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Development of Insulin Resistance after Prolonged Exposure to Glucocorticoid Hormones as One of the Mechanisms of Transformation of Their Gastroprotective Effect into a Proulcerogenic Action

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This work continues our studies of the mechanisms of transformation of the initial gastroprotective action of glucocorticoid hormones into a proulcerogenic action. Experiments on rats tested the suggestion that the development of insulin resistance after prolonged exposure to glucocorticoid hormones may be one of the mechanisms of this transformation. This was addressed by studying the effects of dexamethasone, corticosterone, and hydrocortisone on insulin sensitivity at different time points after single doses of pharmacological size. Insulin sensitivity was evaluated in terms of the decrease in the blood glucose level 1.5 h after administration of insulin (2 IU/kg, i.p.). Decreases in glucose levels were expressed as percentages of baseline (pre-insulin) glucose levels. The results indicated that at those time points at which these hormone had previously been found to have gastroprotective actions, insulin sensitivity remained unaltered from that in control animals. Administration of dexamethasone and hydrocortisone after prolonged exposure led to decreases in insulin sensitivity at those time points at which their proulcerogenic effects had been seen. Increases in the duration of exposure to corticosterone did not produce any changes in insulin sensitivity or transformation of its gastroprotective effect into a proulcerogenic action. These data support the suggestion that the development of insulin resistance after prolonged exposure to glucocorticoid hormones can be regarded as one of the mechanisms of the transformation of their gastroprotective effects into proulcerogenic actions.

Keywords: glucocorticoid hormones, gastric mucosal erosions, glucose, insulin resistance.

Glucocorticoid hormones can have both protective and harmful actions on the gastric mucosa [2, 7, 13, 16]. We have previously demonstrated that single doses of glucocorticoid hormones with short-term exposure produce gastroprotective effects even when hormones are given at pharmacological doses. Increases in the duration of action of glucocorticoids can lead to transformation of their initial gastroprotective effects into proulcerogenic actions, able to damage the gastric mucosa [1, 4, 16]. Analysis of blood glucose levels at different time points after administration of glucocorticoid hormones led to the conclusion that transient maintenance of the blood glucose level due to the actions of glucocorticoids may make a contribution to mediating their gastroprotective effects, while long-term maintenance of glucose levels induced by these hormones may be among the causes of the transformation of the gastroprotective effects of these hormones into proulcerogenic actions [6, 12].

The present study was undertaken for further investigation of the effects of glucocorticoids on carbohydrate metabolism in relation to studies of the mechanisms of transformation of the gastroprotective effects of hormones into proulcerogenic actions. It is well known that administration of glucocorticoid hormones can lead to the development of reductions in insulin sensitivity [10, 19, 20], though the relationship between this effect of glucocorticoids and the du-

