Iranian Journal of Veterinary Surgery

ORIGINAL ARTICLE

Effect of N-Acetylcysteine on Acute Hyperglycemia Induced by Urethane in Rats: Role of α2-Adrenergic Receptor

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ARTICLE INFO

Article History:

Received: 15 March 2025
Revised: 14 May 2025
Accepted: 16 July 2025

Keywords:

Alpha-2 adrenergic receptor
Hyperglycemia
Insulin
N-acetylcysteine
Rats

ABSTRACT

N-acetylcysteine (NAC) is used to treat respiratory, neurodegenerative, and metabolic disorders. In the present study, the effect of NAC was investigated on acute hyperglycemia induced by urethane (URE) in rats. The possible mechanisms including α_2-adrenergic receptors and insulin (INS) involvements were explored by intraperitoneal (IP) injection of yohimbine (YOH, an α_2-adrenergic receptor antagonist) and determination of serum INS level, respectively. Thirty-five rats were divided into seven groups with equal number to receive IP injections of normal saline (NS), NAC, YOH, and a low dose combination of NAC and YOH before IP injection of URE. Another 20 rats were treated with NS, high doses of NAC, YOH, and their combination without receiving urethane. Time-dependent and percentage alterations in blood glucose level were measured and calculated, respectively. Serum INS level was measured with an enzyme-linked immune-sorbent assay (ELISA) kit and expressed as percentage. Time-dependent and percentage alterations of acute hyperglycemia induced by URE were reduced by 25 and 50 mg/kg NAC, 1 mg/kg YOH, and a combination treatment with low doses of NAC (12.5 mg/kg) and YOH (0.25 mg/kg). The urethane alone did not affect INS percentage, but NAC, YOH, and their combination increased it. Conscious rats showed no significant differences in blood glucose and serum INS levels. It is concluded that NAC produced an anti-hyperglycemic effect. This antihyperglycemic action of NAC might be mediated by α_2-adrenergic receptors and pancreatic insulin.

Introduction

Glucose ($C_6H_{12}O_6$) is the primary substrate used by cells to produce energy, and the normal circulatory glucose level is maintained within narrow physiological limits by communication between the brain, gastrointestinal tract, pancreas, liver, adrenal gland and muscle and adipose tissues.[1] Stress, diabetes, and the use of medications such as glucocorticoids, beta-blockers, and renin-angiotensin system inhibitors may cause acute and chronic hyperglycemia by disrupting regulatory signals.[2] In other situations, such as hospitalization, use of anesthetic drugs, and surgery, acute hyperglycemia also occurs, which is known as stress hyperglycemia.[3]

N-acetylcysteine (NAC), a synthetic derivative of the endogenous amino acid L-cysteine, has been frequently used as a mucolytic and as an antidote to acetaminophen toxicity.[4] The NAC modulates oxidative stress, inflammation, apoptosis and mitochondrial dysfunction and exerts an indirect effect on neurotransmitters such as glutamate and dopamine.[5] It has been reported that NAC inhibits biomarkers of oxidative stress and apoptosis induced by hyperglycemia in diabetic rats.[6] In the rat model of

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https://doi.org/10.30500/ivsa.2025.512508.1440

diabetic peripheral neuropathy, NAC has been found to reduce INS resistance with an improving effect on INS sensitivity.[7]

Yohimbine (YOH, $C_{21}H_{26}N_2O_3$) is a naturally occurring indole alkaloid primarily derived from the bark of the *Pausinystalia yohimbe* tree.[8] It selectively blocks the pre and postsynaptic α_2-adrenergic receptors and also binds to other relevant monoaminergic receptors including 5-hydroxytriptamin-1A (5-HT1A), 5HT-1B and dopamine D1, D2 and D3 receptors.[9] The YOH influence functions of multiple organ systems including cardiovascular, neuromuscular, endocrine, and nervous systems.[10]

