Succinate-containing antihypoxic drugs in urgent medicine and in pharmacology

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OXYGEN DEFICIT IN ENVIRONMENT

RESPIRATORY FUNCTIONS
CARDIO-VASCULAR SYSTEM
OXYGEN-TRANSPORT FUNCTION

PATHOLOGY

VENOMS OF RESPIRATORY CHAIN

DECREASE OF OXYGEN DELIVERY INTO CELL

METABOLISM DISORDERS
PRINCIPLES OF HYPOXIA CORRECTION

- Search of targets for AH
- Methodology of therapeutic use of AH
- Study of mechanism of action for AH
- AH selection
- Preclinical study of AH
- Standardization of methods
1878

1990

METHODIC RECOMMENDATIONS
ANTIHYPPOXANTS - DRUGS, FACILITATING THE ORGANISM REACTION ON HYPOXIA OR PREVENTING ITS FORMATION AS WELL AS ACCELERATING THE NORMALIZATION OF CELL FUNCTIONS IN POSTHYPOXIC PERIOD
CLASSIFICATION OF ANTIHYPOXANTS

(1991)

Specific

Elevating transport function of blood

Direct energizing action

Nonspecific

Direct energizing action
ENERGY METABOLISM
COMPENSATED STAGE

DECREASE OF OXYDATION OF NAD-DEPENDENT SUBSTRATES

DECREASE OF OXIDATIVE PHOSPHORILATION

DISORDER OF CREBS’ CYCLE

DISORDER OF ADENINE NUCLEOTIDE TRANSPORT

INCREASE OF RECOVERY OF PYRIDINE NUCLEOTIDES AND FLAVINE

DECREASE OF RESPIRATORY SENSITIVITY TO SPECIFIC INHIBITORS
DECOMPENSATED STAGE

MEMBRANE LABILITY

III MEC

DEGRADATION OF ADENINE NUCLEOTIDES

LPO ACTIVATION

DECREASE OF AOS ACTIVITY

III MEC

b - C
TERMINAL STAGE

IV MEC
CCO

FULL INHIBITION OF OXYDATIVE PHOSPHORILATION

CELL DEATH
I MEC NADH-CoQ

- Quinons
- Substrates of Crebs’ Cycle
- Precursors of Adenine Nucleotides
- Strengthening of Succinate Oxydase Oxydation
- Energy Donating Drugs
USE OF EXOGENOUS SUCCINATE

SUCCINATE

ANTITOXIC

ANTIKETOGENIC

Ca²⁺

ANTIOXIDANT

ANTICHOLESTEROGENIC

ANTIOXYDANT
SUCCINATE + LIMONIC ACID = LIMONTAR
MEXIDOL

INCREASE OF SDH ACTIVITY

3-OXYPIRIDINE +_succinate = MEXIDOL
ACTIVATION OF ENDOGENOUS SUCCINATE FORMATION

- Carboxylation of piruvate and phosphoenolpyruvate
- Transformation of MDH reaction
- Pereamination
- Activation of Robert’s cycle
- Activation of GABA path

Endogenous succinate
DECOMENSATED STAGE

ANTIOXYDANTS

MACROERGKS

CYTOCHROME C

b - C

NAD + Cytochrome C + Inosine = Energostim
HIF-1-alpha is the transcriptional regulator of cellular and developmental response to hypoxia. The dysregulation and overexpression of HIF-1-alpha by either hypoxia or genetic alternations have been heavily implicated in cancer biology, as well as a number of other pathophysiologies, specifically in areas of vascularization and angiogenesis, energy metabolism, cell survival, and tumor invasion.
Succinate and HIF-1-alpha

HIF prolyl hydroxylase (HPH) are involved in specific post-translational modification of HIF1A proline residues (P402 and P564 within the ODD domain), which allows for pVHL association with HIF1A. The hydroxylation of HIF1A proline residue also regulates its ability to associate with co-activators under hypoxia. Succinate, fumarate, 2-oxoglutarate and some analogues can inhibit HIF prolyl hydroxylase, stabilizing HIF1A.
ANTIHYPOXANTS OF INDIRECT ENERGIZING ACTION

Calcium channel blockers

Redox-modulators

Blockers of AC enzyme

α-Adrenomimetics

Antagonists of opioid peptides

Antioxydants
Structural formulas of some actoprotectors and antihypoxants
Pharmacological activity of antihypoxants

- Antihypoxic effect;
- Antioxidant effect for all aminothiols;
- Ability to accelerate reparative and adaptive synthesis of RNA, enzymes, functional and structural proteins in different injuries – hypoxic, infectious, toxic, stressogenic, and adaptation processes in complicated conditions as well.
ANTIHYPOXANT SPECTRUM OF PHARMACOLOGICAL ACTIVITY:

1) increase of efficacy of energy producing respiratory function;
2) produce economization of oxygen by means of inhibition of nonphosphorilated (free radicals) forms of oxidation;
3) defense of membrane structures and antioxidant systems;
4) activate of lactate utilization;
5) decrease of acidosis;
6) produce a lot of other positive effects
TRIMETAZIDINE (PREDUCTAL)

- Hypobaric hypoxia
- Circulating hypoxia
- Hypoxia + ischemia
Specific antihypoxants of metabolic type of action

TRIMETAZIDINE
With direct energizing and secondary antioxidant properties

METAPROT
ETHOMERZOL
With actoprotective, direct energizing and antioxidative properties

AMTIZOL
With direct energizing and antioxidative properties
Comparison of antihypoxic and antioxidant properties of antihypoxic drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Antihypoxic activity</th>
<th>Antioxidant activity</th>
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<tr>
<td></td>
<td></td>
<td>Inhibition of lipid peroxidation</td>
</tr>
<tr>
<td>Amthizol</td>
<td>+        +        +        +</td>
<td>+</td>
</tr>
<tr>
<td>Gutimin</td>
<td>+        +        +        ±</td>
<td>±</td>
</tr>
<tr>
<td>Amthizol succinate</td>
<td>+        +        +        ±</td>
<td>±</td>
</tr>
<tr>
<td>Gutimin succinate</td>
<td>+</td>
<td>+        +</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>±</td>
<td>+        +        +</td>
</tr>
<tr>
<td>T-475 (triazinoindol derivate)</td>
<td>+        +</td>
<td>±</td>
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Conclusions

1. The antihypoxic activity of 6 aminothiol and triazinoindol derivatives was studied in a model of hypobaric (hypoxic) hypoxia in rats.
2. The range of antihypoxic activity was the following: amtizol succinate ≈ amtizol ≈ gutimin > T-475 > gutimin succinate > succinate.
3. One of the mechanism of action for all antihypoxants was the inhibition of lipid peroxidation and recovery of hypoxia-induced antioxidant defense system in the brain, kidneys, liver, heart and muscles (the reduction of the contents of malonic dialdehyde and lipid hydroperoxides, the increase of superoxid dismutase activity and the contents of recovered glutation).
4. Amtizol revealed the most antihypoxic activity. It recovered all negative shifts produced by middle and heavy hypoxia in the organs studied.
5. Succinate did not potentiate antihypoxic and antioxidant properties of amtizol.
6. Gutimin inhibited the activation of lipid peroxidation preventing the increase of malonic dialdehyde and lipid hydroperoxides and the decrease of recovered glutation produced by hypoxia in all organs studied. Besides, gutimin inhibited both superoxid dismutase and catalase activity.
7. Gutimin succinate strengthened the inhibitory action of gutimin on lipid peroxidation and prevented its inhibitory effect on superoxid dismutase activity in all organs studied.
8. Therefore, the parallelism in antihypoxic and antioxidant effects was revealed for the aminothiol and triazinoindol derivatives.
Design of the Experiment

LOW RESISTANT

HIGH RESISTANT

ALTITUDE

5 min 12 000 m

TIME

20 min 12 000 m

TIME

5 min

20 min

ALTITUDE

Design of the Experiment

LOW RESISTANT

HIGH RESISTANT
Design of the Experiment and Drugs

- Metaprot 25 mg/kg
- Piracetam 60 mg/kg
- Metaprot + (+succinic acid) 25 mg/kg + 50 mg/kg
Design of the Experiment and Biochemistry

Creatine phosphate  ATP  ADP  AMP
Energy charge  Lactate  Pyruvate
The energy status of the brain in high and low resistant to hypoxia rats.
The energy status of the brain in high and low resistant to hypoxia rats 14 days after brain injury
Effect of Metaprot, Piracetam and Metaprot + (+succinic acid) on the brain ATP and Lactate/Pyruvate 14 days after brain injury.
Effect of Metaprot, Piracetam and Metaprot + (+succinic acid) on the brain energy charge after brain injury
1. Piracetam, Metaprot and combination of Metaprot with Succinic acid (Metaprot +) produce energy stabilizing effect on brain tissue after brain injury. Cytoprotective action of Metaprot was higher than that of Piracetam. Succinic acid potentiates the action of Metaprot.

2. Metaprot but not Piracetam recovers energy metabolism in the brain on the 30\textsuperscript{th} day after brain injury. Combined Metaprot and Succinic acid (Metaprot +) causes energy stabilizing effect on the 14\textsuperscript{th} day of posttraumatic period.

3. The energy stabilizing effect of Metaprot is higher in the low resistance to hypoxia rats.