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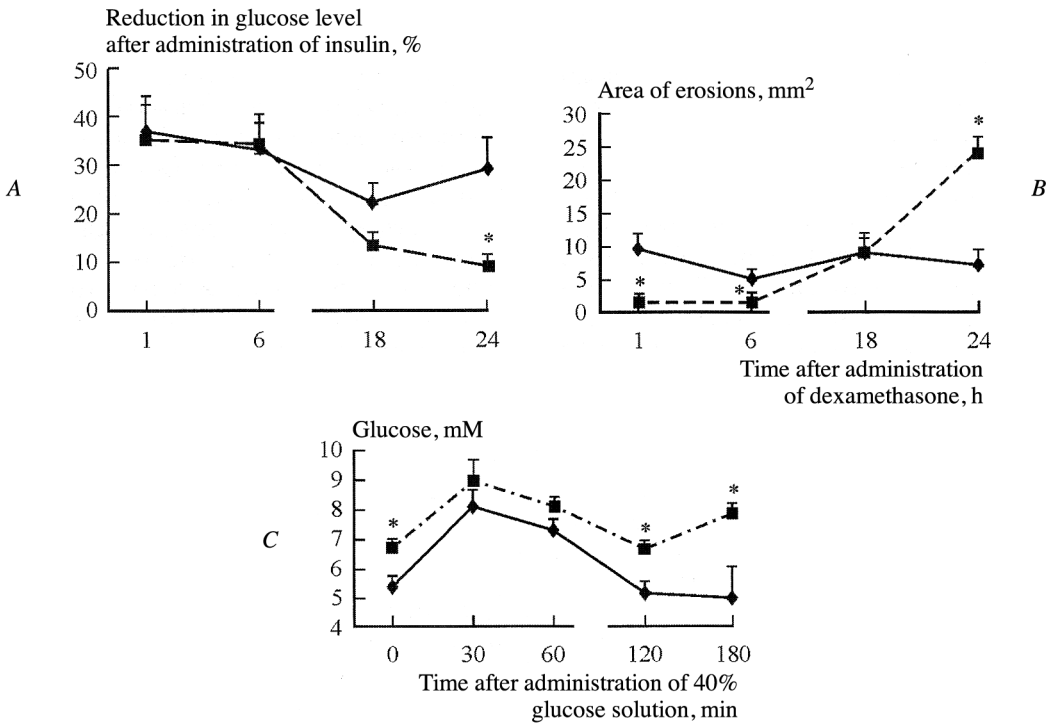

Fig. 1. Effects of dexamethasone (1 mg/kg) at different time points after administration on insulin sensitivity (expressed as the percentage reduction in the blood glucose level) (*A*), on the area of indomethacin (35 mg/kg)-induced erosions in the gastric mucosa (*B*), and glucose tolerance determined 24 h after administration of dexamethasone (*C*). The continuous line shows administration of solvent; the dashed line shows administration of dexamethasone. *Significant differences from control values for the same time point, $p < 0.05$. Each group consisted of 8–10 animals.

ration of their actions is unclear. There is a need to identify this relationship because of our data on the transformation of the gastroprotective effect of glucocorticoids into a proulcerogenic action with increases in the duration of exposure to these hormones. The aim of the present work was to study the effects of glucocorticoid hormones (dexamethasone, corticosterone, and hydrocortisone) on insulin sensitivity depending on the duration of exposure to these hormones, taking account of the doses and time points at which transformation of the gastroprotective effects of the hormones into proulcerogenic actions occurred.

Methods. Experiments were performed on male Sprague–Dawley rats weighing about 300 g. The animals were acclimated to standard laboratory animal-house conditions (temperature 20–22°C, light regime 12 h:12 h, free access to water and food) one week before the experiments started. Without prior starvation, rats received single i.p. doses of glucocorticoid hormones at pharmacological doses: dexamethasone (1 mg/kg), corticosterone (100 mg/kg) or hydrocortisone (300 mg/kg), as use of these glucocorticoid doses produced the effect of transformation of the gastroprotective effects of the hormones into proulcerogenic actions. Possible changes in insulin sensitivity due to these hormones were evaluated using a method (insulin tolerance test) proposed by an Italian group [22], with some modifications (a different insulin dose and a different time after insulin administration). Insulin was given i.p. at a dose of 2 IU/kg and blood glucose levels were measured before administration of insulin (baseline level) and 1.5 h after administration. Insulin sensitivity was evaluated in terms of the decrease in the glucose level after administration of insulin and was expressed as a percentage in relation to the baseline glucose level, which was taken as 100%. Calculation of the decrease in glucose content after administration of insulin as a percentage was used to assess insulin sensitivity at different baseline glucose levels.

Insulin sensitivity was studied at those time points after glucocorticoid hormone administration at which the effects of these hormones on the sensitivity of the gastric mucosa to ulcerogenic actions were studied: 1, 6, 18, and 24 h after administration of dexamethasone, 1 and 24 h after corticosterone, and 3 h, 3 days, and 7 days after hydrocortisone [1, 4, 16]. The ulcerogenic stimulus was indomethacin (35 mg/kg). The area of gastric mucosal erosions was evaluated using computer program ImageJ. Blood glucose contents in individual rats were determined in drops of blood taken by puncture of the tail vein on two occasions – before and after insulin administration.

