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Research report

Histamine restores hemorrhage induced hypotension by activating cholinergic neurons in nucleus tractus solitarius

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ABSTRACT

The purpose of the current study is to investigate the functional connections between the central histaminergic and cholinergic systems at NTS level in hypotensive condition.

Experiments were carried out in male Wistar Albino rats. The hypotension was achieved by withdrawing a total volume of 1.5 ml blood/100 g bodyweight over a period of 10 min. A microdialysis study was performed in NTS area to measure extracellular ACh and Ch levels. The hemorrhage produced a severe and long-lasting decrease in mean arterial blood pressure (MAP) and increase in extracellular ACh and Ch levels in NTS. Administration of histamine intracerebroventricularly (i.c.v.) or into the NTS reversed the hemorrhagic hypotension by increasing MAP and heart rate. I.c.v. injection of histamine also caused the additional increase in extracellular ACh and Ch levels. Moreover, central histamine injection augmented intracytoplasmic AChE immunoreactivity in NTS. These changes were completely blocked by histaminergic H1 receptor antagonist chlorpheniramine, but histaminergic H2 receptor blocker ranitidine and histaminergic H3/H4 receptor antagonist thioperamide failed to produce these effects.

In conclusion, these findings are interpreted that brain histaminergic H1 receptor activation by central histamine injection may promote cholinergic stimulation in the NTS and subsequently reverses the hypotension.

1. Introduction

The nucleus tractus solitarius (NTS), located in the dorsomedial medulla oblongata, is widely accepted as a pivotal brain region involved in the assimilation and integration of multiple viscerosensory processes, including cardiovascular, respiratory, gustatory, hepatic and renal control mechanisms. The importance of the NTS in the regulation of cardiovascular function has been known for so long as the first central relay for baroreceptor and chemoreceptor afferents (Giersbergen et al., 1992; Lawrence and Jarrot, 1996). Although, it is known that histamine plays a critical role to regulate the cardiovascular control from NTS (Bhuiyan et al., 2011), the interaction among different neurotransmitters /neuromodulators in this area in regulating cardiovascular functions has been an active area of research (Giersbergen et al., 1992; Lawrence and Jarrot, 1996).

Histaminergic neurons appear to provide a variety of signaling mechanisms in the brain. Activation of a small number of tuberomammillary cells in hypothalamus is thought to release histamine, which subsequently increases excitability in target cells (Schwartz et al., 1991; Wada et al., 1991). Histaminergic axons originating from a single source, the tuberomamillary nucleus of the posterior hypothalamus, innervate almost all central nervous system regions including NTS (Blandina et al., 2012). Histaminergic neurons affect many central nervous system functions, such as energy balance, drinking, pain perception, learning and memory by activating histaminergic H1, H2, H3 and H4 receptors (Schwartz et al., 1991; Brown et al., 2001; Fogel et al., 2008). Central histaminergic system also has an important role in central control of cardiovascular system. Indeed, centrally injected histamine caused pressor effects in normotensive (Brown et al., 2001; Jochem, 2000) and hemorrhaged hypotensive rats (Jochem, 2002; Jochem, 2003; Yalcin et al., 2009; Altinbas et al., 2015) by activating central histaminergic H1 receptors. Moreover, previous studies show a bidirectional interaction between the histaminergic and cholinergic system in the central cardiovascular regulation (Yalcin et al., 2009; Jochem et al., 2010; Altinbas et al., 2015). Previously, we reported that central cholinergic nicotinic and muscarinic receptors mediated the central histamine induced reversal of hemorrhagic hypotension in rats (Yalcin et al., 2009). We also determined that the

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centrally injected CDP-choline induced resuscitating effect in hemorrhaged hypotensive rats through the activation of H1 histaminergic receptors and increased the posterior hypothalamic extracellular histamine level (Jochem et al., 2010). Recently, we reported that centrally administered histamine, acting via H1 receptors, increases ACh and Ch release from the posterior hypothalamus and causes pressor and tachycardia in hemorrhaged hypotensive anesthetized rats (Altinbas et al., 2015).

Considering the above data, the primary aim of the current study was to show the functional connections between the central histaminergic and cholinergic systems at NTS level in hemorrhaged hypotensive condition using hemodynamic, microdialysis and immunohistochemistry studies.

2. Results

2.1. Cardiovascular effects of centrally injected histamine in hemorrhaged hypotensive anaesthetized rats

Hemorrhage produced severe and long-lasting hypotension in rats (Fig. 1). MAP was decreased by 46 ± 3 mm Hg (n=28) by the end of hemorrhage. I.c.v. injection of histamine (100 nmol) rapidly increased MAP and HR of the hemorrhaged hypotensive anaesthetized rats and reversed hypotension (Fig. 1A, B). The pressor response to histamine reached at its maximum level within 5–10 min after injection and it was significantly higher than those observed in the saline injected group at around 30–40 min ($p < 0.05$) (Fig. 1A, B). I.c.v. administration of histamine increased MAP and HR 40 ± 2 mm Hg, and 76 ± 3 bpm, respectively (Fig. 1A, B).

