Role of the histaminergic system in the central cardiovascular regulation in haemorrhagic shock

Jerzy Jochem, MD, PhD

HISTORY

The history of Turkish-Polish relations dates back to the first quarter of the 15th century – an initial contact between the Ottoman Empire and Poland began in 1414 with a Polish mission sent to Bursa, the empire's first major capital city.

The first official diplomatic relations started in 1439, followed soon by the first trade agreement and the first political treaty (1489). During the following centuries, the two countries signed 27 bilateral peace treaties.

Starting in 1444 and ending in 1699, this series of Ottoman-Polish treaties is said to be the longest sequence of documented Ottoman agreements with a European state.
Relations have been especially strong since the 18th century. When in 1772 Austria-Hungary, Russia and Prussia signed a treaty to share Poland amongst each other, the Ottoman Empire didn't accept that, and thus, it was the only major power in the world that never recognized the dissolution and partitioning of the Kingdom of Poland between the three countries.

Istanbul remained the only capital city in the world to maintain a “Polish ambassador” until the end of World War I and the subsequent recreation of Poland.

Every year, during the meetings with ambassadors, Ottoman Sultans asked about the Polish Ambassador and every year they received the same information that „The Ambassador of Poland is late because of troubles in his travel”.
In 19th century, Sultan Abdülmecit I granted the Polish immigrants an endowment of approximately fifty hectares of land, located within the boundaries of Beykoz, in Istanbul. The village, constructed on March 19th, 1842, was named Adampol after its founder Prince Adam J. Czartoryski. It is now known as Polonezköy.

Abdülmecid I (23/25.04.1823 – 25.06.1861)
the 31st Sultan of the Ottoman Empire

On the other site, on July 23rd, 1923, one day before the signing of the Treaty of Lausanne, Poland was the first European country which recognized the Republic of Turkey.

During the World War II, despite German pressure, Turkish government did not allow to take off the national flag from the building of Polish Ambassy in Ankara.
HAEMODYNAMIC CHANGES RESULTED FROM BLOOD LOSS

TPR – total peripheral resistance
CO – cardiac output
SBP – systolic blood pressure
HR – heart rate
RAP – right atrial pressure


NEURONAL SYSTEMS INVOLVED IN THE CENTRAL CARDIOVASCULAR REGULATION IN HAEMORRHAGIC SHOCK

1. Opioid (endorphins, enkephalins, dynorphins)

2. Non-opioid:
   - proopiomelanocortin-derived peptides (ACTH, α-MSH)
   - acetylcholin
   - serotonin
   - nitric oxide
   - histamine
LOCALISATION OF THE HISTAMINERGIC SYSTEM

(Schwartz et al. Physiol Rev 1991; 71: 1-51)

INFLUENCE OF THE HISTAMINERGIC SYSTEM ON THE CENTRAL CARDIOVASCULAR REGULATION IN NORMOTENSION

- increase in mean arterial pressure (MAP)
- decrease in heart rate – HR (in conscious animals)
- increase in heart rate (in anaesthetised animals)
“There is an activation of the histaminergic system in conditions of disturbed homeostasis, which may lead to mobilisation of compensatory mechanisms.”

(Brown RE et al. Prog Neurobiol 2001; 63: 637-672)
HAEMORRHAGIC SHOCK MODEL

Irreversible haemorrhagic shock, according to the method of Guarini et al., was produced by intermittent blood withdrawal from the catheter inserted into the right jugular vein over a period of 15-25 min, until MAP stabilised at 20-25 mmHg.

(Guarini et al. Arch Int Pharmacodyn 1987; 289: 311-318)

HISTAMINE CONCENTRATIONS IN CNS 20 MIN AFTER METOPRINE ADMINISTRATION IN HAEMORRHAGE-SHOCKED RATS

ENDOGENOUS HISTAMINE-INDUCED CHANGES IN MAP IN NORMOTENSIVE AND HYPOTENSIVE RATS

Normotensive rats

Hypotensive rats

* p<0.05 vs. normotensive rats

(Jochem J. Inflamm Res 2002; 51: 551-556)

I.