The INS is the master regulator of glucose, lipid, and protein metabolism. Following an increase blood glucose, INS secretion by the beta cells of the pancreas is stimulated and causes suppression of endogenous glucose production, stimulation of glucose uptake by muscle, liver, and adipocytes and inhibition of lipolysis.[11] Many conditions, such as diabetes, obesity, stress, and the use of glucocorticoids, antihypertensives, antipsychotics, antidepressants and anesthetics, lead to hyperglycemia by altering INS secretion or sensitivity.[12,13]

Although there are no reports describing the effect of NAC on urethane (URE)-induced hyperglycemia, it has been found that NAC produced improving effects on kidney histopathology and blood creatinine in the rat model of renal ischemia/reperfusion injury under isoflurane anesthesia.[14] The aim of the present study was to investigate the effect of NAC on URE-induced hyperglycemia. The mechanisms of NAC action were evaluated using intraperitoneal (IP) injections of YOH and determination of serum level of INS.

Materials and Methods

Animals

In the current study, 55 male adult Wistar rats weighing between 230–260 g and aged 8–9 months were used. Standard laboratory husbandry conditions (temperature: 22 ± 0.5 °C; humidity: 60-70% and 12 h dark-light cycles). Food and water were given to the animals at 7 AM and 5 PM. All experiments were done between 10 AM–3 PM. Veterinary Ethics Committee of Urmia University Faculty of Veterinary Medicine approved the study protocol (Ethical code: IR-UU-AEC-3/98).

Chemical Compounds and Kits

The used chemical compounds including NAC, YOH and URE were purchased from Sigma-Aldrich (St. Louis, USA). The rat INS enzyme-linked immunosorbent assay kit (Mercodia AB, Sylveniusgatan 8A SE-75450, Uppsala, Sweden) was also purchased. The drugs were dissolved in normal saline 30 min before use.

Study Protocol

In the present study, the following protocol was used for all rats with respect to the time of URE injection (0 min). The animals' food was removed at 7 AM and the animals were transported to the laboratory. The experiments began at 10 AM. The IP injections of NAC, YOH, and their combination were done at 30 min before URE injection. Blood glucose levels were measured 25 and 5 min before and 30, 60, 90, 120, and 150 min after URE injection. The percentage alterations of blood glucose level in the post URE injection period (30-150 min) were calculated. After the last glucose measurement, blood samples were taken from the heart for the determination of serum INS level. During the anesthesia, body temperature was maintained between 36 and 37°C using a controlled heating pad system. At the end of the experiments, the animals were monitored until they regained consciousness. Due to failure to recover from anesthesia, four rats were euthanized by intracardiac injection of 0.5 ml xylazine (Alfasan, Woerden, The Netherlands).

Animal Grouping

In the present study, 40 rats were divided into eight groups of five rats in each as follows: Group 1(NS + NS): in this group, NS was IP injected at -30 and 0 min, respectively. Group 2 (NS + URE): in this group, NS and URE (1.2 g/kg) were IP injected at -30 and 0 min, respectively. Groups 3 (NAC 12.5 + URE), 4 (NAC 25 + URE) and 5 (NAC 50 + URE): in these groups, NAC (12.5, 25, and 50 mg/kg) and URE (1.2 g/kg) were IP injected at -30 and 0 min, respectively. Groups 6 (YOH 0.25 + URE) and 7 (YOH 1 + URE): in these groups, YOH (0.25 and 1 mg/kg) and URE (1.2 mg/kg) were injected at -30 and 0 min, respectively. Group 8 [(NAC 12.5 + YOH 0.25) + URE]: in this group, NAC (12.5 mg/kg) plus YOH (0.25 mg/kg) and URE (1.2 g/kg) were IP injected at -30 and 0 min, respectively.

To clarify the effects of drugs on blood glucose level in conscious animals, 15 healthy rats were divided into three groups of five rats to give NAC (50 mg/kg), YOH (1 mg/kg), and NAC (12.5 mg/kg) plus YOH (0.25 mg/kg). The results of these three experiments were compared with the results of group 1 (NS + NS group). The drug doses used in the current study are consistent with other studies,[15-18] and our preliminary experiments.

IP Injection

The NAC, YOH and URE were dissolved in NS. The IP injections of NS, NAC and YOH were done using 27-guage syringes at a fixed volume of 1 ml/kg. The URE was IP injected by a 23-guage syringe at a volume of 4 ml/kg. In the case of combination treatment, NAC plus YOH was injected at a volume of 2 ml/kg.

