Iranian Veterinary Surgery Association

IRANIAN JOURNAL OF VETERINARY SURGERY

Journal homepage: www.ivsajournals.com

ORIGINAL ARTICLE

Effect of Curcumin, an Active Substance of Turmeric, on Acute Hyperglycemia Induced by Ketamine-Xylazine: Role of α_2-Adrenergic Receptor

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Received: 13 June 2019
Accepted: 7 January 2020
Online: 7 January 2020

Keywords:
Ketamine-xylazine;
Curcumin;
Hyperglycemia;
Insulin;
Rats.

Abstract

Objective - Medicinal plants and their active constituents are frequently used components for treating hyperglycemia. In the present study, the effect of curcumin was investigated on acute hyperglycemia and hyperinsulinemia induced by ketamine-xylazine in rats. To explore the possible mechanism, yohimbine (a α_2-adrenergic receptor antagonist) was also used.

Design - An experimental study.

Animals – Forty-eight healthy male Wistar rats.

Procedures – Rats were divided into eight groups with six rats in each group to receive intraperitoneal injection of normal saline, oral administration of curcumin (12.5, 50 and 200 mg/kg), intraperitoneal injection of yohimbine (0.5 and 2 mg/kg), and oral administration of curcumin (12.5 mg/kg) plus intraperitoneal injection of yohimbine (0.5 mg/kg). After these treatments, ketamine (100 mg/kg) and xylazine (10 mg/kg) were intraperitoneally administered to all groups. Blood glucose concentration was measured at 60 and 5 min before and at, 30, 60, 90 and 120 min after ketamine-xylazine injection. Serum insulin concentration was measured by ELISA kit at the end of experiment.

Result- Ketamine-xylazine increased blood glucose and decreased serum insulin. Curcumin lowered the increased blood glucose and increased the decreased serum insulin. Yohimbine prevented the hyperglycemia and hypoinsulinemia induced by ketamine-xylazine produced the same results as curcumin. Low doses of curcumin and yohimbine induced documented hypoglycemic and hyperinsulinemic effects.

Conclusion and Clinical Relevance- Based on the results, it is concluded that curcumin improves hyperglycemia and hypoinsulinemia induced by ketamine-xylazine and α_2-adrenergic receptor may involve in this effect.

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DOI: 10.30500/ivsa.2020.189763.1186

1. Introduction

Commonly used anesthetics can affect a number of physiological parameters such as cardiovascular, neural, metabolic and behavioral parameters.[1] Ketamine is a commonly used short-acting anesthetic and analgesic agent that induces a trance-like anesthetic state known as dissociative anesthesia in both animals and humans. Xylazine is considered safe when used alone or in combination with other anesthetics and analgesics such as ketamine or isoflurane in animal research.[2] Co-administration of ketamine with xylazine (KX, ketamine/xylazine anesthesia) is a commonly used anesthetic regimen in domestic and laboratory animals including mice and rats.[3,4] In this context, hyperglycemia induced by ketamine-xylazine has been introduced as a preclinical model of acute hyperglycemia and has been used for exploring hyperglycemia mechanisms.[5,6]

Curcumin (diferuloylmethane), an orange-yellow component of turmeric is a polyphenol natural product isolated from the rhizome of the plant Curcuma longa. In recent years, extensive in vitro and in vivo studies suggested curcumin has anticancer, antiviral, antiarthritic, anti-amyloid, antioxidant, and anti-inflammatory properties.[7] Curcumin can reduce blood glucose level by reducing the hepatic glucose production, stimulation of glucose uptake by glucose transporters, stimulation of insulin secretion from pancreatic tissues and improvement in pancreatic cell function.[8] Curcumin also affects receptor function of a variety of neurotransmitters such as serotonin and dopamine.[9]

Glucose is a sugar that circulates the blood, serving as the body's main source of energy. Central and peripheral organs such as brain, pancreas and liver are involved in blood glucose regulation. Pancreas has an important role in regulating blood glucose by insulin secretion.[10] Sympathetic and parasympathetic divisions of autonomic nervous system control insulin secretion and inhibition of sympathetic system induces insulin secretion.[11]

In the present study, the effects of curcumin were investigated on hyperglycemia and hypoinsulinemia induced by ketamine-xylazine in rats. Yohimbine, an α_2-adrenergic receptor antagonist, was also used to explore the possible mechanism.

2. Materials and Methods

Animals

Healthy adult male Wistar rats weighing 220-250 g were used throughout the study. In laboratory under controlled 12 h light-dark cycle and ambient temperature (22 ± 0.5 °C), the animals were maintained with *ad libitum* food and water. All experiments were performed between 10:00 h and 14:00 h. The Animal Ethics Committee of Faculty of Veterinary Medicine of Urmia University approved the research protocol and animal care procedures.