As the transformation of the gastroprotective effect into the proulcerogenic action was clearest after administration of dexamethasone, its effects were studied in more detail: study parameters were tested at more time points, and a

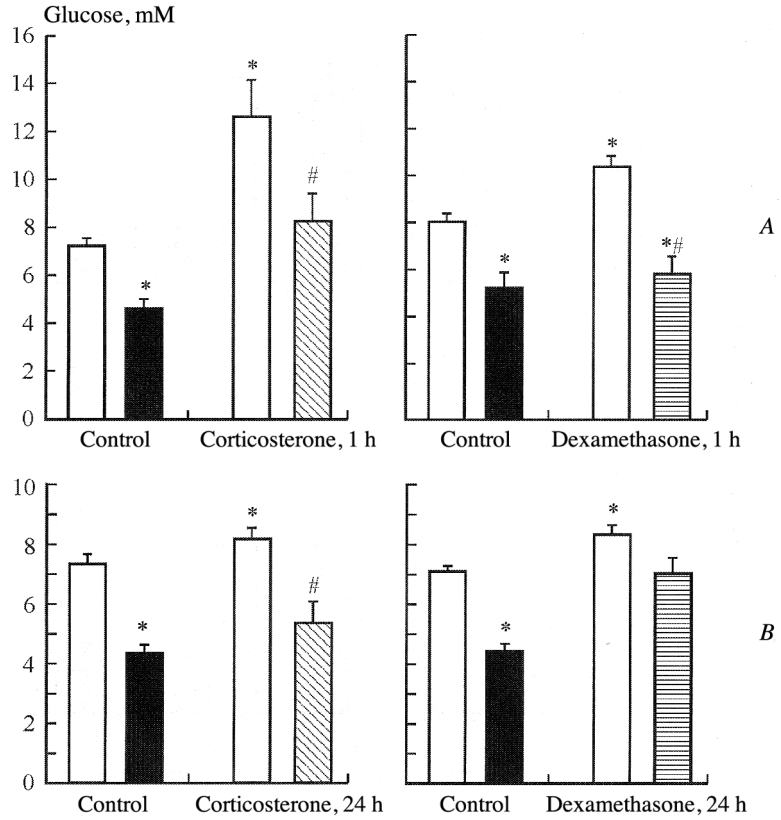

Fig. 2. Blood glucose levels before and after administration of insulin 1 h (*A*) and 24 h (*B*) after administration of corticosterone or dexamethasone. White columns show blood glucose before administration of insulin; black or shaded columns show blood glucose levels after insulin. *Differences from blood glucose before administration of insulin in the Control group; #differences from blood glucose levels before administration of insulin in the Corticosterone and Dexamethasone groups, $p < 0.05$, $n = 8–11$.

glucose tolerance test was run 24 h after administration of dexamethasone. The test was performed on rats after initial starvation for 16 h. After starvation for 16 h, rats were given glucose at a dose of 2 g/kg p.o. and glucose level were measured in drops of blood from the tail vein every 30 min.

Glucose levels were estimated using a "One Touch Ultra" test strip system (USA). Blood corticosterone levels were measured microfluorimetrically [14]. Body, thymus, spleen, and adrenal weights were determined at the end of all experiments to assess the catabolic actions of glucocorticoid hormones. All data were processed statistically. The nonparametric Mann–Whitney method was used for comparison of the areas of gastric mucosal erosions, while other measures were analyzed using Student's *t* test. Experiments were performed using animals from the biological collection of the Institute of Physiology, Russian Academy of Sciences.

