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ORIGINAL RESEARCH

Interaction of Cholinergic and Cannabinoidergic Systems in Hemorrhagic Hypotension

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ABSTRACT

Given the cardiovascular effects of the cholinergic and cannabinoid systems, the present study aimed to investigate the interaction of both systems in hemorrhagic hypotensive conditions. Adult male Sprague Dawley albino rats were used in the study. Under sevoflurane anesthesia, the animals were catheterized in the left carotid arteries and jugular vein for monitoring cardiovascular parameters and producing hemorrhagic hypotension and intravenous (IV) injection, respectively. The hypotension was achieved by withdrawing a total volume of 2.2 mL blood/100g body weight over 10 minutes. The hemorrhage produced a severe and long-lasting decrease in mean arterial pressure (MAP). The IV injection of rimonabant (cannabinoid CB1 receptor antagonist) and DMSO promptly and significantly increased the MAP in the hypotensive rats. When administered at a sub-effective dose CDP-choline showed a slight increase in the MAP. However, when this same dose of CDP-choline was co-administered with DMSO, it elicited a more pronounced and prolonged increase in the MAP compared to the effects observed with CDP-choline or DMSO alone. Rimonabant partially inhibited the MAP-increasing effect of the sub-effective dose of CDP-choline administered with DMSO in the hypotensive rats. These findings suggest that CDP-choline demonstrates a synergistic interaction with DMSO, resulting in a heightened and prolonged increase in MAP during hemorrhagic hypotension. Conversely, it exhibits an antagonistic interaction with rimonabant in terms of their effects on MAP under similar conditions. These results can be interpreted as indicative of an interaction between cannabinoid CB1 receptors and the cholinergic system in the hemorrhagic hypotensive condition.

Keywords: Cannabinoid CB1 receptors. Cardiovascular system. CDP-choline. Hemorrhagic hypotension.

Hemorajik Hipotansiyonda Kolinerjik ve Kannabinoiderjik Sistemlerin Etkileşimi

ÖZET

Kolinerjik ve kannabinoiderjik sistemlerin kardiyovasküler sistem üzerindeki etkileri göz önünde bulundurularak, bu çalışmada her iki sistemin hemorajik hipotansiyon koşullarındaki etkileşiminin araştırılması amaçlanmıştır. Çalışmada erişkin erkek Sprague Dawley albino sıçanlar kullanılmıştır. Sevofluran anestezisi altında, hayvanlara kardiyovasküler parametrelerin izlenmesi, hemorajik hipotansiyon oluşturulması ve intravenöz (IV) enjeksiyon uygulamaları için sırasıyla sol karotis artere ve juguler vene kateter yerleştirilmiştir. Hipotansiyon, 10 dakika içinde 100 gram vücut ağırlığı başına toplam 2,2 ml kan alınarak oluşturulmuştur. Kan alma sonucunda ortalama arter basıncında (MAP) şiddetli ve uzun süreli bir düşüş meydana gelmiştir. Rimonabant (kannabinoid CB1 reseptör antagonisti) ve DMSO'nun IV enjeksiyonu, hipotansif sıçanlarda MAP'ı hızlı ve anlamlı şekilde artırmıştır. Sub-efektif dozda uygulanan CDP-kolin, MAP'ta hafif bir artış göstermiştir. Ancak bu doz CDP-kolin DMSO ile birlikte uygulandığında, CDP-kolin veya DMSO'nun tek başına oluşturduğu etkilere kıyasla daha belirgin ve uzun süreli bir MAP artışı meydana gelmiştir. Rimonabant, hipotansif sıçanlarda DMSO ile birlikte uygulanan sub-efektif doz CDP-kolinin MAP artırıcı etkisini kısmen engellemiştir. Bu bulgular, CDP-kolinin DMSO ile sinerjistik bir etkileşim göstererek hemorajik hipotansiyon sırasında MAP'ta daha güçlü ve uzun süreli bir artış sağladığını ortaya koymaktadır. Öte yandan, benzer koşullar altında CDP-kolin ile rimonabant arasında MAP üzerindeki etkiler açısından antagonistik bir etkileşim bulunduğu görülmektedir. Bu sonuçlar, hemorajik hipotansiyon koşullarında kannabinoid CB1 reseptörleri ile kolinerjik sistem arasında bir etkileşim olduğuna işaret edebilir.