Chemical Compounds

The used chemical compounds including curcumin and yohimbine were purchased from Sigma-Aldrich Chemical Co., St. Louis, USA. Ketamine (Alfasan, Holland) and xylazine (Alfasan, Holland) were purchased from native veterinary pharmacy. Chemical compounds were prepared before administration.

Study Protocol

Figure 1 shows the present study protocol. Rats were placed in a box at 90 min before anesthesia induction. Blood glucose levels were measured at 60 and 5 min before and at 30, 60, 90 and 120 min after anesthesia induction. Curcumin was orally administered and yohimbine intraperitoneally (IP) injected at 50 and 35 min before anesthesia induction, respectively. This time-dependent route of administration was performed in separate and combined treatments with curcumin and yohimbine. At the end of experiment blood sampling via the heart was performed for serum insulin level measurement.

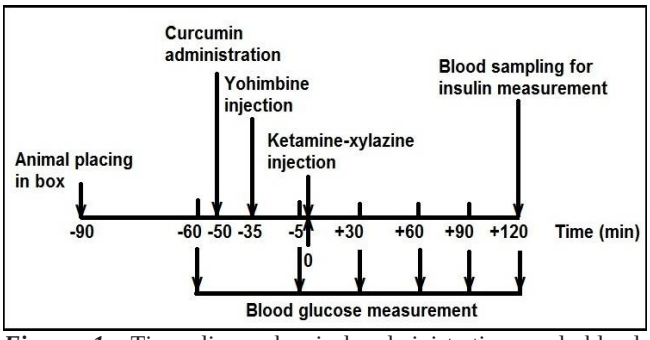

Figure 1. Time line, chemical administration and blood biochemical determination used in the present study.

Animal Grouping

Forty-eight rats were divided into eight groups with six rats in each as the following:

1. NS + NS group received normal saline (PO – IP).
2. NS + KX group received normal saline (PO) plus ketamine-xylazine (IP).
3. Cur 12.5 + KX group treated with curcumin (12.5 mg/kg, PO) plus ketamine-xylazine (IP).
4. Cur 50 + KX group administered with curcumin (50 mg/kg, PO) plus ketamine-xylazine (IP).
5. Cur 200 + KX group treated with curcumin (200 mg/kg, PO) plus ketamine-xylazine (IP).
6. Yoh 0.5 + KX group treated with yohimbine (0.5 mg/kg, IP) plus ketamine-xylazine (IP).
7. Yoh 2 + KX group received yohimbine (2 mg/kg, IP) plus ketamine-xylazine (IP).
8. Cur 12.5 + Yoh 0.5 + KX group treated with curcumin (12.5 mg/kg, PO) plus yohimbine (0.5 mg/kg, IP) plus ketamine-xylazine (IP).

The doses of curcumin and yohimbine used here were in accordance with the other investigations in which curcumin (12.5, 100, and 200 mg/kg) and yohimbine (1-4 mg/kg) have been used.[12,13]

Administration Routes

Curcumin suspended in normal saline and orally administered by gavage at a constant volume of 0.3 ml/rat, and yohimbine was dissolved in normal saline and intraperitoneally injected at a fixed volume of 1 ml/kg.

Induction of Hyperglycemia and Hypoinsulinemia

In the present study, ketamine-xylazine model of hyperglycemia and hypoinsulinemia was used. Briefly, a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg) was IP injected at a constant volume 1 ml/kg. Blood glucose level was measured before and after induction of anesthesia. Serum insulin level was determined at the end of experiment. Hyperglycemia and hypoinsulinemia induced by ketamine-xylazine may be related to xylazine, because alone IP injection of ketamine did not alter blood glucose and serum insulin levels in fed rats.[5] Hyperglycemia and hypoinsulinemia induced by anesthetics such as ketamine-xylazine have been considered as a preclinical model for evaluating acute glucose homeostatic mechanisms.[5,6]

Blood Glucose Measurements

Blood glucose concentration was determined using a digital glucometer (Glucocard 01-mini, Arkray, Japan). For this purpose, a 30-guage needle was inserted 2 mm to the apex of tail and 10 µl blood introduced to the strip of glucometer and 6 s later the amount of glucose was read from the monitor the end of tail was punctured with a 30-gauge needle and 10 µl blood introduced to the strip of glucometer and 6 seconds later the amount of glucose was read from the monitor. Blood glucose concentrations were expressed as mg/dl.[6]

Serum Insulin Determination

After the last blood glucose measurement, a 25-gaug, injection needle was inserted into the heart through 7th and 8th intercostal muscles.[14] Blood samples (0.4 ml) were collected from the heart into non-heparin containing tubes. These tubes were centrifuged at 3500 rpm for 10 min, separated serum samples and transferred to Eppendorf tubes for insulin determination. Serum insulin concentration was detected using an insulin ELISA kit (Rat insulin ELISA kit, Mercodia AB, Sylveniusgatan 8A SE-