Results. These studies identified a clear relationship between the effect of dexamethasone on insulin sensitivity in rats and the duration of its exposure on the one hand and the effect on the gastric mucosa o the other. Transient exposure to dexamethasone at a dose of 1 mg/kg (1 or 6 h), which produced a protective effect on the gastric mucosa (Fig. 1, *B*), insulin sensitivity was no different from that in controls (Fig. 1, *A*). At 18 h after administration of dexamethasone at this same dose, there was a tendency for the rats' insulin sensitivity to decrease, with simultaneous disappearance of the protective effect of dexamethasone on the gastric mucosa. A significant decrease in insulin sensitivity was seen 24 h after administration of dexamethasone at a dose of 1 mg/kg (Fig. 1, *A*), i.e., at the same time point at which this hormone was seen to have a clear proulcerogenic effect (maximum increase in the sensitivity of the gastric mucosa to the ulcerogenic action of indomethacin) (Fig. 1, *B*). At this same time point (24 h) after administration of dexamethasone, glucose tolerance was impaired (Fig. 1, *C*), which is probably a consequence of the development of insulin resistance demonstrated here.

The effect of dexamethasone on insulin resistance was compared with the action of corticosterone, the natural hormone in rats, after administration of single pharmacological doses of 100 mg/kg (Fig. 2). The results of our previous studies indicate that in terms of the gastroprotective effect 1 h after administration, this dose of corticosterone corresponded to a dexamethasone dose of 1 mg/kg [4]. At 1 h after administration of both corticosterone and dexamethasone, administration of insulin led to significant decreases

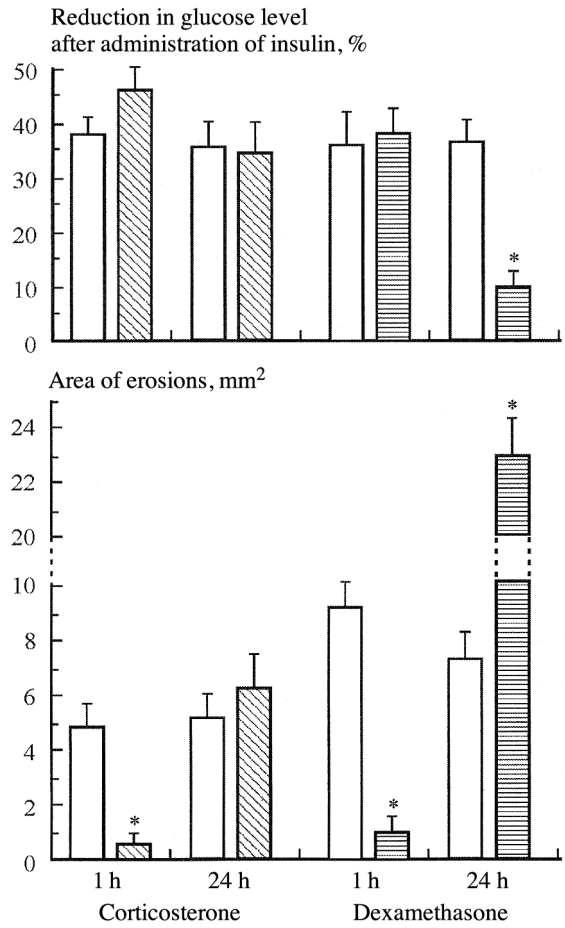

Fig. 3. Comparison of the effects of corticosterone and dexamethasone on insulin sensitivity (expressed as the percentage reduction in blood glucose after administration of insulin) and on erosions of the gastric mucosa induced by indomethacin (35 mg/kg). White columns show administration of solvent (control), shaded columns show administration of corticosterone or dexamethasone. *Differences from control in the "1 h" group and the "24 h" group, $p < 0.05$, $n = 8–11$.