Blood Glucose Measurement

Blood glucose level was measured using a digital glucometer (Farir Teb, Tehran, Iran). For this purpose, the end of tail was punctured with a 30-guage needle, the glucometer strip was dipped with 60 µl blood, and 5 sec later the amount of glucose was read from the monitor. The accuracy of the glucometer was calibrated using a standard glucose quantification kit (Pars Azmoun, Tehran, Iran).

Blood Sampling and Biochemical Assay

Ten min after the last glucose level measurement (160 min), 0.5 ml blood was collected from the heart into non-heparin containing tubes to obtain serum. Blood samples were centrifuged at 3500 rpm for 10 min and separated serum samples transferred to Eppendorf tubes and stored at -80 °C until analysis. Serum INS level was detected using a rat INS enzyme-linked immunosorbent assay kit (Mercodia AB, Uppsala, Sweden) after the serum samples were thawed at room temperature.

Calculating of Blood Glucose and Serum Insulin Values in Percentages

Blood glucose and serum INS levels were determined in mg/dl and µg/l, respectively.[16] The individual values of the groups treated with URE alone, NAC (12.5, 25, and 50 mg/kg), YOH (0.25 and 1 mg/kg), and their combination (NAC 12.5 mg/kg plus YOH 0.25 mg/kg) plus URE and NAC (50 mg/kg), and YOH (1 mg/kg) without URE were subtracted from the average value of normal saline-receiving group and then multiplied by 100.[18]

Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 8 software. Data obtained from glucose measurements before and after URE injection were analyzed by two-way repeated measures analysis of variance (ANOVA) followed by Bonferroni's post hoc test. Data obtained from percentage alterations in blood glucose and serum INS levels were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. In the figures, data are presented as mean ± standard error of the mean (Mean ± SEM). The significant level was considered to be $p < 0.05$.

Results

No significant differences were observed in blood glucose levels (in mg/dl) at 25 (73.96 ± 6.36) and 5 (71.66 ± 8.34) minutes before and at 30 (75.52 ± 5.46), 60 (72.56 ± 5.92), 90 (66.94 ± 6.51), 120 (71.48 ± 5.45), and 150 (67.96 ± 5.62) min after NS injection. Compared to NS, injection of URE significantly ($p < 0.001$) increased blood glucose levels (in mg/dl) at 30 (162.88 ± 13.59), 60 (179.74 ± 14.61), 90 (170.82 ± 13.18), 120 (158.58 ± 11.41), and 150 (161.50 ± 10.45) min. Blood glucose levels at 25 and 5 min before URE injection did not show significant differences in all groups (Figure 1). The percentage changes of blood glucose significantly ($p < 0.001$) reached to 234.79 ± 11.66% after URE injection (Figure 2). The serum insulin percentage non-significantly ($p > 0.05$) increased by urethane to 122.54 ± 6.57 % (Figure 3).

Figure 1 shows the effects of NAC, YOH, and their combination on time-dependent alterations in blood glucose level after URE injection. Analysis of data related to NAC injection (Figure 1A) data with two-way repeated measures ANOVA revealed significant difference among treatments ($F(4,140) = 94.35$, $p < 0.0001$), times ($F(6,140) = 43.77$, $p < 0.0001$), and interactions ($F(24,140) = 7.310$, $p < 0.0001$). Subsequent analysis with Bonferroni's *post hoc* test indicated that NAC at a dose of 12.5 mg/kg had no effects, whereas at doses of 25 and 50 mg/kg, it reduced blood glucose levels at all time-points at significant levels of $p < 0.05$ and $p < 0.01$, respectively (Figure 1A). Analysis of time-dependent data obtained from YOH injection (Figure 1B) with two-way repeated measures ANOVA revealed significant difference among treatments ($F(3,112) = 118.7$, $p < 0.0001$), times ($F(6,112) = 30.03$, $p < 0.0001$), and interactions ($F(18,112) = 9.419$, $p < 0.0001$). Subsequent analysis with Bonferroni's *post hoc* test indicated that blood glucose levels were significantly reduced by YOH (0.25 mg/kg) at 30 min after URE injection ($p < 0.05$). The YOH at a dose of 1 mg/kg, significantly ($p < 0.01$) reduced blood glucose levels at all time points after URE injection (Figure 1B). Analysis of time-dependent data obtained from NAC plus YOH (Figure 1C) with two-way repeated measures ANOVA revealed significant difference among treatments ($F(4,140) = 81.59$, $p < 0.0001$), times ($F(6,140) = 62.28$, $p < 0.0001$), and interactions ($F(24,140) = 7.004$, $p < 0.0001$). Subsequent analysis with Bonferroni's *post hoc* test showed that a combination treatment with IP injections of NAC (12.5 mg/kg) plus YOH (0.25 mg/kg) significantly decreased blood glucose levels at 30 min ($p < 0.01$) and at 60, 90, 120, and 150 min ($p < 0.05$) after URE injection. (Figure 1C).

