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Original Article

Diabetes alters the blood glucose response to ketamine in streptozotocin-diabetic rats

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Abstract: Ketamine is a commonly used short-acting anesthetic and recently attempted to treat pain which is a complication of diabetes. In this study we investigated the effect of ketamine on glucose levels of normal rats and diabetic rats. The results showed that no significance between the glucose levels in ketamine treatment group and saline treatment group at all time points was observed in normal rats. Ketamine did not produce hyperglycemia in normal fasted rats. However, ketamine dose dependently elevated glucose in diabetic rats from 80 mg/kg to 120 mg/kg at 1 hour after injection. The glucose did not return to the levels before treatment in streptozotocin (STZ) induced diabetic rats. Insulin revealed a powerful potency in decreasing glucose levels in diabetic rats. Ketamine did not induce acute hyperglycemia any more after diabetic rats pretreated with insulin. Serum corticosterone was significantly increased in all treatment groups including saline group after 1 hour treatment compared with baseline values. Then the corticosterone declined in both saline treatment groups. However, ketamine induced a more significant increase in corticosterone at 1 hour after injection compared with that of saline control group of diabetic rats. And no decline trend of corticosterone was observed after ketamine treatment 2 hours. Insulin did not reduce the elevated corticosterone level induced by ketamine either. The results suggested that the diabetic rats had a risk of hyperglycaemia when they were treated with ketamine. Pretreatment with insulin is a good symptomatic treatment for hyperglycaemia induced by ketamine.

Keywords: Diabetes, ketamine, anesthesia, insulin, stress

Introduction

Ketamine which was first used as an anesthetic in 1964 displays a good safety profile in humans [1]. It is still widely prescribed for surgery, especially in veterinary anesthesia today. The pharmacological actions are clearer now. There are three main receptors that may mediate the anesthetic effect of ketamine. Firstly, ketamine is a non-competitive antagonist of the N-methyld-aspartate (NMDA) receptor [2]. NMDA receptor, together with a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors are three ionophoreionophore-linked postsynaptic receptors activated by the major excitatory neurotransmitter glutamate. NDMA receptor plays key roles in synaptic plasticity and synaptic communication which would affect the learning and memory. Secondly, Ketamine potentiates GABA-induced Cl-currents which result in synaptic inhibition [3]. Thirdly, Ketamine is also a weak agonist of opioid receptors [4]. Theanesthetic effect induced by ketamine is characterized by profound analgesia and amnesia without heart rate or breath alterations, which is called "dissociative anesthetic". Apart from application as an anesthetic medicine, ketamine has been used to produce ecstasy tablets since it is found that ketamine can make a"rave" scene [5]. More and more people use ketamine for non-medical therapeutic purposes, although it is illegal in many countries. Another important application for managing pain has been investigated [6]. Especially in neuropathic pain management, ketamine combined with amitriptyline shows efficacy potential on pain relief [7]. Neuropathic pain is a common and severe complication of diabetes. Up to 15% diabetic people suffers the neuropathic pain [8]. The current treatment includes antidepressant drug [9]. Ketamine has been investi-

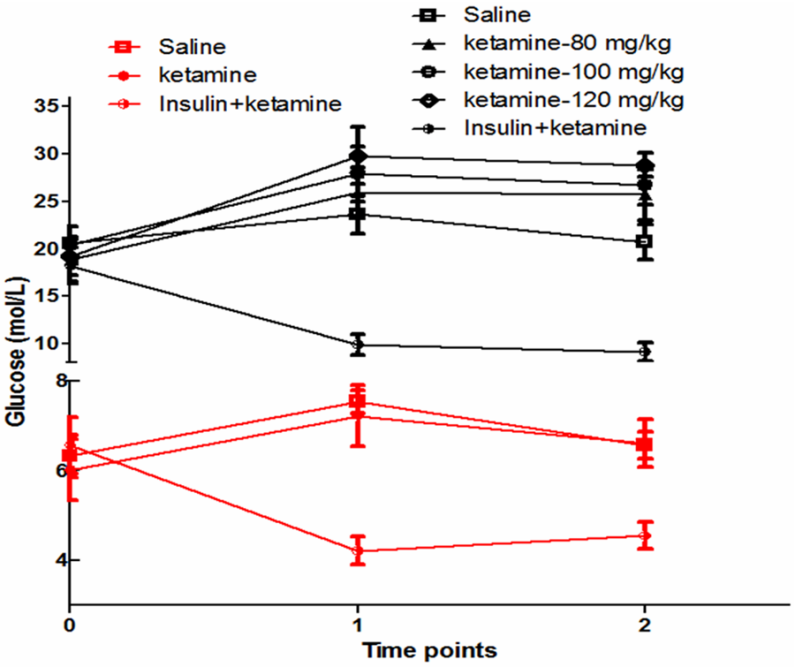

Figure 1. The glucose levels of normal rats which received different treatment. Red curves represented the glucose levels of normal rats which received different treatment. Black curves represented the glucose levels of diabetic rats induced by STZ which received different treatment.