INVOLVEMENT OF THE SYMPATHETIC NERVOUS SYSTEM IN THE RESUSCITATING EFFECT OF HISTAMINE
PLASMA NORADRENALIN CONCENTRATIONS IN HAEMORRHAGE-SHOCKED RATS AFTER METOPRINE (20 μg icv) TREATMENT

Before bleeding | After bleeding | 20 min. after metoprine treatment
--- | --- | ---
Noradrenalin (pg/ml)

* p<0.05
** p<0.01 vs. pre-bleeding value
## p<0.01 vs. control group

(Jochem J. Naunyn-Schmiedeberg's Arch Pharmacol 2004, 369: 418-427)

PLASMA ADRENALIN CONCENTRATIONS IN HAEMORRHAGE-SHOCKED RATS AFTER METOPRINE (20 μg icv) TREATMENT

Before bleeding | After bleeding | 20 min. after metoprine treatment
--- | --- | ---
Adrenalin (pg/ml)

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#### ****

(Jochem J. Naunyn-Schmiedeberg's Arch Pharmacol 2004, 369: 418-427)
INFLUENCE OF ADRENOCEPTOR ANTAGONISTS ON MAP AFTER METOPRINE TREATMENT IN HAEMORRHAGE SHOCKED RATS

Δ - prazosin (0.5 mg/kg)
◊ - yohimbin (1 mg/kg)
□ - propranolol (1 mg/kg)
○ - control group

Since 10 min in all groups, except for propranolol-treated, p<0.05 in comparison to metoprine-injected animals

[Jochem J. Naunyn-Schmiedeberg’s Arch Pharmacol 2004, 369: 418-427]

INFLUENCE OF ADRENOCEPTOR ANTAGONISTS ON HR AFTER METOPRINE TREATMENT IN HAEMORRHAGE SHOCKED RATS

Δ - prazosin (0.5 mg/kg)
◊ - yohimbin (1 mg/kg)
□ - propranolol (1 mg/kg)
○ - control group

Since 15 min in all control groups and in propranolol-treated group p<0.05 vs. metoprine-treated animals

[Jochem J. Naunyn-Schmiedeberg’s Arch Pharmacol 2004, 369: 418-427]
INFLUENCE OF ADRENOCEPTOR ANTAGONISTS ON RENAL BLOOD FLOW AFTER METOPRINE TREATMENT IN HAEMORRHAGE-SHOCKED RATS

Δ - prazosin (0.5 mg/kg)
◊ - yohimbin (1 mg/kg)
□ - propranolol (1 mg/kg)
○ - control group

* p<0.05 vs. metoprine-treated group

(Jochem J. Naunyn-Schmiederg’s Arch Pharmacol 2004, 369: 418-427)

II.

INVolVEMENT OF ARGININE VASOPRESSIN (AVP) IN THE RESUSCITATING EFFECT OF HISTAMINE
PLASMA AVP CONCENTRATIONS IN HAEMORRHAGE-SHOCKED RATS AFTER METOPRINE (20 μg icv) TREATMENT

Since 15 min, in all control groups and in V1A receptor antagonist-treated group p<0.05 in comparison to metoprine-treated animals

INFLUENCE OF AVP RECEPTOR ANTAGONISTS ON MAP AFTER METOPRINE TREATMENT IN HAEMORRHAGE-SHOCKED RATS

Δ - [β-mercapto-β-cyclopentamethylenepropionyl,O-me-Tyr²,Arg⁸]AVP (10 μg/kg)
○ - SSR149415 (10 mg/kg)
◊ - [adamantaneacetyl,O-Et-D-Tyr²,Val⁴,aminobutyryl]AVP (10 μg/kg)
INFLUENCE OF AVP RECEPTOR ANTAGONISTS ON HR AFTER METOPRINE TREATMENT IN HAEMORRHAGE-SHOCKED RATS

Since 10 min, in all control groups p<0.05 in comparison to metoprine-treated animals

(Jochem J. Inflamm Res 2004, 53: 269-276)

\( \Delta \) - control group
\( \Delta \) - [\( \beta \)-mercapto-\( \beta \)-cyclopentametylenopropionylo\( ^1\),O-me-Tyr\( ^2\),Arg\( ^8\)]AVP (10 \( \mu \)g/kg)
\( \circ \) - SSR149415 (10 mg/kg)
\( \diamond \) - [adamantaneacetylo\( ^1\),O-Et-D-Tyr\( ^2\),Val\( ^4\),aminobutrynlylo\( ^6\),Arg\( ^8\)]AVP (10 \( \mu \)g/kg)

INFLUENCE OF AVP RECEPTOR ANTAGONISTS ON HINDQUARTERS BLOOD FLOW AFTER METOPRINE TREATMENT IN HAEMORRHAGE-SHOCKED RATS

* p<0.05 in comparison to metoprine-treated animals

(Jochem J. Inflamm Res 2004, 53: 269-276)

\( \square \) - control group
\( \Delta \) - [\( \beta \)-mercapto-\( \beta \)-cyclopentametylenopropionylo\( ^1\),O-me-Tyr\( ^2\),Arg\( ^8\)]AVP (10 \( \mu \)g/kg)
\( \circ \) - SSR149415 (10 mg/kg)
\( \diamond \) - [adamantaneacetylo\( ^1\),O-Et-D-Tyr\( ^2\),Val\( ^4\),aminobutrynlylo\( ^6\),Arg\( ^8\)]AVP (10 \( \mu \)g/kg)
III.