Figure 2 shows the effects of NAC, YOH, and their low dose combination on percentage alterations (in the 30-150 min period) in blood glucose level in URE-treated rats. Analysis of percentage data with one-way ANOVA showed significant differences ($F(7,32) = 43.32$, $p < 0.0001$) among treated groups. Subsequent analysis by Tuckey's test revealed that NAC at a dose of 12.5 mg/kg had no effect, whereas at a dose of 25 mg/kg it significantly ($p < 0.001$) decreased blood glucose percentage to 171.99 ± 7.05%. The blood glucose percentage was reduced to the control percentage (118.19 ± 7.37 %) by 50 mg kg NAC (Figure 2). The YOH

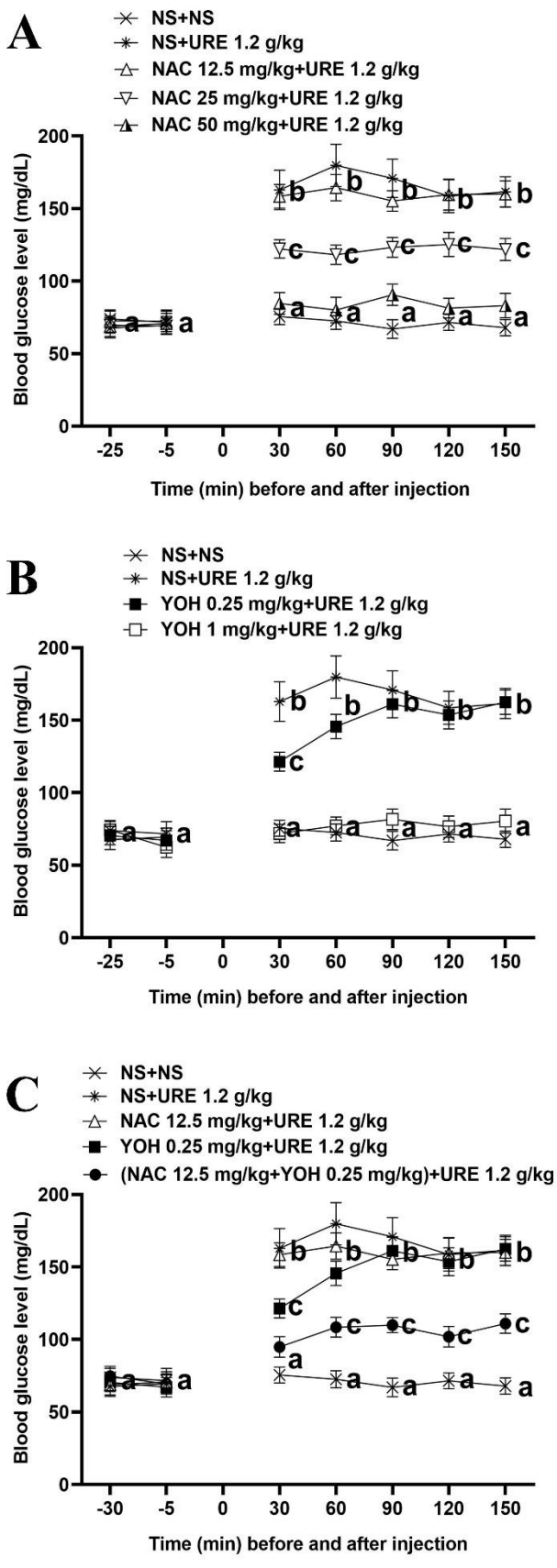

Figure 1. Effects of (A) n-acetylcysteine (NAC), (B) yohimbine (YOH) and (C) NAC plus YOH on time-dependent hyperglycemia induced by urethane (URE) in rats. The NAC, YOH, and NAC plus YOH were injected 30 min before UT injection. Normal saline (NS) was used to obtain basal data. Data are the means ± SEM obtained from five rats. Non-similar letters show significant differences among groups (a vs b: $p < 0.01$, a vs c: $p < 0.05$, and b vs c: $p < 0.05$).

at a dose of 0.25 mg/kg was without significant effect, whereas at a dose of 1 mg/kg, it decreased blood glucose percentage near to control (109.26 ± 8.42 %, Figure 2). A combination treatment with 12.5 mg/kg NAC and 0.25 mg/kg YOH significantly ($p < 0.01$) reduced this percentage to 154.02 ± 6.49 % (Figure 2).