Anahtar Kelimeler: Kannabinoid CB1 reseptörleri. Kardiyovasküler sistem. CDP-kolin. Hemorajik hipotansiyon.

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Hemorrhagic shock is the leading cause of death worldwide[1,2]. Excessive bleeding disrupts the balance between systemic oxygen consumption and delivery in the body[3,4], which results in hemodynamic instability, coagulopathy, diminished oxygen presentation to the tissues, decreased tissue perfusion, cellular hypoxia, multiple organ failure, and eventually death[5,6].

Cytidine 5'-diphosphate (CDP) choline is an endogenous mononucleotide compound that plays a role as an intermediate product during cell membrane phospholipid synthesis[7]. CDP-choline administration has been proven to be useful during several conditions like Alzheimer's disease[8], Parkinson's disease[9], cerebral ischemia-reperfusion injury[10], and glaucoma[11]. Our previous studies also reported that CDP-choline dose-dependently reverses sepsis and hemorrhage-induced hypotension by activating cholinergic nicotinic receptors and protects tissue damage during septic shock[12-14].

The endocannabinoids were reported to be secreted during hemorrhagic shock and cause vascular hypo-reactivity, which contributes to a mean arterial blood pressure (MAP) decrease during hemorrhagic shock[15-17]. These studies also reported that rimonabant, a cannabinoid CB1 receptor antagonist, prevents or attenuates hemorrhage-induced hypotension.

Central cholinergic and cannabinoidergic systems play important roles in several physiological processes, including movement control, learning and memory, nociception, and endocrine function[18-22]. It was reported that the administration of cannabinoids modulates cholinergic transmission, while the administration of nicotine modulates endocannabinoid concentration at several brain regions[23-28]. Despite the significant evidence supporting bidirectional interaction between the cannabinoidergic and cholinergic systems, there has been no study investigating a therapy targeting both systems in the context of hemorrhagic shock. The present study aimed to investigate the interaction between the cannabinoidergic and cholinergic systems by targeting both systems pharmacologically in the context of hemorrhagic shock.

Material and Method

All experimental procedures were approved by the Uludağ University Animal Experiments Local Ethics Committee (Bursa Uludağ University Local Ethics Committee; Approval No: 2017-07/02; Date: 18 April 2017) and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Animals

Fifty adult male Sprague Dawley albino rats (275–325 g), obtained from the Experimental Animal Breeding and Research Center of Uludağ University, were used in this study. Animals were housed under controlled environmental conditions (25 ± 2 °C, 12 h light/dark cycle), with free access to standard rat chow and tap water. Rats were housed two per cage. Each animal was used only once and allocated to a single experimental group, receiving a single pharmacological treatment protocol.

Experimental Groups

Rats were randomly assigned to ten experimental groups (n = 5 per group), resulting in a total of 50 animals.

The sample size (n=5 per group) was determined based on previous hemorrhagic hypotension and shock studies from our laboratory and others, in which similar group sizes were sufficient to detect significant changes in MAP and cardiovascular responses [12–14, 29]. In addition, a repeated-measures experimental design was employed, allowing each animal to serve as its own control over time, thereby increasing statistical power and reducing inter-animal variability. Considering ethical principles for animal experimentation and the severity of the hemorrhagic shock model, the minimum number of animals required to obtain reliable and reproducible results was used.

Protocol 1 (Single treatments):

Saline; 66% DMSO; Rimonabant (1 mg/kg); Rimonabant (3 mg/kg); CDP-choline (50 mg/kg).

Protocol 2 (Combined treatments):

Saline + Saline; 66% DMSO + Saline; 66% DMSO + CDP-choline; Rimonabant (1 mg/kg) + Saline; Rimonabant (1 mg/kg) + CDP-choline.

Surgical Procedures

All surgical procedures were performed under sevoflurane anesthesia (4–5% in 100% O_2). Polyethylene catheters (PE-50 tubing filled with heparinized saline, 100 U/mL) were inserted into the left carotid artery for arterial pressure recording and into the left jugular vein for intravenous drug administration. Catheters were tunneled subcutaneously, exteriorized at the dorsal neck region, and secured to prevent displacement. Animals were allowed to recover for 4–5 hours before experimentation.