75450, Uppsala, Sweden) after the serum samples were thawed at room temperature. Serum insulin levels were expressed as µg/L

Statistical Analyses

Statistical comparisons were performed using GraphPad Prism version 5.3 (GraphPad software Inc., San Diego, USA). The data obtained from glucose measurement on time points before and after anesthesia were analyzed by two-way analysis of variance (ANOVA) followed by the Bonferroni *post hoc* test. Data obtained from insulin concentrations were analyzed using one-way ANOVA followed by Tukey's post hoc test. Area under the curve (AUC) for blood glucose levels was calculated by the trapezoidal method,[15] and analyzed by unpaired t-test in Figure 2B and one-way ANOVA in Figure 3B-5B. In figures, data are expressed as the mean ± SEM. A value of $p < 0.05$ was considered statistically significant.

3. Results

Figure 2 shows the blood glucose level changes after intraperitoneal injection of normal saline and ketamine-xylazine. There were significant differences among treatments ($F_{(1,60)} = 145.402$, $p < 0.0001$), across times ($F_{(5,60)} = 48.072$, $p < 0.001$), and between interactions ($F_{(5,60)} = 48.231$, $p < 0.001$) in the effects of normal saline and xylazine on blood glucose level (Figure 2A). Unpaired t-test analysis of AUC revealed a significant (df = 6, t = 6.616, $p < 0.001$) increase of blood glucose level in ketamine-xylazine group (Figure 2B).

Figure 3 shows the effects of curcumin on blood glucose changes induced by ketamine-xylazine. Significant differences were observed among treatments ($F_{(4,150)} = 103.012$, $p < 0.0001$), across times ($F_{(5,150)} = 94.025$, $p < 0.0001$), and between interactions ($F_{(20,150)} = 11.112$, $p < 0.01$) in the effects of curcumin on hyperglycemia induced by ketamine-xylazine (Figure 3A). One way ANOVA analysis of AUC showed significant ($F_{(4,19)} = 19.361$, $p < 0.001$) differences among treated groups. Curcumin at a dose of 12.5 mg/kg produced no significant ($p > 0.05$) effect, whereas at doses of 50 mg/kg ($p < 0.01$) and 200 mg/kg ($p < 0.001$) it significantly decreased the increased blood glucose (Figure 3B).

Figure 4 shows the effects of yohimbine on blood glucose changes induced by ketamine-xylazine. There were significant differences among treatments ($F_{(3,120)} = 190.794$, $p < 0.0001$), across times ($F_{(5,120)} = 80.252$, $p < 0.0001$), and between interactions ($F_{(20,150)} = 21.181$, $p < 0.001$) in the effects of yohimbine on blood glucose level changes induced by ketamine-xylazine (Figure 4A). One way ANOVA analysis of AUC showed significant ($F_{(3,15)} =$

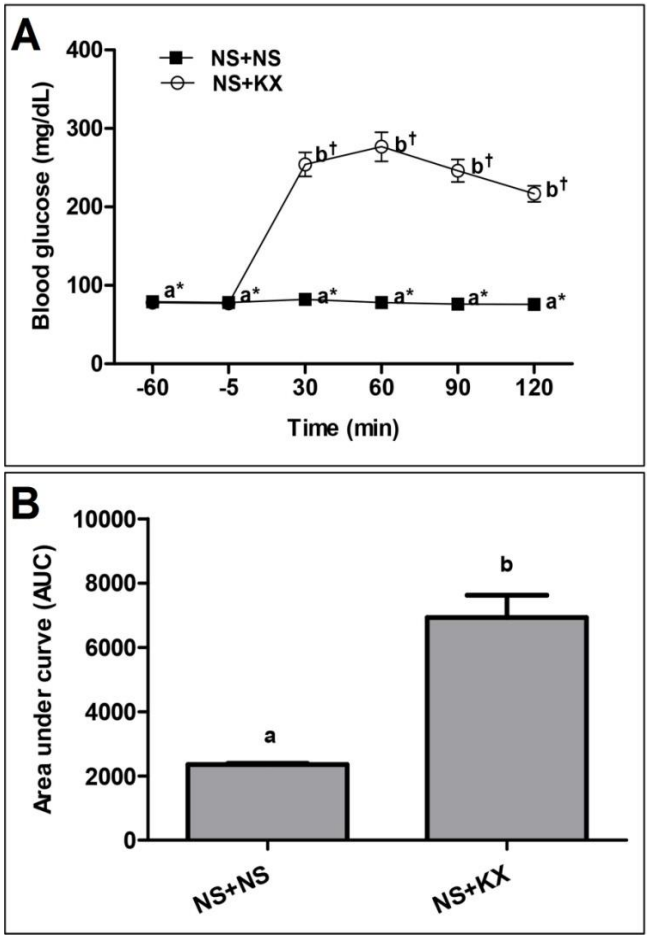

Figure 2. Time-dependent **(A)** and area under curve **(B)** concentrations of blood glucose before and after normal saline and ketamine-xylazine injection. Data are the means ± SEM obtained from six rats. Similar letters and similar symbols indicate no significant differences and non-similar letters and non-similar symbols indicate significant differences. NS; normal saline, KX: ketamine-xylazine.

