The effects of hypoglycemic and alcoholic coma on the blood-brain barrier permeability

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ABSTRACT

In this investigation, the effects of hypoglycemic coma and alcoholic coma on the blood-brain barrier (BBB) permeability have been compared. Female adult Wistar albino rats weighing 180-230 g were divided into three groups: Control group (n=8), Alcoholic Coma Group (n=18), and Hypoglycemic Coma group (n=12). The animals went into coma approximately 3-4 hours after insulin administration and 3-5 minutes after alcohol administration. Evans blue (4mL/kg) was injected intravenously as BBB tracer. It was observed that the alcoholic coma did not significantly increase the BBB permeability in any of the brain regions when compared to control group. Changes in BBB permeability were significantly increased by the hypoglycemic coma in comparison to the control group values (p<0.01). Our findings suggest that hypoglycemic and alcoholic coma have different effects on the BBB permeability depending on the energy metabolism.

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KEY WORDS: blood-brain barrier, hypoglycemic coma, alcoholic coma.

INTRODUCTION

Brain tissue is protected by blood-brain barrier (BBB). It is a specialized structure consisting of endothelial cells and tight junctions between them, a continuous basal lamina which surrounds these cells. The tight junctions are reinforced by the foot processes of the astrocytes [1]. There are several reports investigating the effects of convulsions, acute hypertension, brain tumors, ischemia on the BBB permeability [2-7], however, only a few studies have examined effects of the state of coma [8, 9]. Hypoglycemic coma leads to energy deficiency due to a reduction in plasma glucose concentrations, ATP and other nucleoside triphosphates [9]. The energy deficiency with concomitant disruption of the ion homeostasis may cause dysfunctionality of both the neurons and the cerebral endothelial cells composing the BBB [10-12]. Increased BBB permeability causes vasogenic edema under pathological conditions. However, the changes in the BBB permeability during hypoglycemic coma have not precisely been understood. It has been suggested that both acute and chronic administrations of alcohol have disruptive effects on many structures and their functions including the cerebral capillary endothelial cells of the central nervous system [13-16]. While some studies have shown that acute administrations of alcohol increased the BBB permeability, others have suggested that it had no effect [16-19]. There are gender related differences in the central nervous system, and acute and chronic administration of alcohol appears to affect the female brain much more than that of male [20,21]. The reported brain morphological abnormalities could also occur more precociously in alcoholic women than in men [22]. Especially social and environmental, physiological, genetic and neurobiological ones have been demonstrated to contribute to the sex difference in response to alcohol intake, as well as the development of alcoholic complications. A number of neurotransmitters and growth factors may be partially involved in these differences between men and women [23]. In the present study, we have comparatively investigated the effects of hypoglycemic coma and alcoholic coma on BBB permeability in the female rats.

MATERIALS AND METHODS

Animals and Procedure

The procedures were in accordance with the Helsinki Declaration 2008. The female adult Wistar albino rats weighing 180-230 g were used in the experiments. The rats were divided into three groups: 1. Control (n=8), 2. Alcoholic Coma
Experimental Groups | Mean Arterial Pressure | Blood Glucose Levels (mg/dl) | Rapoport criteria Degree of BBB breakdown
--- | --- | --- | ---
Control (n=8) | 89±3 | - | 0 +1 +2 +3
Hypoglycemic Coma (n=12) | 89.5±3 | 85±7 | 21±2.5 | 3 2 3 4
Alcoholic Coma (n=18) | 88±5 | 87±10 | 131±43 | 14 4 - -

### RESULTS

The values of blood pressure, blood glucose and the changes in BBB permeability with respect to Rapoport criteria [27] are shown in Table 1. The baseline mean value of arterial blood pressure was 89.5±3 mmHg for hypoglycemic coma group and was 88±5.2 mmHg for the alcoholic coma group. No significant change was seen in arterial blood pressure values of the rats after they went into hypoglycemic coma and alcoholic coma (87±10 mmHg, 85±7 mmHg). Plasma glucose levels of the rats in alcoholic coma were found to be within the normal range (4±6±0 mg/dl), whereas those of rats in hypoglycemic coma were 5±2 ± 2.5 mg/dl (Table 1). It has been observed that the alcoholic coma did not increase the BBB permeability significantly in any of the brain regions (p>0.05) when the Evans Blue concentrations in the regions of left hemisphere, right hemisphere, cerebellum and the brain stem (0.33±0.03, 0.33±0.03, 0.33±0.06, 0.47±0.09 μg/mg tissue respectively) of Alcoholic Coma Group were compared with those of Control Group (0.22±0.07, 0.21±0.07, 0.32±0.04, 0.31±0.03 μg/mg tissue respectively) (Figure 1).
Contrarily, increased BBB permeability was observed in 9 of 12 experimental animals that went into hypoglycemic coma (Table 1). Evans Blue concentrations in the regions of left hemisphere, right hemisphere, cerebellum and the brain stem (1.3±0.03, 1.3±0.034, 0.6±0.02, 0.86±0.15 μg/mg tissue respectively) of Hypoglycemic Coma Group were compared with those of Control Group (Figure 1). It was determined that hypoglycemic coma increased the BBB permeability significantly in all of the brain regions (p<0.01).