gated to treat diabetic neuropathic pain in clinic. But it is a problem to be worried about that some studies suggest that ketamine has possibility to induce hyperglycemia in fed rats. To confirm the effect of ketamine on blood glucose, we used streptozotocin (STZ) diabetic rats treated with ketamine to demonstrate the effect.

Material and methods

Materials

Ketamine injection was from Fujian Gutian Pharmaceutical Co., Ltd. Insulin was from Roche. ELISA kit of corticosterone was purchased from Uscn Life Science Inc.

Experimental animal

Male Sprague-Dawley (SD) rats were obtained from the Experimental Animal Center of Suzhou Aiermaite technology Co. Ltd. (SPF grade, Certificate No. SCXK20140007). All rats were housed in polycarbonate cages. Each cage contained less than 5 animals. All animals had free access to diet and water. But rats were fasted 12 hours before experiment started. The animal room was maintained at a temperature of 20-25°C with 12 h light-dark alternation. All animal research protocols were approved by the Institutional Animal Care and Use Committee (IACUC) of Weifang Yidu Central Hospital and all procedures were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996.

Experiment design

Diabetic rat model was induced by STZ. Briefly, males were intraperitoneally injected with 60 mg/kg STZ for continues two days. One week after injection blood was collected from tail for glucose determination. A value of 16.65 mmol/L was set as threshold.

Fifty STZ induced diabetic rats and thirty normal rats were used in the study. Fifty STZ induced diabetic rats were divided into 6 groups by body weight. Ten rats in each group were treated with saline, 80, 100, 120 mg/kg ketamine and 5 u/kg insulin followed by 120 mg/kg ketamine respectively. Thirty normal rats were randomly divided into 3 groups by body weight. Ten rats in each group were treated with saline, 120 mg/kg ketamine and 5 u/kg insulin followed by 120 mg/kg ketamine respectively. Glucose was determined at three time points by glucose meter: prior administration, 1 hour post administration and 2 hours post administration. Blood samples were collected from orbital venous plexus for corticosterone determination at the same time points. There was a 2 hours interval between the first blood collection and administration. Blood samples were centrifuged and serum was used for corticosterone determination. Corticosterone was determined by ELISA kit according to the procedure provided by the producer.

Table1. The corticosterone levels of normal rats which received different treatment (ng/ml)

Groups	Before anesthesia	An hour after the anesthetic	Two hour after the anesthetic
Saline	109±23	242±26	220±34
Ketamine-80 mg/kg	126±14*	306±26*	294±38*
Ketamine-100 mg/kg	127±18*	320±40*	310±28*
Ketamine-120 mg/kg	122±21*	332±64*	320±36*
Insulin + Ketamine	125±16*	310±22*	296±42*

Values are mean ± SD. *P<0.05 vs. Saline group.

Statistics

All results were expressed as means ± SD. Inter-group difference of means of quantitative parameters was statistically analyzed by using one way analysis of variance (ANOVA) followed by LSD test using SPSS 17.0. A value of $P<0.05$ was considered statistically significant.

Results

As **Figure 1** shown, glucose in normal fasted rats was about 6.32 mM. When rats were treated with saline, the glucose was slightly elevated to 7.73 mM after intraperitoneal injection 1 hour. One hour later, the glucose returned to normal level. This indicated that external stimulus like grabbing and injection could induce an acute stress in rats, which caused glucose slightly increase but quickly return to normal level within 2 hours. Rats treated with ketamine showed the similar features on the change of glucose. There was no significance between the glucose levels in ketamine treatment group and saline treatment group at all time points. Therefore, the results suggested that ketamine did not produce hyperglycemia in normal fasted rats. Similarly, glucose was increased in STZ induced diabetic rats in saline treatment group after injection 1 hour and decreased after 2 hours. Ketamine exhibited a different profile in diabetic rats from normal rats. Ketamine dose dependently elevated glucose from 80 mg/kg to 120 mg/kg at 1 hour after injection. The glucose did not return to the levels before treatment in STZ induced diabetic rats, though a slight decrease was observed at 2 hours after injection. Insulin revealed a powerful potency in decreasing glucose levels in diabetic rats. When the diabetic rats were treated with insulin, the glucose level was significantly reduced even to the normal level. Ketamine did not induce acute hyperglycemia any more after diabetic rats pretreated with insulin.