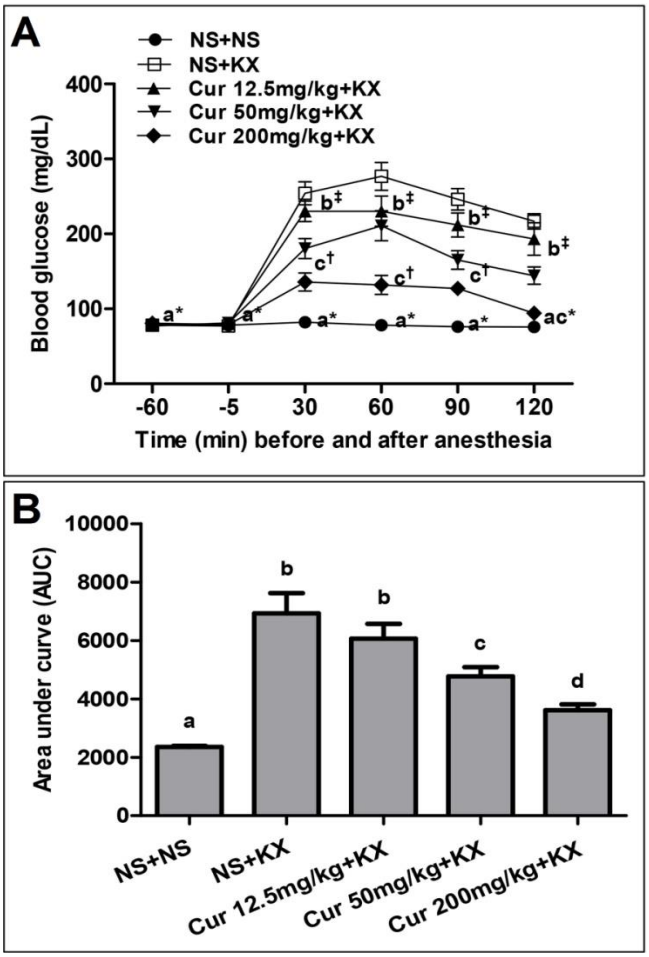

Figure 3. Effect of oral administration of curcumin on time-dependent **(A)** and area under curve **(B)** concentration changes of blood glucose induced by ketamine-xylazine. Data are the means ± SEM obtained from six rats. Curcumin was orally administered 50 min before induction of anesthesia. Similar letters and similar symbols indicate no significant differences, whereas non-similar letters and non-similar indicate significant differences. NS: normal saline, KX: ketamine-xylazine, Cur: curcumin.