Cardiovascular Measurements and Hemorrhage Protocol

Arterial catheters were connected to a pressure transducer coupled to a PowerLab data acquisition system (ADInstruments, Australia). After baseline

recording, hemorrhagic hypotension was induced by withdrawing 2.2 ml of blood per 100 g body weight over 10 minutes. After stabilization, drugs were administered intravenously and MAP and heart rate (HR) were continuously recorded for 120 minutes.

Drugs and Drug Preparation

CDP-choline and rimonabant hydrochloride were purchased from Sigma-Aldrich (Deisenhofen, Germany). CDP-choline was dissolved in saline and administered at 50 mg/kg (IV). Rimonabant hydrochloride was dissolved in 66% DMSO and administered at doses of 1 or 3 mg/kg (IV). All injections were delivered at a volume of 1 ml/kg. Drug doses were selected based on previous experimental studies demonstrating their cardiovascular effects in hemorrhagic shock and hypotensive conditions [12–14,15–17,29].

Statistical Analysis

Data are presented as mean ± SEM. Statistical analyses were performed using SPSS software (version 22.0, IBM Corp., USA). Two-way repeated-measures ANOVA followed by Fisher's LSD post hoc test was used. A value of $p<0.05$ was considered statistically significant. All statistical analyses were performed using absolute MAP values (mmHg) obtained at each time point. Percentage changes shown in the graphical presentations were used solely for illustrative purposes to facilitate visual comparison of time-dependent responses and were not subjected to statistical testing.

Results

The rats' basal MAP and HR before the hemorrhage procedure were 122.51±2.16 mmHg and 325.79±7.09 bpm, respectively. The hemorrhage procedure caused a statistically significant decrease in MAP and HR to 51.44±1.31 mmHg and 269.52±11.37 bpm, respectively ($p<0.05$). After ten minutes of recovery period, the MAP and HR of the rats were elevated to 56.74±1.84 mmHg and 276.29±10.63 bpm, respectively. All MAP values reported in the Results section represent raw measurements and were used directly for statistical evaluation.

The IV injection of rimonabant (1 and 3 mg/kg) swiftly and significantly elevated the MAP of the hypotensive-conscious rats ($p<0.05$; Figure 2). CDP-choline injected at a sub-effective dose (50 mg/kg; IV) resulted in a slight increasing trend in MAP, but this increase was not statistically significant (Figure 2). When CDP-choline at a sub-effective dose was applied together with 66% DMSO, it statistically significantly caused a stronger and longer-lasting increase in MAP than CDP-choline alone ($p<0.05$; Figure 3). Rimonabant (1 mg/kg; IV) statistically significant partially reversed the MAP-increasing effect of CDP-choline in hypotensive rats ($p<0.05$; Figure 3). In single (Figure 2) and combined (Figure 3) treatments, the MAP effect began in the first minutes of the injection and continued for approximately 20 minutes. Although numerical differences in HR values are observed between groups in Tables I and II, these variations did not reach statistical significance ($p>0.05$ for all comparisons). Therefore, HR data are presented descriptively, and no statistical significance indicators are shown in the tables. Importantly, the absence of significant HR changes indicates that the observed MAP responses were not secondary to chronotropic effects. Since the MAP effectiveness of the treatments lasted for about 20 minutes, the HR effects of all treatments were given until the 20th minute in the tables.

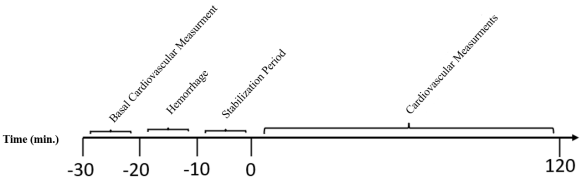

Figure 1.
Experimental timetable. "0" shows the IV drug injection time point.