in blood glucose, analogous to the decrease in control rats (Fig. 2, *A*). Administration of insulin at 24 h after dexamethasone produced no significant reduction in the blood glucose level in the rats (Fig. 2, *B*). At the same time, in the case of prior administration of corticosterone both 1 and 24 h before injection of insulin, administration of the latter led to a significant decrease in the blood glucose level (Fig. 3), which is evidence that insulin resistance did not develop in this case. Making a parallel with the effect of corticosterone on the sensitivity of the gastric mucosa to the ulcerogenic action of indomethacin (Fig. 3), we can see that 1 h after administration the hormone had a protective effect on the stomach, though as the period of exposure increased to 24 h, the gastroprotective effect of corticosterone disappeared, without being transformed into a proulcerogenic action (Fig. 3), which corresponds to the absence of any change in insulin sensitivity 24 h after administration of corticosterone. For comparison, we note that at this time point after administration of dexamethasone, there was a significant increase in the area of indomethacin-induced erosions and a decrease in insulin sensitivity (Fig. 3).

The study investigated another model of the transformation of the gastroprotective effects of glucocorticoids into proulcerogenic actions, using administration of hydrocortisone at the pharmacological dose of 300 mg/kg. Previous studies demonstrated blockade of the function of the hypothalamo-hypophyseal-adrenocortical system (HHACS) 7 days after administration of hydrocortisone and demonstrated the proulcerogenic effect of hydrocortisone [1, 15]. Studies of the relationship between the influence of hydrocortisone on the sensitivity of the gastric mucosa to ulcerogenic factors and the duration of exposure showed that administration of hydrocortisone, even at this large dose, had a protective effect on the gastric mucosa on administration of hormone 3–12 h before indomethacin. Three days after administration of hydrocortisone, its gastroprotective effect disappeared, though the proulcerogenic action was still absent, appearing only seven days after hormone administration.

Using this model, we investigated insulin resistance at different time points after administration of hydrocortisone to rats at a dose of 300 mg/kg. At 3 h and 3 days after administration of hydrocortisone, glucose levels decreased significantly in response to administration of insulin (Fig. 4), the percentage decrease in blood glucose in relation to the pre-insulin baseline not being any different from that in controls (Fig. 5). These facts provide evidence that there were no changes in insulin sensitivity at these time points after administration of hydrocortisone. The sensitivity of the gastric mucosa to the ulcerogenic action of indomethacin at 3 h was significantly reduced (a gastroprotective effect was seen), while there was no difference from controls at three days (Fig. 5).

At seven days after administration of hydrocortisone, glucose levels before and after administration of insulin were not significantly different from each other (Fig. 4), which corresponded to a small percentage decrease in glucose after administration of insulin (Fig. 5). Thus, a reduction in insulin sensitivity was seen at seven days after administration of hydrocortisone and the proulcerogenic effect of this hormone became apparent (Fig. 5).

Comparison of the effects of the study hormones on blood glucose levels (before insulin administration) showed that significant increases in blood glucose occurred 1 h after administration of dexamethasone and corticosterone (Fig. 2, *A*) and 3 h after administration of hydrocortisone (Fig. 4). By 24 h after administration of corticosterone, the glucose level decreased significantly, though it remained higher than the control level (Fig. 2, *B*), while the glucose level at this time after administration of dexamethasone (Fig. 2, *B*) was no different from the level seen after exposure to hormones for 1 h. At three days after administration of hydrocortisone, the glucose level increased significantly, but decreased to normal by seven days (Fig. 4).

TABLE 1. Effects of Administration of Dexamethasone, Corticosterone, and Hydrocortisone on Changes in Body Weight in Rats and Relative Thymus, Spleen, and Adrenal Weights