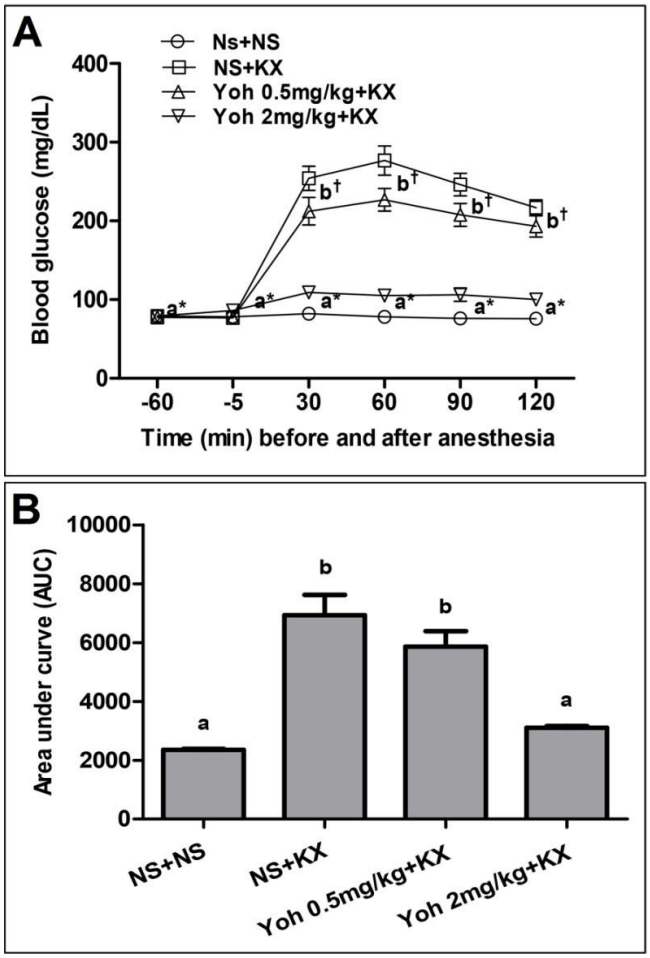

Figure 4. Effect of intraperitoneal injection of yohimbine on time-dependent **(A)** and area under curve **(B)** concentration changes of blood glucose induced by ketamine-xylazine. Data are the means ± SEM obtained from six rats. Yohimbine was intraperitoneally injected 35 min before induction of anesthesia. Similar letters and similar symbols indicate no significant differences, whereas non-similar letters and non-similar indicate significant differences. NS: normal saline, KX: ketamine-xylazine, Yoh: yohimbine.

25.156, $p < 0.001$) differences among treated groups. The increased blood glucose level induced by ketamine-xylazine was not affected by 0.5 mg/kg yohimbine. Yohimbine at a dose of 2 mg/kg ($p < 0.001$) significantly decreased the increased blood glucose (Figure 4B). No significant differences were observed between normal saline plus normal saline and yohimbine plus ketamine-xylazine groups (Figure 4A and 4B).

Figure 5 shows the effects of curcumin plus yohimbine on blood glucose concentration changes induced by ketamine-xylazine. Significant differences were observed among treatments ($F_{(3,100)} = 14.446$, $p < 0.01$), across times ($F_{(4,100)} = 59.493$, $p < 0.001$), and between interactions ($F_{(12,100)} = 4.449$, $p < 0.05$) in the effects of curcumin plus yohimbine on hyperglycemia induced by ketamine-xylazine (Figure 5A). One way analysis of AUC showed significant ($F_{(4,19)} = 17.174$, $p < 0.001$) differences among treated groups. Curcumin (12.5 mg/kg) plus yohimbine (0.5 mg/kg) produced a significant ($p < 0.001$) decreasing effect on the hyperglycemia induced by ketamine-xylazine (Figure 5B).

Figure 6 shows the effects of curcumin, yohimbine and their combination on the serum insulin levels alteration induced by ketamine-xylazine. One-way ANOVA revealed

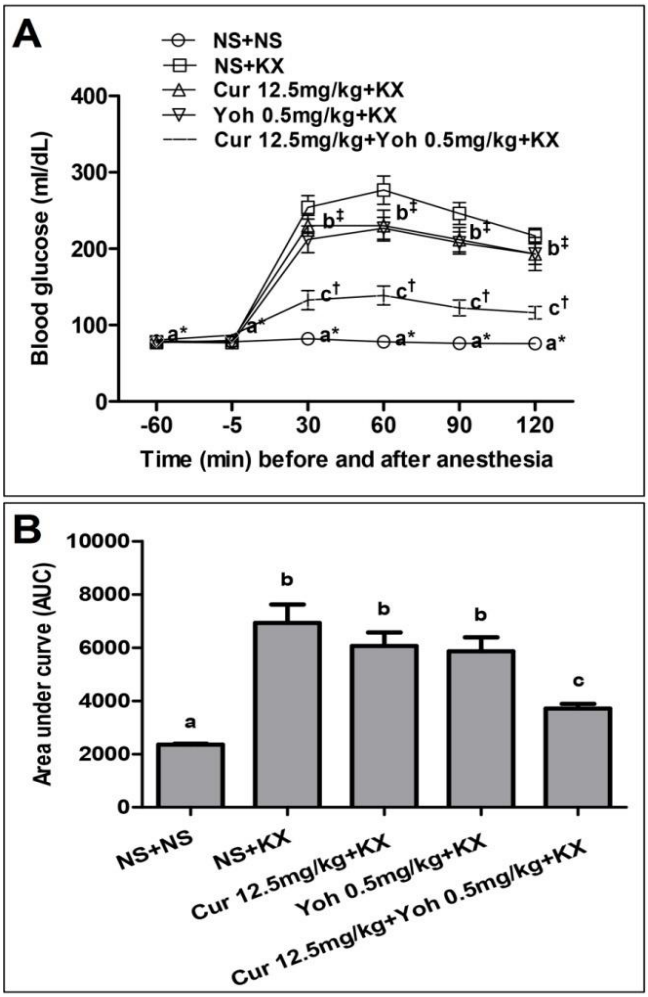

Figure 5. Effect of together oral administration of curcumin and intraperitoneal injection of yohimbine on time-dependent **(A)** and area under curve **(B)** concentration changes of blood glucose induced by ketamine-xylazine. Data are the means ± SEM obtained from six rats. Curcumin was orally administered and yohimbine was intraperitoneally injected 50 and 35 min before induction of anesthesia, respectively. Similar letters and similar symbols indicate no significant differences, whereas non-similar letters and non-similar indicate significant differences. NS: normal saline, KX: ketamine-xylazine, Cur: curcumin, Yoh: yohimbine.