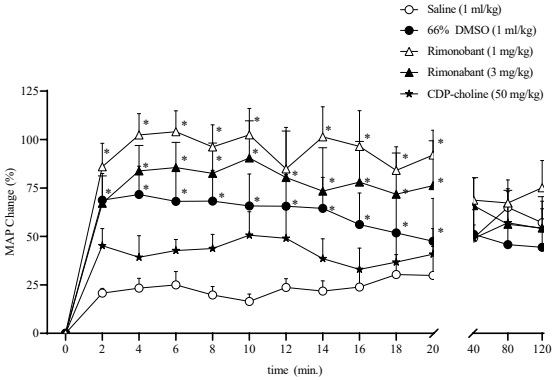

Figure 2.
*Effect of single treatment with CDP-choline and rimonabant on MAP of hemorrhagic hypotensive rats. The rats were subjected to acute hemorrhage and received a single treatment with saline (1 ml/kg; IV), 66% DMSO (1 ml/kg; IV), rimonabant (1 or 3 mg/kg; IV) or CDP-choline (50 mg/kg; IV). Before and after the treatments, the MAP of the rats was recorded. Data are presented as mean ± SEM of five measurements. *p< 0.05 is significantly different from the saline group. Statistical analyses were conducted on absolute MAP values.*

Table I. Effect of single treatment with CDP-choline and rimonabant on HR of hemorrhagic hypotensive rats. HR values are presented for descriptive purposes; no statistically significant differences were detected among groups. Each experimental group consisted of five animals (n = 5)

Time	Saline (1 ml/kg)	66% DMSO (1 ml/kg)	Rimonabant (1 mg/kg)	Rimonabant (3 mg/kg)	CDP-choline (50 mg/kg)
4.min	308.37 ± 29.76	288.21 ± 32.70	327.74 ± 23.92	243.38 ± 10.91	281.16 ± 17.03
8.min	307.58 ± 30.81	305.94 ± 39.70	303.58 ± 17.20	278.85 ± 38.38	291.17 ± 20.45
12.min	308.66 ± 33.52	315.14 ± 34.11	293.42 ± 24.22	278.85 ± 38.38	306.76 ± 19.72
16.min	312.66 ± 30.32	314.63 ± 32.12	292.47 ± 19.20	286.79 ± 31.45	291.99 ± 15.03
20.min	334.72 ± 29.34	297.82 ± 30.52	286.56 ± 23.02	289.71 ± 33.89	291.92 ± 17.77

Time	Saline + Saline	66% DMSO + Saline	66% DMSO + CDP-choline	Rimonabant + Saline	Rimonabant + CDP-choline
4.min	308.37 ± 29.76	288.20 ± 32.70	305.79 ± 23.82	327.74 ± 23.92	252.12 ± 22.14
8.min	307.58 ± 30.81	305.94 ± 39.70	334.37 ± 26.51	303.58 ± 17.20	276.45 ± 17.75
12.min	308.66 ± 33.52	315.14 ± 34.10	337.16 ± 12.15	293.42 ± 24.22	264.53 ± 24.26
16.min	312.66 ± 30.32	314.63 ± 32.10	344.02 ± 14.77	292.47 ± 19.2	256.94 ± 20.03
20.min	333.70 ± 29.34	297.82 ± 30.50	336.96 ± 12.41	286.56 ± 23.02	260.58 ± 17.42

Table II. Effect of combined treatment with CDP-choline and rimonabant on HR of hemorrhagic hypotensive rats. HR data are shown descriptively, as no significant treatment-related differences were observed. Each experimental group consisted of five animals (n = 5)

Time	Saline + Saline	66% DMSO + Saline	66% DMSO + CDP-choline	Rimonabant + Saline	Rimonabant + CDP-choline
4.min	308.37 ± 29.76	288.20 ± 32.70	305.79 ± 23.82	327.74 ± 23.92	252.12 ± 22.14
8.min	307.58 ± 30.81	305.94 ± 39.70	334.37 ± 26.51	303.58 ± 17.20	276.45 ± 17.75
12.min	308.66 ± 33.52	315.14 ± 34.10	337.16 ± 12.15	293.42 ± 24.22	264.53 ± 24.26
16.min	312.66 ± 30.32	314.63 ± 32.10	344.02 ± 14.77	292.47 ± 19.2	256.94 ± 20.03
20.min	333.70 ± 29.34	297.82 ± 30.50	336.96 ± 12.41	286.56 ± 23.02	260.58 ± 17.42

The rats were subjected to acute hemorrhage and applied combined treatment as saline (1 ml/kg; IV) + saline (1 ml/kg; IV), 66% DMSO (1 ml/kg; IV) + saline (1 ml/kg; IV), 66% DMSO (1 ml/kg; IV) + CDP-choline (50 mg/kg; IV), rimonabant (1 mg/kg; IV) + saline (1 ml/kg; IV) or rimonabant (1 mg/kg; IV) + CDP-choline (50 mg/kg; IV). Before and after the combined treatments the HR of the rats was recorded. Data are presented as mean ± SEM of five measurements.