Corticosterone was also determined in the study (**Table 1**). Serum corticosterone was significantly increased in all treatment groups including saline group after 1 hour treatment compared with beginning values. Then the corticosterone declined in both saline treatment groups. However, ketamine induced a more significant increase in corticosterone at 1 hour after injection compared with that of saline control group of diabetic rats. And no decline trend of corticosterone was observed after ketamine treatment 2 hours. Insulin did not reduce the elevated corticosterone level induced by ketamine either.

Discussion

Ketamine which is a commonly used short-acting anesthetic recently reveals an impression of the treating pain and depression patients [6]. However, ketamine treatment has been linked to various side effects including CNS-related symptoms, cardiovascular stimulation and liver injury. Our results might make diabetic patients treated with ketamine to call additional attention to the influence on the hyperglycemia, which is a major initiator of diabetic complications such as Neuropathy and microvascular complications [10]. Many mechanisms of hyperglycemia induced damage have been advocated. The reactive oxygen intermediate theory is one classic and predominant well-researched theory of them [10]. High glucose levels increased the free radicals such as superoxide aniongeneration as byproducts of mitochondrial oxidative phosphorylation. The free radicals can damage cells and organisms and finically result in the complications occurrence. Antioxidants successfully blocking the complications of diabetes in animal models strongly support the reactive oxygen theory [11]. Not only chronic hyperglycemia but also acute hyperglycaemia activates oxidative stress [12]. Ketamine induced hyperglycaemia has a risk to aggravate the complications of diabetes. This alertsdiabetic patients to strictly control glucose levels, especially when the patients receive ketamine.

As an anesthetic, ketamine was commonly accompanied with aversive stimuli (stressors) like surgery and bleeding. The stressors activate a complex stress response involving the endocrine systems. The Hypothalamic-pituitary-adrenal (HPA) axis is a major part of the neuroendocrine system that controls the reactions to stress. HPA axis has a central role in regulating many homeostasis. HPA activation is a double-edged sword for humans in the setting of stress [13]. On one hand, it allows major organisms to adapt to the adverse environment partly by supplying enough energy for survival [14, 15]. On the other hand, glucocorticoid secretion is associated with metabolic syndrome including hypertension, glucose intolerance, diabetes mellitus, and hyperlipidemia [16]. Corticosterone, the natural glucocorticoid in the rat [17], is a widely accepted biomarker of stress [18]. In our study the profile of corticosterone concentration of diabetic rats treated with ketamine was not coincident with that of normal rats treated with ketamine. Our results indicated that ketamine prolonged the stress duration of diabetic rats compared with that of normal rats. Diabetes altered the response to stress induced by ketamine. When the stimulus generated by ketamine, signals deviated from the stimulus is delivered to hypothalamus. Then hypothalamus begins to secrete corticotropin-releasing hormones. The hormones in turn make pituitary gland tosecrete adrenocorticotropic hormone. Final key messenger in the cascade, corticosteroneis released from adrenal gland mediated by adrenocorticotropic hormone. Some groups report that ketamine-induced hyperglycaemia could be mediated by activation of α2-adrenoceptors [19]. When the stressor or threat is no longer present, heightened levels of corticosterone is delivered to the pituitary gland and hypothalamus. Then the feedback inhibition is activated and HPA axis' stress-response cascade is turned off. The longer stress duration induced by ketamine on diabetic rats suggests that the HPA axis stress-response circle is altered by diabetes. However, whether the stress response to stimulus is more sensitive or the negative feedback effect is blocked in diabetic rats are not clear now. It still needs to further study in future.

Insulin and corticosterone are two reciprocal signals for energy balance [20]. Glucocorticoids inhibited and insulin increased energy gain. Insulin is a prescription drug for diabetes. Our results indicated that when insulin was employed to diabetic rats with or without ketamine, blood glucose was controlled to the similar level. In contrary, blood glucose of ketamine treated rats was significantly increased at absence of insulin. However, the influence of insulin on the corticosterone was not observed. It indicated that insulin did not release the stress induced by ketamine.

From the results we conclude that the diabetic patients might have a risk of hyperglycaemia when they are treated with ketamine. Pretreatment with insulin is a good symptomatic treatment for hyperglycaemia induced by ketamine. Of cause, there is more work needed to do in the future. For example, the detailed mechanism of ketamine on glucose metabolism needs to been found out and a better etiological treatment needs to be employed.

Disclosure of conflict of interest

None.

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