

Temperature Control in Health and Disease

Edited by
V.N. Gourine

Minsk 1997

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Artwork, design & layout:

D.B. Sandakov
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ISBN 985-6178-05-3

NITRIC OXIDE SYNTHESIS IN HYPOTHALAMIC NUCLEI OF EXPERIMENTAL ANIMALS AFTER APPLICATION OF FREUND'S COMPLETE ADJUVANT AND LOW AMBIENT TEMPERATURES

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In the last years, the involvement of nitric oxide (NO) in the central mechanisms of thermoregulation in heating [8] and experimental fever [1,3] has been demonstrated. At the same time it is still unclear how the production of this free radical molecule changes upon exposure of the organism to pyrogenic factors in a period preceding a body temperature rise and to cold. So, we studied changes in the content of NO-synthesizing cells in different hypothalamic nuclei after injection of Freund's complete adjuvant (FCA) in a period preceding a rise in body temperature and after prolonged exposure to low ambient temperatures.

Materials & Methods

Experiments were performed in Wistar male rats weighing 180-220 g. Group I experimental animals received FCA containing 0.1% killed and dried Mycobacterium butyricum into the cushions of hind paws as 0.1 ml per rat. Group II animals were exposed to 4-6°C for 48 h in laboratory premises. Intact animals, as those of group I, were kept at an ambient temperature 20-22°C. Control and experimental rats were anesthetized with intraperitoneal sodium thiopental in a dose 50 mg/kg. After opening of the thorax the right atrial wall was incised, and the cardiovascular system was perfused through the left ventricle with Ringer's solution containing 10 mM NaNO₂, 0.1 M phosphate buffer (pH 7.4), and 4% paraformaldehyde in

0.1 M phosphate buffer (pH 7.4). After decapitation the brains were removed and the hypothalamus was isolated and fixed for 60 min in 4% paraformaldehyde on phosphate buffer (0.1 M, pH 7.4). Then it was washed off in cold six times for 30 min each using 0.1 M Tris-HCl (pH 8.0) and incubated in 10% and 25% sucrose on Tris-HCl (0.1 M, pH 8.0) for 1.5 and 12 h, respectively. After cryostat freezing of hypothalamic samples at -25°C sections 25 μm thick were prepared. The staining method for NADPH-diaphorase (NO-synthase) was used to identify NO-synthesizing cells [4,5]. NADPH-diaphorase-positive neurons were counted with a Leitz-TAS image analysis system (Germany) and expressed as per 1 mm^2 of the section area [2].

Results & Discussion

We found earlier that administration of FCA to rats increased deep body temperature 2.5-3 h after the injection [7] and that NO may be a factor of the antipyretic system in febrile states including adjuvant-induced hyperthermia [1,3,6]. The present study deals with NO synthesizing processes in neurons of the lateral preoptic (LPO), paraventricular (PAV) and periventricular (PEV) hypothalamic nuclei 2 h after application of FCA with a view to clarifying the involvement of this antipyretic system level in the central thermoregulatory mechanisms in a period preceding the body temperature elevation. It was shown that in this period the quantity of NO-synthesizing neurons (NADPH-diaphorase-positive) increased by 15.4% ($p < 0.05$) in LPO, by 21.0% ($p < 0.01$) in PAV, and did not significantly differ from control in PEV. The data suggest that the NO-synthase activity induction by FCA occurs in hypothalamic regions that have relation to the control of thermoregulatory processes and reflects activation of the NOergic link of the antipyretic system already in a period preceding a body temperature rise. This probably conforms to the known physiological principle that any excitation in the organism is combined with activation of inhibitory processes limiting the excessive response and making the quantitative and qualitative characteristics of the response correspond to the acting stimuli.

A study of the activity of NO synthesis in the hypothalamic nuclei after prolonged (48 h) exposure to cold did not reveal any marked changes in the indices as compared to control. This

may be due to the absence of response of NOergic system of the hypothalamus to low ambient temperatures in the range studied, as well as reflect compensatory processes in the CNS bringing about adaptation of the animal organism to cold.