significant ($F_{(7,47)}$ = 73.933, $p < 0.0001$) differences among groups. Serum insulin level was significantly ($p < 0.001$) decreased by ketamine-xylazine. Curcumin (12.5 mg/kg) and yohimbine (0.5 mg/kg) had no significant ($p > 0.05$) effects, whereas curcumin at doses of 50 mg/kg ($p < 0.01$) and 200 mg/kg ($p < 0.01$), yohimbine at a dose of 2 mg/kg ($p < 0.01$) and a combined treatment with 12.5 mg/kg curcumin and 0.5 mg/kg yohimbine ($p < 0.05$) significantly increased the decreased levels of serum insulin (Figure 6).

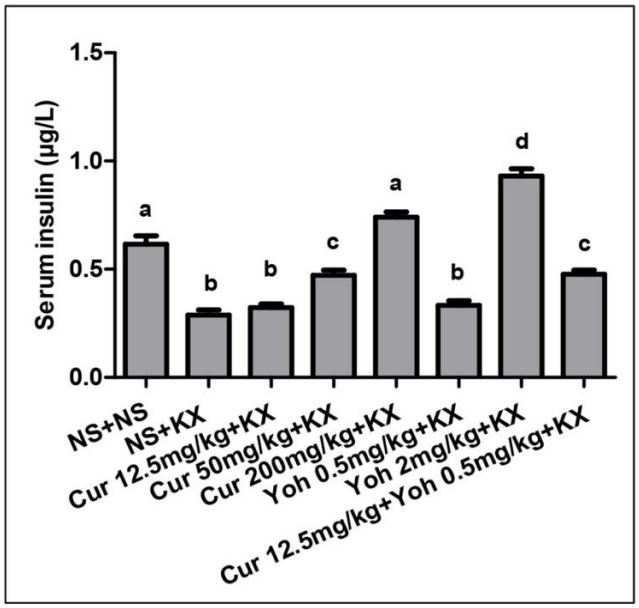

Figure 6. Effect of alone and together administrations of curcumin and yohimbine on serum insulin changes induced by ketamine-xylazine. Data are the means ± SEM obtained from six rats. Oral administration of curcumin and intraperitoneal injection of yohimbine were performed 50 and 35 min before ketamine-xylazine administration, respectively. Similar letters indicate no significant differences. Non-similar letters indicate significant differences. NS: normal saline, KX: ketamine-xylazine, Cur: curcumin, Yoh, yohimbine.

4. Discussion

The results of the present study showed hyperglycemic and hypoinsulinemic effects of ketamine-xylazine. These effects of ketamine-xylazine were prevented by prior administration of yohimbine. These results indicate that peripheral α_2-adrenoceptors are involved in glucose homeostasis, and are in accordance with the findings of other investigations. For example, intramuscular (IM) injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) produced potent hyperglycemia and hypoinsulinemia in fed rats and these effects were prevented by prior administration of yohimbine.[5,6] In addition to well-known dissociative anesthetic property, ketamine has many pharmacological effects such as analgesic and antidepressant properties.[16] Anesthetic and analgesic properties of ketamine are attributed to direct inhibition of N-methyl-D-aspartate (NMDA) receptors, whereas other functions are related to dopamine, serotonin, opioids and

voltage-gated sodium channels.[17] Xylazine, 2(,6-dimethyl phenylamine)-4-H-5,6-dihydro-1,3-thiazine hydrochloride, is widely used as a sedative, analgesic and relaxant in veterinary medicine.[18] Xylazine is a typical α_2-adrenergic receptor agonist and this receptor is distributed with high densities in hypothalamic neurons and endocrine pancreas.[19,20] Sympathetic nervous system through α_2-adrenoceotprs influences insulin release from B cells of the pancreas and subsequent blood glucose concentration and increased α_2-adrenoceptor signaling in these regulatory systems may result in beta-cell dysfunction leading to metabolic syndrome.[19,21] In this context, intravenous injection of dexmedetomidine, an α_2-adrenergic receptor agonist, increased and decreased blood glucose and serum insulin levels in dogs, respectively, and these effects were prevented by MK-467, an α_2-adrenergic receptor antagonist.[22] The above-mentioned findings and the results of the present study confirm the involvement of α_2-adrenergic receptor in blood glucose homeostatic mechanisms.