Figure 3 shows the effects of NAC, YOH, and their low dose combination on percentage alterations in serum INS level in URE-treated rats. Analysis of percentage data with one-way ANOVA showed significant differences ($F(7,32) = 25.48$, $p < 0.0001$) among treated groups. Subsequent analysis by Tuckey's test revealed that NAC at a dose of 12.5 mg/kg had no effect, whereas at doses of 25 and 50 mg/kg it significantly increased serum INS percentage to 159.72 ± 7.09 ($p < 0.01$) and 196.81 ± 8.46% ($p < 0.001$), respectively (Figure 3). The YOH at a dose of 0.25 mg/kg was without significant effect, whereas at a dose of 1 mg/kg, it increased serum INS percentage to 202.61 ± 11.62 % ($p < 0.001$, Figure 3). A combination treatment with 12.5 mg/kg NAC plus 0.25 mg/kg YOH significantly ($p < 0.01$) increased serum INS percentage to 162.92 ± 8.05 % (Figure 3).

In conscious rats (not receiving urethane, Figure 4) treated with NS, NAC (50 mg/kg), YOH (1 mg/kg), and NAC (12.5 mg/kg) plus YOH (0.25 mg/kg), the time-dependent [treatments: $F(3,112) = 05346$, $p > 0.05$; times: $F(6,112) = 1.464$, $p > 0.05$ and interaction: $F(18.112 = 0.215$, $p > 0.05$, Figure 4A] and percentage changes in blood glucose ($F(3,16 = 0.4761$, $p > 0.05$, Figure 4B) and percentage of serum INS ($F(3,16) = 0.2046$, $p > 0.05$, Figure 4C) levels showed no significant differences.

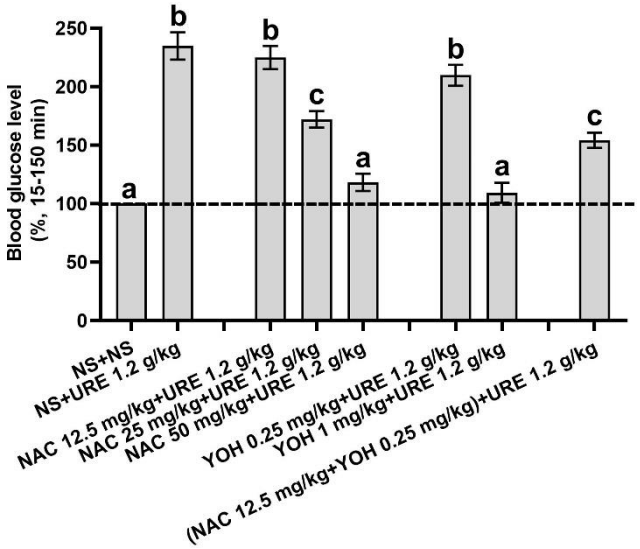

Figure 2. Effects of n-acetylcysteine (NAC), yohimbine (YOH), and NAC plus YOH on percentage alteration in blood glucose after urethane (URE) injection in rats. The NAC, YOH, and NAC plus YOH were injected 30 min before UT injection. Normal saline (NS) was used to obtain basal data. Data are the means ± SEM obtained from five rats. Non-similar letters show significant differences among groups (a vs b: $p < 0.01$, a vs c: $p < 0.05$, and b vs c: $p < 0.05$).