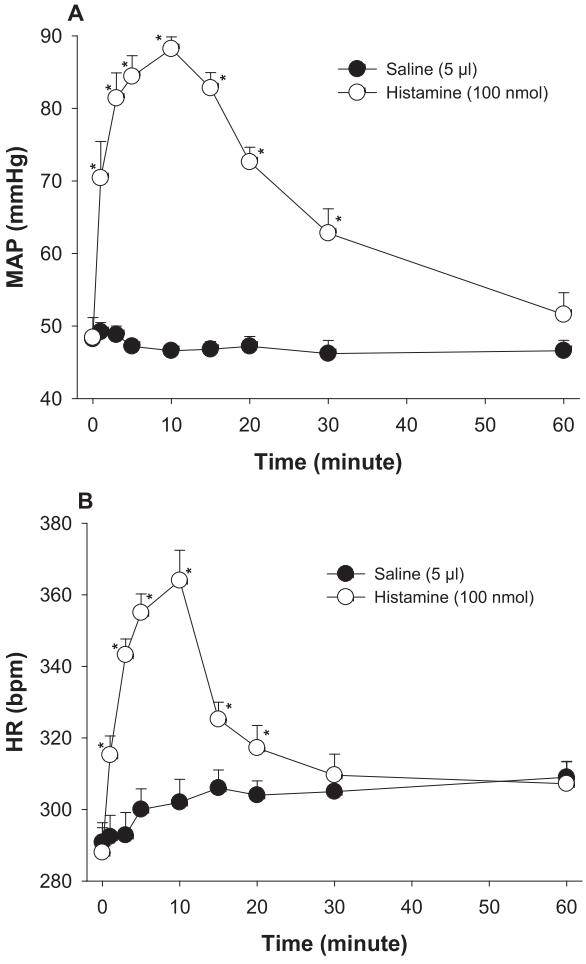

Fig. 1. Cardiovascular effects of i.c.v. injected histamine in hemorrhaged-hypotensive anaesthetized rats. Following the acute hemorrhage procedure, rats were treated with histamine (100 nmol; i.c.v.) or saline (5 µl; i.c.v.) and then MAP (A) and HR (B) were monitored for the next 60 min. Data are given as means ± S.E.M. of seven measurements. "0" shows time of histamine or saline injection. Statistical analysis was performed using two-way RM-ANOVA with post hoc *Bonferroni* test. $^{*}p < 0.05$, significantly different from the value of the saline group.

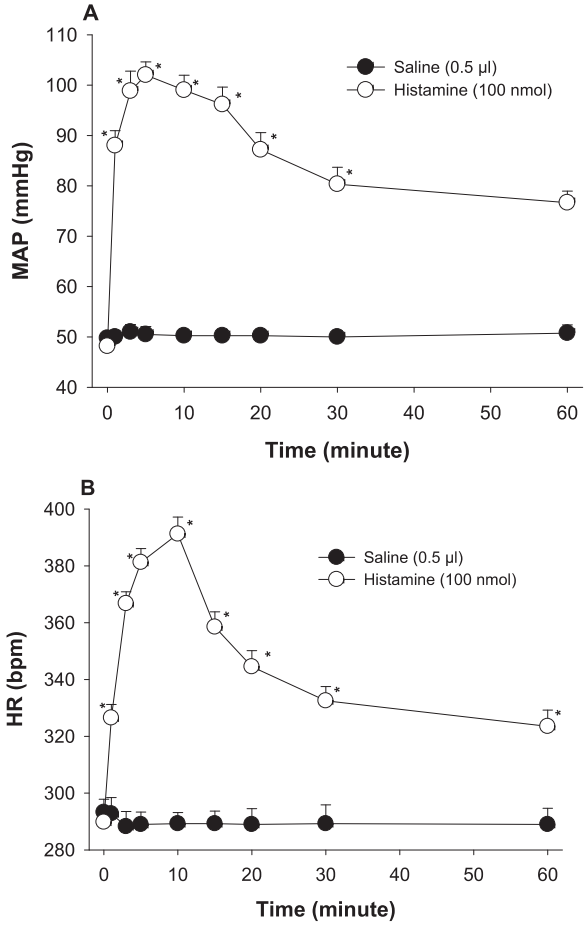

Fig. 2. Cardiovascular effects of NTS microinjected histamine in hemorrhaged-hypotensive anaesthetized rats. Following the acute hemorrhage procedure, rats were treated with histamine (100 nmol; NTS) or saline (1 µl; NTS) and then MAP (A) and HR (B) were monitored for the next 60 min. Data are given as means ± S.E.M. of seven measurements. "0" shows time of histamine or saline injection. Statistical analysis was performed using two-way RM-ANOVA with post hoc *Bonferroni* test. $^{*}p < 0.05$, significantly different from the value of the saline group.

It was subsequently investigated that the MAP and HR responses were elevated following histamine (100 nmol) injection into the NTS, which is the first synapse of the baroreflex loop, under hemorrhagic hypotension conditions. Acute hemorrhage decreased MAP in a similar manner observed in other groups, and histamine injection into the NTS caused long lasting and significant increase in MAP and HR ($p < 0.05$) (Fig. 2A, B), similar to i.c.v. injection of histamine. The MAP and HR of rats increased to a maximum level within 10–20 min followed by a decline over 60 min to the basal levels.

2.2. Effect of i.c.v. injected histamine on NTS extracellular ACh and Ch levels in hemorrhaged hypotensive anaesthetized rats

The extracellular ACh and Ch levels in the NTS perfusates before hemorrhage were 0.14 ± 0.001 and 2.80 ± 0.01 pmol, respectively (Fig. 3A, B). Hemorrhage itself activated cholinergic activation in NTS and caused significant increase in ACh (Fig. 3A) and Ch

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