DISCUSSION

Glucose is the main substrate the brain uses to generate energy, which penetrates into the brain by facilitated diffusion through BBB [28]. Hypoglycemia due to the reduced plasma glucose levels below normal range leads to brain dysfunctions [29]. Hypoglycemia is a relatively common condition primarily affecting diabetic patients treated with insulin or other hypoglycemic drugs and insulinoma patients. Hypoglycemic effects on the CNS include various symptoms such as irritability and lack of concentration, disruption of cognitive functions, convulsions and unconsciousness. Even a single hypoglycemic episode with convulsions and/or coma may, if prolonged and severe enough, cause permanent degenerative alterations in the cerebral cortex [30]. These symptoms of hypoglycemia suggest the presence of increased intracranial pressure and cerebral edema [31]. In a hypoglycemic coma, neurons and especially cerebral endothelial cells composing the BBB may face energy failure [32]. Endothelial cells of brain capillaries differ than the others with their relatively higher metabolism [33]. The cerebral capillary endothelial cells have mitochondria in large quantities [34] and contain comparatively 500-fold more Na+-K+-ATPase enzymes than the umbilical endothelial cells [35]. Hypoglycemia causes the dysfunctionality of active Na+-K+-ATPases in cerebral endothelial cell membranes due to the energy deficiency. Due to this dysfunctionality, potassium ions exit and ions like sodium and calcium penetrate into the cerebral endothelial cells and the cytotoxic edema occurring as a result of these changes. Thus, it may cause swelling of the endothelial cells and the tight connections between them may detach. The vasogenic edema, occurring as a result of the elevated amount of albumin due to the increased permeability, may be responsible for dysfunctionality of neurons in case of hypoglycemia [9]. Finally, it can not be excluded that hypoglycemia has detrimental effects on mitochondria at the level of the axon, affecting energy production in the axon itself, in the associated Schwann cells, in the local blood vessels and/or in the perineural sheath [36]. Sekimoto et al. [37] have demonstrated that hypoglycemia damaged the endothelial ultrastructure of cerebral arteries. Hsu and Hedley-Whyte [32] have reported that severe hypoglycemia in mice caused deletion in cerebral vessel walls. It has also been observed in our study that, the hypoglycemia coma significantly increased the BBB permeability in the left cortex, right cortex, cerebellum and brain stem regions of the brain. In addition, lack of any significant change in arterial blood pressure in rats during the hypoglycemic coma suggests that the blood pressure has no effect on the increased BBB permeability in case of hypoglycemia. It has been found that the glucose extraction in the cerebellum is twice more than that of other parts of the brain [38] so that the cerebellum conserves the cellular energy better than the cerebral cortex in case of hypoglycemic coma [10, 39]. Thus, less BBB damage in the cerebellum has been reported in comparison to the other parts of the brain [10, 40]. Similarly, we found less Evans blue-albumin extravasation in the cerebellum when compared to the cerebral cortex.

Alcohol is a soluble substance in both water and oil and can easily penetrate the lipid membranes of all the cells in the body. Thus, alcohol can penetrate the BBB easily [41]. Alcohol could affect the blood flow of the brain, brain glucose metabolism, synthesis and catabolism of various neurotransmitters [42-44], and also affects many structures and functions including the capillary endothelial cells in central nervous system [13]. In alcoholics, also many physiological dysfunctions occur beside the structural changes in the brain [20]. However, the effects of acute alcohol administration on BBB permeability are controversial, there are studies suggesting that alcohol has no effect on BBB permeability beside the studies indicating that alcohol has increased the BBB permeability against the various tracers [16-19]. Rossner et al. [45], have demonstrated that 10 % ethanol (1-3 g/kg i.v.) increased Evans blue permeability of BBB in a short term. Similarly, Eriksson et al. [46] have administered 20% ethanol (2 g/kg i.p.) and have observed increased BBB permeability in rats. However, Hillbom and Tervo [47] have observed no increase in BBB permeability after administration of 10% ethanol (5 g/kg i.p.) in rats. Effects of ethanol on BBB permeability have also been studied by using 14C-sucrose tracer in rats [16]. They have found that BBB permeability did not increase when they have administered acutely 10% ethanol as 4 g/kg i.p. Gulati et al. [18], using sodium fluorescent as tracer, have injected ethyl alcohol of 30%, 60%, and 90% as 0,568 mg/kg i.v. and consequently found that the BBB permeability has increased significantly. They suggested a correlation between alcohol concentration and BBB permeability, and the ethyl alcohol of 90% has increased the permeability more than the concentrations of 30% and 60%. However, no change in BBB permeability in rats has also been reported following administration of 20% etha-
Alcohol is common cause of coma in all age ranges. Authors do not have any commercial affiliations, or potential conflicts of interest associated with this work submitted for publication.

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