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Contents

Short Reviews and Theoretical Articles

- AN ESSAY ON NEURONAL MODELS FOR THE
CENTRAL MECHANISMS OF AUTONOMIC
THERMOREGULATION REPRESENTING
PUTATIVE DISINHIBITORY AND EXCITATORY
PATHWAYS TO PACEMAKERS 13
V.N.Gourine
- THERMOREGULATION IN EXERCISING
WOMEN 20
R.Grucza, I.Okora, H.Pekkarinen & O.Hanninen
- CECAL LIGATION AND PUNCTURE IN RATS
AS AN EXPERIMENTAL MODEL OF
PROLONGED BACTERIAL-INDUCED FEVER 27
A.V.Gourine, K.Rudolph, A.S.Korsak & M.J.Kluger
- FROM PHYSIOLOGY TO PATHOPHYSIOLOGY
DURING HEAT STRESS 35
J.R.S.Hales & M.Horowitz
- EFFECTS OF M- AND N- CHOLINERGIC
SUBSTANCES ON THERMOREGULATION 49
N.A.Losev & O.M.Yefremov
- WAYS OF ADAPTATION OF AQUATIC ANIMALS
TO DIFFERENT ENVIRONMENTAL
TEMPERATURES AND DOSED SPEED
EXERCISE 51
V.A.Matukhin
- SOME PROBLEMS OF HUMAN ADAPTATION
TO HIGH AND LOW TEMPERATURES 54
V.I.Medvedev

DEVELOPMENT OF HEAT LOSS MECHANISMS IN AVIAN EMBRYOS <i>M.Nichelmann, P.Murzenok & S.Holland</i>	57
TEMPERATURE BOUNDARIES BETWEEN EUTHERMIA, NOCTURNAL HYPOTHERMIA, AND SHALLOW AND MODERATE TORPOR IN HOMEOTHERMS: REM SLEEP AS AN INDICATOR <i>Yu.F.Pastukhov, M.E.Rashotte, I.E.Chepkasov, E.L.Polyakov, R.P.Henderson, E.G.Serkina & O.A.Sapach</i>	70
HYPOTHERMIA UPON HIBERNATION: REGULATION OF FUNCTIONAL PROPERTIES OF SKELETAL MUSCLE MYOSIN <i>Z.A.Podlubnaya, N.A.Lukyanova & S.N.Udaltsov</i>	77
INHIBITORY ACUTE PHASE PROTEINS - POSSIBLE REGULATORS OF FEBRILE RESPONSE <i>D.B.Sandakov</i>	79
A CENTRAL MODEL OF SUBFEBRILITY <i>I.N.Semenenya</i>	84
THE BIOENERGY OF HOMEOTHERMIA AND THE LIMITS OF CRYORESISTANCE <i>N.N.Timofeyev</i>	87
MATHEMATICAL ANALYSIS OF HEAT TRANSFER PROCESSES IN MAN IN ARID HOT ENVIRONMENTS <i>I.I.Yermakova</i>	90

Research Papers and Short Reports

- SUBMICROSCOPIC CHARACTERIZATION OF CHANGES IN MICROCIRCULATORY BED OF SKELETAL MUSCLES AND SYMPATHETIC GANGLIA DURING HYPO- AND HYPERTHERMIA
L.I.Archakova & N.P.Denisenko 94
- INFLUENCE OF DIFFERENT INCUBATION TEMPERATURES ON THE NEURONAL HYPOTHALAMIC THERMOSENSITIVITY IN 10 DAYS OLD MUSCOVY DUCKS (*CAIRINA MOSCHATA*)
D.Basta, B.Tzschentke & M.Nichelmann 97
- CHANGES IN BODY TEMPERATURE AND SYMPATHETIC EFFERENT ACTIVITY IN FEMORAL SKIN NERVE OF RATS DURING LOCAL COOLING OF THE ILEUM
A.G.Chumak, O.L.Borisov & V.V.Soltanov 104
- ULTRASTRUCTURAL CHANGES IN THE SKELETAL MUSCLE OF RATS EXPOSED TO GENERAL COOLING AND HEATING
N.P.Denisenko 107
- INFLUENCE OF ESSENTIAL UNSATURATED FATTY ACIDS ON EXPERIMENTALLY INDUCED FEVER
N.P.Denisenko, P.P.Denisenko, A.F.Safonova, N.V.Fedorova & S.V.Viklenko 112
- NEUROTRANSMITTER PROCESSES IN THE VENTRAL BRAINSTEM AFTER INTRAPERITONEAL APPLICATION OF *E. COLI* LIPOPOLYSACCHARIDE
T.V.Dudina & A.I.Yolkina 115

