these mice.

On the other hand, one of the limitations of this study is that after this experiment, one cannot conclude if pitolisant just has an anxiolytic-like effect or attenuated the corticosterone's effect. It is essential to see in the future if pitolisant has an effect on naive mice. The second limitation is that pitolisant and corticosterone were administered for only 21 days. More prolonged administration could show whether weight reduction in the group treated with pitolisant together with corticosterone is increasing and if it becomes significant enough to take into account the effectiveness of the metabolic disorders reduction. In the

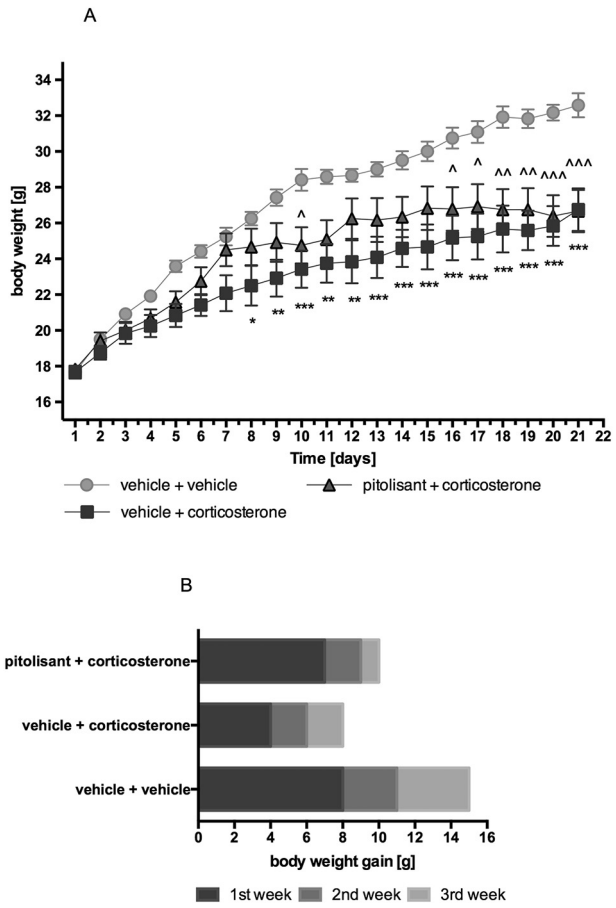

Fig. 4. Effect of pitolisant on body weight under chronic administration of corticosterone.
A. Changes of body weight per day, B. Cumulative body changes per week. Statistical analysis: two-way ANOVA (Bonferroni post hoc) (A); *p < 0.05, **p < 0.01, ***p < 0.001 corticosterone control (vehicle + corticosterone) vs control (vehicle + vehicle); ^p < 0.05, ^^p < 0.01, ^^^p < 0.001 pitolisant (pitolisant + corticosterone) vs corticosterone control (vehicle + corticosterone); mean ± SEM, n = 8.

rodent model of metabolic disorders which are caused by the administration of corticosterone, after the initial weight loss (which is associated with the development of insulin intolerance and metabolic disorders) the weight of the animals significantly increase in the fifth and subsequent weeks (after glucose intolerance starts and with the appearance of insulin resistance) showing corticosterone-induced obesity is developing (Matsumura et al., 2019). It would be interesting to investigate what effect a more extended administration of the pitolisant and corticosterone combination has on the metabolic disorders that develop during longer corticosterone administration. This would allow us to evaluate if pitolisant can compensate for certain metabolic disorders (Dudek et al., 2016; Kotańska et al., 2018). The experiments described in this article should be considered preliminary research.

5. Conclusion

The data gathered in this study suggests that pitolisant possess anxiolytic-like activity, although further and more comprehensive studies need to be undertaken to prove the accuracy of this statement fully. Therefore, the use of pitolisant to reduce specific side effects of chronic glucocorticoid administration appears to have potential but will require more research.

Ethical approval

All applicable international laws for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted. This article does not contain any studies with human participants performed by any of the authors.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Author contributions

Magdalena Kotańska conceived and designed research and conducted experiments. Katarzyna Kieć-Kononowicz contributed new reagents or analytical tools. Magdalena Kotańska, Kinga Sałaciak, Karolina Pytka, Kamil Mika, Jacek Sapa, Lee Wheeler analysed data. Magdalena Kotańska, Karolina Pytka, Lee Wheeler, Kinga Sałaciak, Kamil Mika wrote the manuscript. All authors read and approved the final manuscript.

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