IN Volvement of the Renin-Angiotensin System in the Resuscitating Effect of Histamine


Plasma Angiotensin II (ANG II) Concentrations in Haemorrhage-Shocked Rats After Metoprine (20 μg icv) Treatment

INFLUENCE OF CAPTOPRIL AND ANG II RECEPTOR ANTAGONISTS ON MAP AFTER METOPRINE TREATMENT IN HAEMORRHAGE SHOCKED RATS

Since 15 min, in all groups, except for PD123319-treated group p<0.05 in comparison to metoprine-treated animals


INFLUENCE OF CAPTOPRIL AND ANG II RECEPTOR ANTAGONISTS ON HR AFTER METOPRINE TREATMENT IN HAEMORRHAGE SHOCKED RATS

Since 15 min in all control groups p<0.05 in comparison to metoprine-treated animals

INFLUENCE OF CAPTOPRIL AND ANG II RECEPTOR ANTAGONISTS ON RENAL BLOOD FLOW AFTER METOPRINE TREATMENT IN HAEMORRHAGE-SHOCKED RATS

○ - control group
Δ - captopril (30mg/kg)
◊ - ZD 7155 (0.5 mg/kg)
□ - PD 123319 (10 mg/kg)

* p<0.05 vs. metoprine-treated animals


IV.

INvolvement of Proopiomelanocortin (POMC)-Driven Peptides in the Resuscitating Effect of Histamine
PLASMA ACTH CONCENTRATIONS IN HAEMORRHAGE-SHOCKED RATS AFTER METOPRINE (20 μg icv) TREATMENT

![Graph showing ACTH concentrations before and after bleeding, and 20 min after metoprine treatment.](image)


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PLASMA α-MSH CONCENTRATIONS IN HAEMORRHAGE-SHOCKED RATS AFTER METOPRINE (20 μg icv) TREATMENT

![Graph showing α-MSH concentrations before and after bleeding, and 20 min after metoprine treatment.](image)

INFLUENCE OF HS014 AND MIFEPRISTONE ON MAP AFTER METOPRINE TREATMENT IN HAEMORRHAGE SHOCKED RATS

○ - control group
Δ – HS014 (5 μg i.c.v.)
□ - mifepristone (30 mg/kg)

Since 15 min, in all groups, except for mifepristone-treated group, p<0.05 in comparison to metoprine-treated animals

Influence of HS014 and Mifepristone on HR after Metoprine Treatment in Haemorrhage Shocked Rats

○ - control group
Δ – HS014 (5 μg i.c.v.)
□ - mifepristone (30 mg/kg)

Since 10 min, in all control groups, p<0.05 in comparison to metoprine-treated animals

INFLUENCE OF HS014 AND MIFEPRISTONE ON RENAL BLOOD FLOW AFTER METOPRINE TREATMENT IN HAEMORRHAGE-SHOCKED RATS

○ - control group
Δ – HS014 (5 μg i.c.v.)
■ - mifepristone (30 mg/kg)

* p<0.05 vs. metoprine-treated animals

(INFLUENCE OF HS014 AND MIFEPRISTONE ON RENAL BLOOD FLOW AFTER METOPRINE TREATMENT IN HAEMORRHAGE-SHOCKED RATS)


INTERACTIONS OF THE HISTAMINERGIC SYSTEM IN THE CENTRAL CARDIOVASCULAR REGULATION IN HAEMORRHAGIC SHOCK

1. Serotonergic system:

2. Orexynergic system:

3. Cholinergic system
CONCLUSIONS

1. An increase in endogenous central histamine concentrations leads to the resuscitating in haemorrhagic shock in rats.

2. Effector mechanisms responsible include an activation of the sympathetic nervous system the renin-angiotensin system and an increase in AVP and POMC-derived peptides release.

3. There are interactions between the histaminergic and other neuronal systems (the serotonergic, orexynergic and cholinergic systems) in the central cardiovascular regulation in haemorrhagic shock.
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OUR HISTORY AND FUTURE...