EXACERBATED FEBRILE RESPONSE TO LPS AFTER CHEMICAL INACTIVATION OF THE NUCLEUS TRACTUS SOLITARIII IN RATS <i>A.V.Gourine, A.S.Korsak & V.N.Gourine</i>	117
EFFECT OF ADAPTATION OF HYPOTHALAMIC NEURONES IN BRAIN SLICES TO DIFFERENT LOCAL TEMPERATURES <i>P.Haug & Fr.-K.Pierau</i>	121
INVOLVEMENT OF NERVE GROWTH FACTOR (NGF) AND EPIDERMAL GROWTH FACTOR (EGF) IN GENERATION OF CELL RESPONSE TO HEAT SHOCK <i>V.N.Kalunov, R.I.Gronskaya, I.B.Lukashevich, V.S.Lukashevich & G.A.Shpak</i>	128
BEHAVIORAL ACTIVITY OF RATS AFTER INTRAPERITONEAL APPLICATION OF ESCHERICHIA COLI LIPOPOLYSACCHARIDE <i>T.S.Kandybo & E.V.Melenchuk</i>	132
TEMPERATURE SENSITIVITY OF SKIN IN HEALTHY MAN <i>I.Y.Kleinbok, E.Z.Gabdullina & V.I.Tsitsurin</i>	135
ANALYSIS OF CENTRAL AND PERIPHERAL MECHANISMS OF GENERATION OF NOCICEPTIVE AND TEMPERATURE RESPONSES IN RATS AFTER INTRAPERITONEAL APPLICATION OF ENDOTOXIN <i>S.V.Koulchitsky & V.N.Gourine</i>	137
THE BROWN FAT IN THE THERMOREGULATORY RESPONSE OF VAGOTOMIZED RATS TO LIPOPOLYSACCHARIDE <i>V.A.Kulchitsky, A.A.Romanovsky, C.T.Simons, N.Sugimoto, & M.Szekely</i>	141

EFFECTS OF LIPOPOLYSACCHARIDE AND ALPHA-1-ANTITRYPSIN ON OXYGEN CONSUMPTION IN NEWBORN RATS <i>I.V.Laman, D.B.Sandakov & V.A.Matukhin</i>	146
MODULATION OF ELECTRICAL AND METABOLIC ACTIVITY IN SOME SYMPATHETIC AND PARASYMPATHETIC NERVES AND GANGLIA DURING SHORT- TERM COOLING <i>V.I.Lapsha, O.A.Azev, V.N.Bocharova, T.M.Lukashenko, E.A.Shelayeva, L.N.Utkina & V.N.Gourine</i>	149
CHANGES IN M-CHOLINOCEPTORS OF RAT BRAIN CORTEX MEMBRANES AFTER HEAT SHOCK <i>B.N.Manukhin, L.A.Nesterova, E.A.Smurova & T.P.Kichikulova</i>	153
CHANGES IN AUTONOMIC NERVE ACTIVITY IN RAT THYMUS AFTER INTRAPERITONEAL INJECTION OF INTERLEUKIN-1 β <i>P.P.Murzenok, T.Y.Danilova, N.K.Vikentjeva & T.I.Zhytkevitch</i>	157
METABOLIC DISORDERS IN SUBFEBRILITY <i>N.I.Nechipurenko, E.P.Titovets & G.T.Maslova</i>	161
CHANGES IN THE FINE STRUCTURE OF RAT THYMUS UNDER PROLONGED HEAT EXPOSURE <i>N.I.Netukova & T.I.Zhytkevich</i>	165
EFFECT OF A MODIFIED POLYSACCHARIDE ON BODYTEMPERATURE AND ISCHEMIC DISTURBANCES OF CARDIAC RHYTHM IN HIGH TEMPERATURE-EXPOSED RATS <i>G.S.Polukhovich</i>	168

- DETERMINATION OF BODY TISSUE THERMAL STATE BY COMBINED APPLICATION OF THERMOGRAPHY AND SUPER-HIGH FREQUENCY TECHNIQUE
E.L.Polyakov, Zh.V.Prahova, S.N.Kolesov & Yu.F.Pastukhov 171
- EFFECT OF MET-ENKEPHALIN ON ELECTRICAL ACTIVITY IN LUMBAR SPLANCHNIC NERVES DURING EXPERIMENTAL FEVER
V.M.Rubakhova & Y.B.Yolkin 174
- THERMOREGULATORY EFFECTS OF INTRAVENOUSLY APPLIED α_1 -ANTITRYPSIN IN RATS
D.B.Sandakov & A.V.Gourine 177
- CENTRAL THERMOSENSITIVITY IN A PASSERINE BIRD, THE GREENFINCH (*CHLORIS CHLORIS*)
E.V.Sedounova 181
- NITRIC OXIDE SYNTHESIS IN HYPOTHALAMIC NUCLEI OF EXPERIMENTAL ANIMALS AFTER APPLICATION OF FREUND'S COMPLETE ADJUVANT AND LOW AMBIENT TEMPERATURES
I.N.Semenenya & V.I.Dunai 185
- CHANGES IN SOME INDICES OF LIPID METABOLISM IN RATS UNDER PROLONGED INFLUENCE OF HIGH AND LOW AMBIENT TEMPERATURES
I.N.Semenenya & S.M.Koposhilova 188
- RESPONSES OF IDENTIFIED *LYMNAEA STAGNALIS* NEURONS TO TEMPERATURE DECREASE AND NITRIC OXIDE
A.V.Sidorov, V.B.Kazakevich, N.N.Petrashevskaya & V.N.Gourine 191