Indicators	Dexamethasone (1 mg/kg, 24 h)*		Corticosterone (100 mg/kg, 24 h)*		Hydrocortisone (300 mg/kg, 7 days)*	
	control (solvent)	hormone	control	hormone	control	hormone
Change in body weight, g	+5.7 ± 1.6	–8.3 ± 1.3#	+2.9 ± 1.0	–3.3 ± 1.5 $p = 0.05$	+51.9 ± 2.7	–75 ± 8.9#
Thymus weight, mg/100 g	239 ± 15.7	124.7 ± 9.6#	285.7 ± 12.0	231.3 ± 14.0#	254 ± 11.2	72.6 ± 4.8#
Spleen weight, mg/100 g	360 ± 18.9	244.2 ± 11.4#	421.4 ± 47	390.4 ± 50.5	347 ± 16.3	191.2 ± 14.5#
Adrenal weight, mg/100 g	20.7 ± 0.3	17.9 ± 1.1#	23.0 ± 1.3	21.1 ± 1.5	19.2 ± 0.6	16.5 ± 0.7#

*Numbers in parentheses are hormone doses and times of administration. In the row "Change in body weight," + indicates an increase in weight, – indicates a decrease in weight. #Significant difference from control, $p < 0.05$.

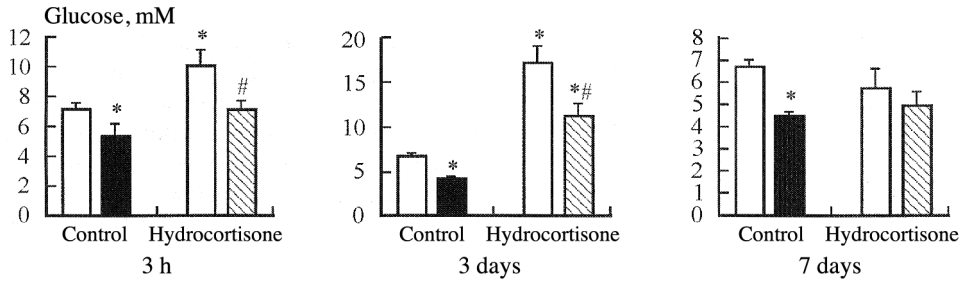

Fig. 4. Blood glucose levels before and after administration of insulin at different time points after administration of hydrocortisone. White columns show blood glucose levels before insulin; shaded or black columns show blood glucose levels after insulin. *Differences from glucose levels before insulin in the Control group; #differences from the glucose level before administration of insulin in the Hydrocortisone group, $p < 0.05$, $n = 7–9$.

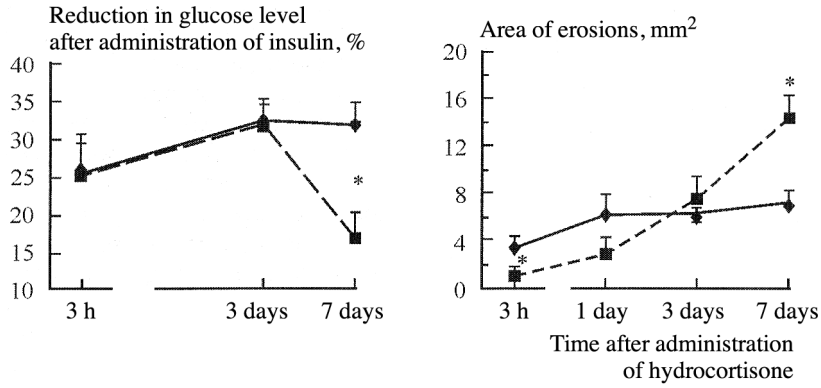

Fig. 5. Effects of hydrocortisone on insulin sensitivity (percentage reduction in glucose level) and indomethacin-induced erosions of the gastric mucosa at different time points after administration. Continuous lines show administration of solvent; dashed lines show administration of hydrocortisone. *Differences from control values at the corresponding time point, $p < 0.05$, $n = 7–11$.

Blood corticosterone levels were low (1.2–2.0 μg/dl) at all study time points after administration of dexamethasone, which is evidence of blockade of HHACS function. At 1 h after administration of corticosterone, its blood level was much higher than that in controls (65.5 ± 8.8 μg/dl) due to exogenous hormone, while the corticosterone level at 24 h remained elevated (16.6 ± 1.8 μg/dl). At three days after administration of hydrocortisone, the corticosterone level was not significantly different from the control level (7.8 ± 0.8 and 6.3 ± 0.8 μg/dl, respectively), and at seven days the corticosterone level decreased significantly (to 2.7 ± 0.7 μg/dl) as a result of blockade of HHACS function. The corticosterone level in control rats ranged from 7.5 to 10.5 μg/dl.