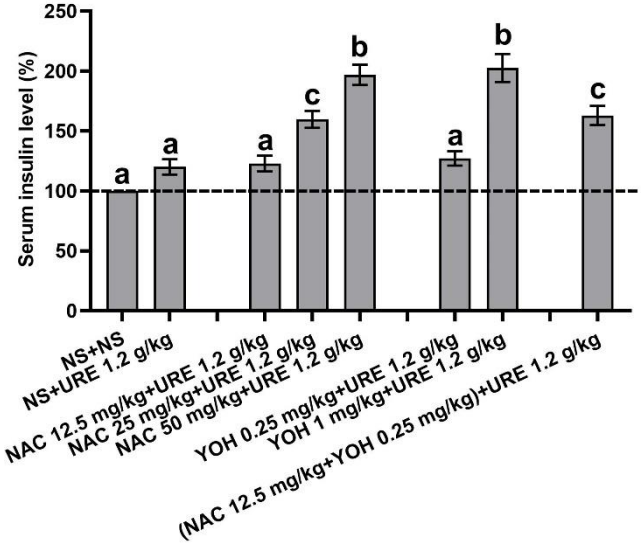

Figure 3. Effects of n-acetylcysteine (NAC), yohimbine (YOH), and NAC plus YOH on percentage alteration in serum insulin (INS) after urethane (UT) injection in rats. The NAC, YOH, and NAC plus YOH were injected 30 min before UT injection. Normal saline (NS) was used to obtain basal data. Data are the means ± SEM obtained from five rats. Non-similar letters show significant differences among groups (a vs b: $p < 0.01$, a vs c: $p < 0.05$, and b vs c: $p < 0.05$).

Discussion

In this study, we observed that URE injection significantly increased blood glucose levels for 2.5 h. The URE (ethyl carbamate) is a water-soluble compound widely used as a general anesthetic to induce long-term stability of physiological functions in animal experiments.[19] The hyperglycemic effect of URE observed in the current study is consistent with other findings in which IP injection of URE at doses of 1.25 and 1.5 g/kg caused an increase in blood glucose for up to 4 h.[20-22] In addition to hyperglycemia, the current study results showed a non-significant increase in serum INS after URE injection. These metabolic effects (hyperglycemia with no alteration in INS) of UT can be explained by stimulating sympathetic nervous system to adrenal medulla and liver as well as reducing glucose uptake by cells. It has been reported that URE slightly stimulates the sympathetic nervous system of the pancreas and liver, causing glycogenolysis leading to hyperglycemia.[23] On the other hand, it has been shown that URE can cause INS resistance in brain neurons.[24] It is worth noting that some other anesthetics, including isoflurane and sevoflurane in dogs and propofol in rats, have been found to cause INS resistance in tissues such as the liver and skeletal and cardiac muscles.[25,27]

In the current study, NAC was able to exert an antihyperglycemic effect against URE-induced hyperglycemia by reducing both time-dependent and percentage alterations in blood glucose levels. It also increased INS elevation. Although the effect of NAC on URE-induced hyperglycemia and insulin alteration has