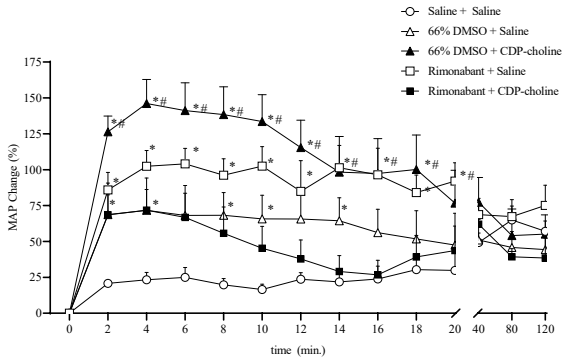

Figure 3.

*Effect of combined treatment with CDP-choline and rimonabant on MAP of hemorrhagic hypotensive rats. The rats were subjected to acute hemorrhage and applied combined treatment as saline (1 ml/kg; IV) + saline (1 ml/kg; IV), 66% DMSO (1 ml/kg; IV) + saline (1 ml/kg; IV), 66% DMSO (1 ml/kg; IV) + CDP-choline (50 mg/kg; IV), rimonabant (1 mg/kg; IV) + saline (1 ml/kg; IV) or rimonabant (1 mg/kg; IV) + CDP-choline (50 mg/kg; IV). Before and after the combined treatments the MAP of the rats were recorded. Data are presented as mean ± SEM of five measurements. *p<0.05, other groups are significantly different from "saline + saline" combined treatment group. #p<0.05, "66% DMSO + CDP-choline" combined treatment group was significantly different from other groups. Statistical analyses were conducted on absolute MAP values.*

Discussion and Conclusion

The findings reveal that IV administration of rimonabant and 66% DMSO, as the vehicle of rimonabant, significantly increased MAP in hemorrhage-induced hypotensive rats. The IV administration of CDP-choline at a sub-effective dose tended to increase MAP, but this increase was not statistically significant in hemorrhagic hypotension. Furthermore, combining 66% DMSO with a sub-effective dose of CDP-choline potentiated and prolonged the pressor compared to that induced by only DMSO. Interestingly, rimonabant partially inhibited the pressor effect of 66% DMSO and the sub-effective dose of CDP-choline combined treatment in hypotensive rats. Because the combination of rimonabant in 66% DMSO and a sub-effective dose of CDP-choline's pressor response was shorter and weaker than the pressor response induced by the combination of 66% DMSO and the sub-effective dose of CDP-choline.

CDP-choline administered IV at a dose of 50 mg/kg to hemorrhagic hypotensive rats produced a non-statistically significant increasing trend in MAP. Our department has previously reported CDP-choline's cardiovascular effects on the hypotension induced by

several circulatory shock models[12-14,29]. According to our studies, peripheral or central administration of CDP-choline during hemorrhagic hypotension dose- and time-dependently increased MAP and reversed hemorrhage-induced hypotension by activating cholinergic nicotinic receptors[12-14,29]. In these previous studies[12-14,29], the CDP-choline dose we used in the current study was reported as the sub-effective dose and showed similar results to the results we obtained in the study. The sub-effective dose of CDP-choline was deliberately selected to avoid a ceiling effect and to enable detection of potential pharmacological interaction with the vehicle (DMSO) and with CB1 receptor blockade. Using an effective dose could mask synergistic or antagonistic interactions by producing a maximal pressor response on its own. Therefore, the sub-effective dose provides a more sensitive condition to reveal interaction-dependent changes in MAP.