Our present results showed that curcumin decreased the elevated level of blood glucose and increased the decreased concentration of insulin induced by ketamine-xylazine. There are no reports showing the effects of curcumin on hyperglycemia and hypoinsulinemia in ketamine-xylazine model. It has been reported that curcumin increases glucagon-like peptide-1 secretion, which leads to a reduction of blood glucose levels via the stimulation of insulin secretion.[23] In addition, curcumin was found to cause insulin secretion from rat-isolated pancreatic islets.[24] In other conditions such as diabetes, curcumin produces beneficial effects on blood glucose and serum insulin. For example, a mixture of curcumin hesperidin and rutin ameliorated hyperglycemia and subsequent oxidative stress in streptozotocin (STZ)-induced type-1 diabetic mice.[25] In this context, curcumin prevented beta-cell structural changes induced by streptozotocine in rats.[26] Curcuminoids including curcumin, demethoxycurcumin and bisdemethoxycurcumin decreased blood glucose level and improved insulin resistance by reducing plasma free fatty acids and increasing fatty acid oxidation in skeletal muscle of type-2 diabetic rats.[27] Taken together, it seems that curcumin can affect glucose homeostasis by stimulation of insulin secretion and subsequent glucose utilization.

In the present study, curcumin and yohimbine produced comparable anti-hyperglycemic and anti-hypoinsulinemic effects with superior effects of yohimbine. In addition, a synergistic effect was observed between curcumin and yohimbine when used together. This indicates that curcumin affects glucose homeostatic mechanisms through interaction with α_2-adrenoceptors. Although there are no reports showing the interaction between curcumin and α_2-adrenoceptors receptors in glucose regulation, curcumin mediated dilation and constriction of peripheral arterioles via adrenergic receptors.[28] In addition, curcumin trough activation of muscarinic M1 cholinoceptors increased glucose uptake into skeletal muscle isolated from rats.[29] Curcumin was found to have ability to interact with cell membrane proteins such as toll-like receptors for producing regulating effects on cell function.[30] In addition, curcumin ameliorated aging-related increase of brain thiobarbituric acid-reactive substances and elevated aging-related decrease of glutathione in hippocampus by switching VDCC calcium source into NMDA receptor-dependent one.[31] Therefore, based on all data collected here there is enough evidence to support that glucose homeostasis could be affected by curcumin in contribution with α_2-adrenergic system.

In our present study, the 5 min point before ketamine-xylazine injection expressed blood glucose levels alteration in un-anesthetized condition. Regarding this time point results, we did not show significant effects of curcumin, yohimbine and their combination on blood glucose levels. These results reflect that curcumin and yohimbine may not affect blood glucose in normal conditions. However, it needs to further experiments concerning chronic administration effect of curcumin on blood glucose and serum insulin levels.

In conclusion, the results of the present study showed that ketamine-xylazine produced acute hyperglycemia and hypoinsulinemia. Blockade of α-2 adrenoceptor by yohimbine reversed ketamine-xylazine hyperglycemic and hypoinsulinemic effects. Oral administration of curcumin prevented hyperglycemia and hypoinsulinemia induced by ketamine-xylazine. A synergistic effect was observed between curcumin and yohimbine.

Conflict of Interests

The authors declare that there are no conflicts of interest.