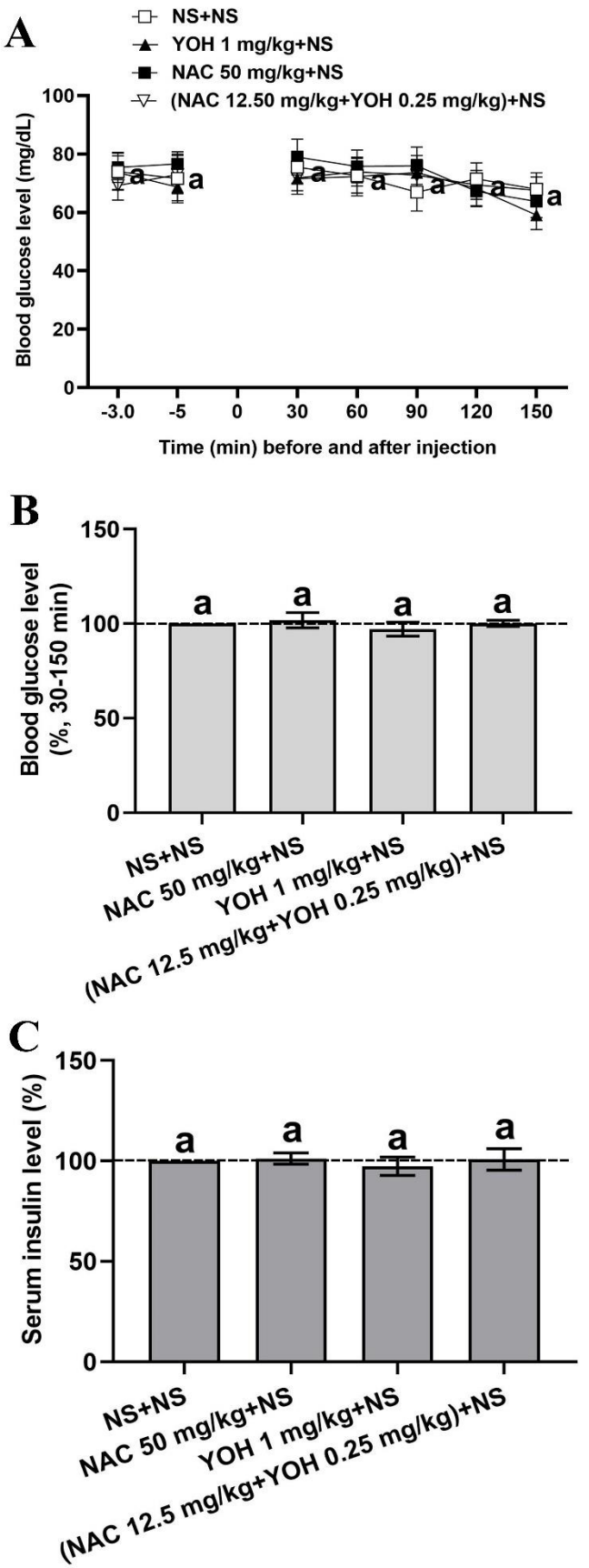

Figure 4. Effects of n-acetylcysteine (NAC), yohimbine (YOH), and NAC plus YOH on (A) time-dependent and (B) percentage alterations of blood glucose level and (C) percentage changes in serum insulin (INS) level in conscious (not-receiving URE) rats. Normal saline (NS) was used to obtain basal data. The NAC, YOH, and NAC plus YOH were injected 30 min before NS injection. Data are the means ± SEM obtained from five rats. Similar letters indicate no significant differences.

not been reported, the use of NAC before general anesthesia and surgery has been recommended to prevent unwanted life-threatening effects. Potential perioperative benefits of NAC include arrhythmia prevention after cardiac surgery, decreased contrast-induced nephropathy, improved post-transplant liver function and superior pulmonary outcomes with general anesthesia.[27] It has been reported that administration of NAC during isoflurane anesthesia preserves liver functions at one and 24 hours after laparoscopic surgery.[28] Adding NAC to local anesthetic solutions such as lidocaine and adrenaline has been shown to promote wound healing in a dorsal skin incision model in rats by reducing scar size and width.[29] The NAC affects acute and chronic hyperglycemia as well as INS resistance. For example, a short-lasting hyperglycemia induced by streptozotocin (STZ) in adipocytes has been found to reduce effectively by NAC.[30] Moreover, it was found that NAC alleviated INS resistance in vitamin-D deficient mice as well as STZ-induced type 2 diabetes.[7,31]