Administration of glucocorticoid hormones, as in our previous studies [1, 4], was followed by detection of their catabolic influences: significant decreases in body and thymus weight as compared with values in control animals. Furthermore, administration of dexamethasone (24 h) and hydrocortisone (3 and 7 days) was followed by reductions in spleen and adrenal weight (see Table 1).

Discussion. The results obtained here indicate that after transient (1, 3, and 6 h) exposure to glucocorticoid hormones (dexamethasone, hydrocortisone, and corticosterone), which produces a protective effect on the gastric mucosa [1, 4, 7], insulin sensitivity is no different from that in controls. However, prolonged exposure to hormones (24 h for dexamethasone and seven days for hydrocortisone), where a proulcerogenic action is seen, led to a significant reduction in insulin sensitivity. Prolonged exposure to corticosterone did not change insulin sensitivity and did not lead to transformation of the gastroprotective effect of the hormone into a proulcerogenic action.

These data provide evidence that the development of insulin resistance after prolonged exposure to glucocorticoid hormones may be one of the mechanisms of the transformation of their gastroprotective effects into proulcerogenic actions, promoting increases in the sensitivity of the gastric mucosa to harmful factors.

The development of insulin resistance under the influence of glucocorticoid hormones is well known and has been confirmed [10, 11, 19, 20]. New from the present study is that we approach this effect from the point of view of being a possible mechanisms underlying the transformation of the initially gastroprotective effect of glucocorticoid hormones into a proulcerogenic action. We believe it is important to study the possible mechanisms of transformation of the initially gastroprotective effect of glucocorticoids into the proulcerogenic action seen with hormones given at pharmacological doses, as pharmacological doses of glucocorticoids are used in clinical practice.

Glucocorticoid hormones have a key role in regulating carbohydrate metabolism and "counteracting" insulin is an important component of this regulation. Although the mechanism of suppression of insulin sensitivity by glucocorticoids is not entirely clear, it is known that important constituents are suppression of glucose transport within cells [23–25] and stimulation of gluconeogenesis in the liver [10, 11, 18, 20]. In addition, studies have shown that glucocorticoid hormones can weaken the effects of glucagon-like peptide and incretins on the pancreas [10]. An important mechanism of the action of glucocorticoids is their inhibitory effect on glucose transport within cells, mainly in muscle and fat tissue [23–25]. This effect may be linked with decreased translocation of the glucose transporter (GLUT4) to the cell surface. The effect of glucocorticoid hormones on insulin resistance is mediated via their actions on carbohydrate, fat, and protein metabolism (which are directly opposite to the actions of insulin): increases in gluconeogenesis in the liver and increases in blood glucose levels, proteolysis in muscles with increases in blood amino acid levels, lipolysis in fatty tissues, and delivery of large quantities of free fatty acids and triglycerides to the blood [10, 11, 18, 20]. The hormones have effects on substance metabolism via activation or inhibition of a number of enzymes [8, 10, 19]. In addition, impairments to several components of the insulin signal network due to glucocorticoid hormones have been demonstrated [10, 11, 20].