References

1. Merry AF, Mitcell SJ. Complications of anaesthesia. *Anaesthesia*, 2018; 73: 7-11.
2. Veilleux-Lemieux D, Castel A, Carrier D, Beaudry F, Vachon P. Pharmacokinetics of ketamine and xylazine in young and old Sprague-Dawley rats. *Journal of the American Association for Laboratory Animal Science*, 2013; 52: 567-570.
3. Dugassa J, Fromsa A. Review on dissociative anaesthetics and compatible drug combinations in veterinary clinical practice. *Veterinary Medicine*, 2018; 3: 21-30.
4. Davis JA. Mouse and rat anesthesia and analgesia. Current Protocols in Neurosciences 2008; 42: 1-21.
5. Saha JK, Xia J, Grondin JM, Engle SK, Jakubowski JA. Acute hyperglycemia induced by ketamine/xylazine anesthesia in rats: mechanisms and implications for preclinical models. *Experimental Biology and Medicine (Maywood)*, 2005; 230: 777-784.
6. Erfanparast A, Tamaddonfard E, Mohammadi E, Mohammadi A. Effect of vitamine B_{12} on acute model of hyperglycemia induced by ketamine xylazine in rats. *Urmia Medical Journal*, 2017; 28: 28-38.
7. Zhou H, Beevers CS, Huang S. The targets of curcumin. *Current Drug Targets* 2011; 12: 332-347.
8. Ghorbani Z, Hekmatdoost A, Mirmiran P. Anti-hyperglycemic and insulin sensitizer effects of turmeric and its principle constituent curcumin. *International Journal Endocrinology and Metabolism*, 2014; 12: e18081.
9. Kulkarni S, Dhir A, Akula KK. Potentials of curcumin as an antidepressant. *Scientific World Journal*, 2009; 9: 1233-1241.
10. Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. *Experimental and Molecular Medicine*, 2016; 48: e219.
11. Chandra R, Liddle RA. Modulation of pancreatic exocrine and endocrine secretion. *Current Opinion in Gastroenterology*, 2013; 29: 517-522.
12. Cabral AD, Kapusta DR, Kenigs VA, Varner KJ. Central alpha2-receptor mechanisms contribute to enhanced renal responses during ketamine-xylazine anesthesia. *American Journal of Physiology*, 1998; 275: 1867-1874.
13. Tamaddonfard E, Erfanparast A, Hamzeh-Gooshchi N, Yousofizadeh S. Effect of curcumin, the active constituent of turmeric, on penicillin-induced epileptiform activity in rats *Avicenna Journal of Phytomedicine*, 2012; 2: 196-205.
14. Moradi-Arzeloo M, Farshid AA, Tamaddonfard E, Asri-Rezaei S. Effects of histidine and vitamin C on isoproterenol-induced acute myocardial infarction in rats. *Veterinary Research Forum*, 2016; 7: 47-54.
15. Taati M, Tamaddonfard E. Ventrolateral orbital cortex oxytocin attenuates neuropathic pain through periaqueductal gray opioid receptor. *Pharmacological Reports*, 2018; 70: 577-583.
16. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. *Anesthesia and Essays Research*, 2014; 8: 283-290.
17. Tyler MW, Yourish HB, Ionescu DF, Haggarty SJ. Classics in chemical neuroscience: ketamine. *ACS Chemical Neuroscience*, 2017; 8: 1122-1134
18. Greene SA, Thurmon JC. Xylazine - a review of its pharmacology and use in veterinary medicine. *Journal of Veterinary Pharmacology and Therapeutics*, 1988; 11: 295-313.
19. Fagerholm V, Haaparanta M, Scheinin M. α2-adrenoceptor regulation of blood glucose homeostasis. *Basic and Clinical Pharmacology and Toxicology*, 2011; 108: 365-370.
20. Kitano T, Kobayashi T, Yamaguchi S, Otsuguro KI. The α2A -adrenoceptor subtype plays a key role in the analgesic and sedative effects of xylazine. Journal of *Veterinary Pharmacology and Therapeutics*, 2019; 42: 243-247.
21. Singh A, Gibert Y, Dwyer KM. The adenosine, adrenergic and opioid pathways in the regulation of insulin secretion, beta cell proliferation and regeneration. *Pancreatology*, 2018; 18: 615-623.
22. Restitutti F, Raekallio M, Vainionpää M, Kuusela E,

Vainio O. Plasma glucose, insulin, free fatty acids, lactate and cortisol concentrations in dexmedetomidine-sedated dogs with or without MK-467: a peripheral α-2 adrenoceptor antagonist. *Veterinary Journal*, 2012; 193: 481-485.

23. Kato M, Nishikawa S, Ikehata A, Dochi K, Tani T, Takahashi T, Imaizumi A, Tsuda T. Curcumin improves glucose tolerance via stimulation of glucagon-like peptide-1 secretion. *Molecular Nutrition & Food Research*, 2017; 61: 3.
24. Abdel Aziz MT, El-Asmar MF, El Nadi EG, Wassef MA, Ahmed HH, Rashed LA, Obaia EM, Sabry D, Hassouna AA, Abdel Aziz AT. The effect of curcumin on insulin release in rat-isolated pancreatic islets. *Angiology*, 2010; 61: 557-566.
25. Parmar MS, Syed I, Gray JP, Ray SD. Curcumin, hesperidin, and rutin selectively interfere with apoptosis signaling and attenuate streptozotocin-induced oxidative Stress-mediated hyperglycemia. *Current Neurovascular Research*, 2015; 12: 363-374.
26. Meghana K, Sanjeev G, Ramesh B. Curcumin prevents streptozotocin-induced islet damage by scavenging free radicals: a prophylactic and protective role. *Euroupean Journal of Pharmacology*, 2007; 577: 183-191.
27. Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, Meng M, Li XX, Sun CH. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. *Molecular Nutrition & Food Research*, 2013; 57: 1569-1577.
28. Dewar AM, Clark RA, Singer AJ, Frame MD. Curcumin mediates both dilation and constriction of peripheral arterioles via adrenergic receptors. *Journal of Investigative Dermatology*, 2011; 131: 1754-1760.
29. Cheng TC, Lin CS, Hsu CC, Chen LJ, Cheng KC, Cheng JT. Activation of muscarinic M-1 cholinoceptors by curcumin to increase glucose uptake into skeletal muscle isolated from Wistar rats. *Neuroscience Letter*, 2009; 465: 238-241.
30. Boozari M, Butler AE, Sahebkar A. Impact of curcumin on toll-like receptors. *Journal of Cellular Physiology*, 2019; 234: 12471-12482.
31. Cheng YF, Guo L, Xie YS, Liu YS, Zhang J, Wu QW, Li JM. Curcumin rescues aging-related loss of hippocampal synapse input specificity of long term potentiation in mice. *Neurochemical Research*, 2013; 38: 98-107.