In the present study, YOH decreased time-dependent and percentage elevations of blood glucose level and increased serum INS level. This means that YOH produces an antihyperglycemic effect by increasing INS release. It has been reported that oral administration of YOH, but not prazosin (an α_1-adrenergic receptor antagonist) and propranolol (a β-adrenergic blocker), prevent URE-induced hyperglycemia.[32] In support of the involvement of alpha$_2$-adrenergic receptors in anesthesia-induced hyperglycemia, it should be noted that in a study targeting ketamine-xylazine-induced hyperglycemia, YOH was found to produce an antihyperglycemic effect by increasing INS level.[16,17] However, in conscious animals, the role of alpha$_2$-adrenergic receptors in the brain, spinal cord and peripheral organs has been suggested in causing hyperglycemia. For example, IP, intrathecal and ICV injections of YOH produced potent antihyperglycemic effects in mice under immobilization stress.[33] Because YOH crosses the blood-brain barrier, the use of alpha$_2$-adrenergic antagonists that do not cross the blood-brain barrier such as L-659,066 and MK-467 (vatinoxan) seems necessary to distinguish its peripheral and central effects. In this regard, MK-467 has produced an antihyperglycemic effect against a sedative and preanesthetic drug combination including fentanyl (an opioid receptor agonist)-midazolam (a benzodiazepine receptor agonist) and medetomidine (an α_2-adrenergic receptor agonist) in rats.[34] In isolated rat pancreatic beta cells, it has been found that adding glucose stimulates INS secretion, dexmedetomidine (an α_2-adrenergic receptor agonist) inhibits glucose-dependent INS secretion, and adding YOH removes the inhibitory effect of dexmedetomidine and induces INS secretion.[35] Because injection of xylazine (an alpha-2 adrenergic receptor agonist) in normoglycemic and diabetic monkeys increased blood glucose level due to decreased glucose utilization, the role of the α_2-adrenergic receptor in altering INS sensitivity has been suggested.[36] It seems that the decrease in blood glucose level and increase in serum INS level observed in the present study could be due to the stimulating effects on INS release and sensitivity (reduction in INS resistance).

In the present study, the combined use of a low dose NAC (12.5 mg/kg) with a low dose YOH (0.25 mg/kg) produced antihyperglycemic and increased serum INS level. Although there has been no report demonstrating a collaboration between NAC and the alpha$_2$-adrenergic receptor in attenuating URE-induced hyperglycemia, NAC was found to have an ability to alter sympathetic nervous system activity. It has been reported that systemic administration of NAC prevents the hypertensive effect of asprosin (an adipokine) injected into the paraventricular nucleus of the hypothalamus by reducing sympathetic outflow on the heart and blood vessels.[37] In addition, microinjection of NAC into the paraventricular nucleus of the hypothalamus prevented the increase in sympathetic system activity and pressor response induced by microinjection of GLP into the same area.[38] Furthermore, NAC has been found to prevent intermittent hypoxia-induced sympathetic stimulation in humans.[39] As discussed above, NAC exerts very beneficial effects in reducing INS resistance in various conditions such as diabetes and vitamin D deficiency.[7,31] It has been reported that NAC, by attenuating pyrin domain containing 3 (NLRP3) inflammasome/thioredoxin interacting protein (TXNIP) pathway, reduces INS resistance and improves INS-dependent glucose utilization in skeletal muscle cells.[40]

In conclusion, the results of the present study demonstrated that URE without any significant effect of serum INS, increased blood glucose level. Alone and combined treatments with NAC and YOH suppressed the URE-induced hyperglycemia. In addition, these treatment (NAC, YOH, and NAC plus YOH) elevated serum INS. It seems that α_2-adrenergic receptor and INS might be involved in antihyperglycemic action of NAC.

Acknowledgement

We hereby express our appreciation and gratitude to the Vice Chancellor for Research, Faculty of Veterinary Medicine, Urmia University. This work was financially supported by Office of Vice Chancellor for Research of Urmia University, Urmia, Iran (Thesis No. 28136/1403-08-23).

Conflict of Interest

The authors declare that there are no conflicts of interest.

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