Again, 66% DMSO caused a pressor response in hypotensive animals. Consistent with our findings, DMSO, in various cardiovascular studies, has been reported to cause a pressor response by itself[15-17]. The pressor response to intravenous DMSO has been reported in cardiovascular studies and may reflect acute changes in vascular tone and/or sympathetic outflow. Although an irritant/pain-related sympathoadrenal activation could theoretically contribute, our data do not support a dominant nociceptive mechanism because HR did not show a significant parallel increase (Tables I–II), which would be expected with pain-driven sympathetic activation. In addition, the vehicle-control group (66% DMSO) was included specifically to quantify and control for the hemodynamic contribution of DMSO itself, and all rimonabant-related interpretations were made relative to this vehicle effect. The findings show that rimonabant dissolved in 66% DMSO, injected IV at doses of 1 and 3 mg/kg under hypotensive conditions, produced effects similar to the MAP response caused by 66% DMSO itself alone. Beyond central mechanisms, accumulating evidence indicates that the endocannabinoid system contributes to cardiovascular depression during hemorrhagic shock via CB1 receptor–mediated vascular hyporeactivity, and CB1 antagonism has been reported to attenuate hemorrhage-induced hypotension. Accordingly, rimonabant's pressor responses observed in hemorrhagic shock models support a functional role of CB1 signaling in peripheral cardiovascular regulation under shock conditions. In this context, our findings extend the literature by suggesting that CB1 blockade can also modulate the pressor response observed when a cholinergic precursor (CDP-choline) is administered with its vehicle under hemorrhagic hypotension. Similar to the findings obtained in our study, previous studies have reported a pressor effect of similar doses of rimonabant, which is dissolved in DMSO during hemorrhagic shock[15,17].

Differences across studies regarding the hemodynamic effects of "vehicle" are likely attributable to marked variability in solvent composition, DMSO fraction, injection volume, route of administration, species/strain, and—critically—the underlying hemodynamic state (normotension vs. shock/ hypotension). In formulations where DMSO is highly diluted (e.g., mixed with surfactant and buffered saline), its direct vascular effects may be minimal, whereas a higher DMSO fraction may produce measurable pressor responses, particularly under hemorrhagic hypotension. In our study, DMSO was intentionally tested as a standalone control group to quantify this contribution, and the interpretation of rimonabant effects was therefore made in the context of a demonstrable vehicle-related pressor component.

The interesting finding in the present study is that a sub-effective dose of CDP-choline potentiates the pressor effect in hemorrhagic hypotension when administered together with 66% DMSO. However, while the combination of 66% DMSO and CDP-choline significantly elevated arterial blood pressure, the combination of rimonabant and CDP-choline failed to elicit the same pressor response during hemorrhagic hypotension. These results suggest that CDP-choline exhibits a synergistic interaction with 66% DMSO while demonstrating an antagonistic interaction with rimonabant in terms of their effect on blood pressure during hemorrhagic hypotension. Although both groups received the same amount of DMSO, the pressor response was partially suppressed in the rimonabant-treated animals. This finding suggests a modulatory role of CB1 receptor blockade on the interaction between CDP-choline and DMSO. Findings supporting this interaction we found in our study have been reported before. It was reported that central nicotinic cholinergic and endocannabinoidergic systems play important roles in several physiological processes[18-,22]. The expression of the CB1Rs and nAChRs overlaps at several brain regions was known[30-32]. Also, administration of the cannabinoids modulates cholinergic transmission at different brain regions, while administration of nicotine modulates endocannabinoids concentration at different brain regions[23-28]. Furthermore, CB1R blockage inhibits nicotine's rewarding effect, while nicotinic alpha-7 cholinergic receptors blockage inhibits cannabinoids' rewarding effect[23,24,33,25-28]. Considering those reports, a significant amount of evidence supports bidirectional interaction between cannabinoidergic and cholinergic systems. Nevertheless, a therapy that targets both systems interaction was not studied under hemorrhage-induced hypotension; the current study has been the first in this respect.

The results of the study show that sub-effective doses of CDP-choline induce a more potent MAP response

and reverse hypotension when administered with DMSO in hemorrhagic hypotensive conditions. Moreover, the partial reversal of this MAP response by rimonabant in hypotensive conditions suggests that there is at least a partial interaction between cannabinoidergic CB1 receptors and the cholinergic system.

Although these preliminary data provide evidence for an interaction between cannabinoidergic CB1 receptors and the cholinergic system during hemorrhagic hypotension, further studies are required to elucidate the underlying mechanisms and to evaluate whether targeting both systems may offer a therapeutic strategy to improve hemodynamic stability in hemorrhagic shock.

Researcher Contribution Statement:
Idea and design: S.C., MSY; Data collection and processing: Y.B.Y., BA, S.C., M.Y., M.S.Y.; Analysis and interpretation of data: M.Y.; Writing of significant parts of the article: All authors
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