Systematic experimental studies of the relationship between the effect of glucocorticoids on insulin sensitivity and the dose and duration of exposure do not appear from the literature to have been conducted. However, there are data, obtained mainly in humans, on the influences of single doses of glucocorticoid hormones on insulin sensitivity with different durations of exposure [21, 26]. Single doses of dexamethasone 1 mg to healthy people have been found not to affect glucose metabolism, though two weeks of hormone treatment led to a significant reduction in the ability of insulin to influence glucose consumption and oxidation [21]. Investigations of patients subjected to prolonged glucocorticoid therapy showed that increases in insulin resistance develop within the first 4 h of infusion of methylprednisolone, after which it does not change during two months of treatment [26]. Single doses of dexamethasone 0.5 mg 2.5 h before glucose loading led to an increase in glucose tolerance, though there was no change in insulin sensitivity. Study results provide evidence of a quite rapid effect of glucocorticoids on changes in glucose tolerance and insulin sensitivity in humans. There are fewer such studies on animals. I.p. administration of dexamethasone 1 mg/kg to rats 4 h before insulin led to a decrease in insulin sensitivity but had no effect on the blood glucose level [19]. The dexamethasone dose and route of administration were the same as in our study, though we found a decrease in insulin sensitivity only 24 h after giving dexamethasone. This difference in results may be due to methodological factors – use of a) different animal strains (Wistar in the study cited, Sprague–Dawley here); b) different solvents for dexamethasone (alcohol and propylene glycol); c) different insulin doses (3 and 2 IU), and d) different methods for assessing insulin sensitivity. The study cited [19] used the so-called euglycemic hyperinsulinemic clamp method [9], which is often used by other authors. In this method, insulin, like glucose, is given by infusion over a number of hours (in this case 3 h). We used a method proposed in [22], in which insulin was given i.p. and insulin resistance was assessed in terms of the reduction in the glucose level as a percentage of the initial level. The euglycemic hyperinsulinemic clamp method is more sensitive: the study demonstrated increased insulin resistance, with no change in the blood glucose level. However, in our case it was also important to observe changes in blood glucose levels, as this measure is significant for the state of the gastric mucosa [16].

As expected, exogenous glucocorticoid hormones led to increases in blood glucose levels in rats at 1 and 24 h after administration. Our previous studies [4] indicate that by three days after administration of corticosterone and dexamethasone, the blood glucose level decreased to control levels, though by three days after administration of hydrocortisone the glucose level, conversely, increased significantly. It is not clear what this increase in blood glucose is connected

with. Seven days after administration of hydrocortisone, glucose decreased to control levels and insulin sensitivity dropped to below the control level; at this time the blood corticosterone level was very low and hydrocortisone had a significant proulcerogenic effect.

The level of corticosterone, the natural hormone in rats, is affected by two factors: the effect of the glucocorticoids given and insulin. Glucocorticoid hormones given at pharmacological doses, operating by a feedback mechanism, suppress the production of endogenous hormones [5], while administration of insulin can increase the blood corticosterone level in rats [17]. The effects of glucocorticoids given at pharmacological doses were clearly dominant in our experiments, as there was either a strong reduction in corticosterone at all time points after administration of dexamethasone and seven days after administration of hydrocortisone or an increase after administration of a large dose of corticosterone. At 24 h after administration of dexamethasone and seven days after administration of hydrocortisone, a very low corticosterone concentration was accompanied by a very high sensitivity of the gastric mucosa to ulcerogenic factors and low sensitivity to insulin. The high blood level persisted 24 h after administration of corticosterone, and the sensitivity of the gastric mucosa to ulcerogenic factors and insulin sensitivity were no different from those in controls. The presence of endogenous hormone in the rats' blood is important for maintenance of the normal sensitivity of the stomach to ulcerogenic factors and insulin sensitivity.

This work is the first to pose the question of the possible influence of the development of insulin resistance on the sensitivity of the gastric mucosa to ulcerogenic actions. Our results cannot be compared with published data because there are none. That a normal insulin level or normal insulin sensitivity is important for the state of the gastric mucosa is also evidenced by our data showing increased gastric mucosal sensitivity to ulcerogenic actions in rats in an experimental model of streptozotocin-induced diabetes [3].

Overall, the results obtained in the present study with administration of three different glucocorticoid hormones allow the reduction in insulin sensitivity to be regarded as one of the mechanisms of the transformation of the gastroprotective effects of these hormones into proulcerogenic actions.

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