NEUROPEPTIDE REGULATION OF HIBERNATION PROCESSES IN VERTEBRATE PHYLOGENESIS <i>T.N.Sollertinskaja & E.N.Nuritdinov</i>	196
CHANGES IN AFFERENT AND SYMPATHETIC EFFERENT IMPULSE ACTIVITY AND IN BODY TEMPERATURE AFTER APPLICATION OF LIPOPOLYSACCHARIDE INTO THE INTESTINE OF RATS <i>V.V.Soltanov</i>	198
THE FUNCTIONAL STATE OF MYOCARDIUM IN HEAT ACCLIMATION AND NATURAL ADAPTATION TO HOT CLIMATE <i>F.F.Sultanov, K.A.Amannepesov, G.F.Sultanov & G.O.Ovezgeldieva</i>	201
ANALYSIS OF NEUROENDOCRINE REGULATION IN HEAT STRESS <i>F.F.Sultanov, G.M.Klochkova, H.A.Mezidova, S.V.Ronzhina & M.D.Hudaiberdyev</i>	203
IS THERE A CORRELATION BETWEEN CHANGES IN SEROTONIN METABOLISM IN THE BRAIN AND SMALL INTESTINE AND CHANGE IN NOCICEPTIVE REFLEXES DURING EXPERIMENTAL FEVER IN RATS ? <i>G.K.Troptnikova, G.P.Mironova, V.S.Levkovets, S.V.Koulchitsky, L.E.Rozhnova, N.V.Akulich & V.A.Kulchitsky</i>	205
SOME FEATURES OF FORMATION OF HEAT ADAPTATION IN RATS UNDER PROLONGED RADIATION-THERMAL EXPOSURES <i>G.F.Tsikhun, N.K.Vikentjeva & T.B.Bokut</i>	208
INFLUENCE OF BOMBESIN ON THERMOSENSITIVITY OF AVIAN HYPOTHALAMIC NEURONS <i>B.Tzschentke, A.Gourine & D.Basta</i>	212

- WARMING ACTIVATES BURSTING NEURONS
IN HIPPOCAMPAL SLICES OF THE GUINEA
PIG
V.Y.Vasilenko & T.A.Petruchuk 220
- ACTION OF BOMBESIN FRAGMENTS ON
THERMOSENSITIVE NEURONS IN RAT
HYPOTHALAMIC SLICES
*V.Y.Vasilenko, T.A.Petruchuk, V.P.Golubovich,
E.N.Galuk & A.A.Akhrem* 223
- ROLE OF VENTRAL BRAINSTEM
NORADRENERGIC STRUCTURES IN THE
NEUROCHEMICAL MECHANISMS OF
THERMOREGULATION DURING
PYROGENAL FEVER
F.I.Vismont 226
- CHANGES IN MET-ENKEPHALIN AND
NORADRENALINE IN THE CENTRAL
NERVOUS SYSTEM AND INFERIOR
MESENTERIC GANGLION DURING HYPO-
AND HYPERTHERMIA
F.I.Vismont & Y.B.Yolkin 229
- THE CHARACTERIZATION OF INTERLEUKIN-
6 CAPACITY TO INDUCE T-LYMPHOCYTE
ACTIVATION AND PROLIFERATION
A.V.Voznjuk, V.V.Smolnykova & M.P.Potapnev 234
- PLASTICITY OF NEURONAL TEMPERATURE
SENSITIVITY: RECEPTOR SPECIFIC EFFECTS
OF DIFFERENT OPIOID AGONISTS AND
ANTAGONISTS ON TEMPERATURE
SENSITIVITY OF HYPOTHALAMIC NEURONES
K.Yakimova, Fr.-K.Pierau & H.Sann 240
- EFFECTS OF HIGH TEMPERATURE AND
PYROGENS ON THE LEVEL OF METABOLIC
AND CHOLINERGIC PROCESSES IN THE
ANTERIOR HYPOTHALAMUS
I.V.Yekimova. & S.B.Kondrashova 247

THE FUNCTIONAL STATE OF IMMUNOCOMPETENT CELLS IN ANIMALS DURING COLD ADAPTATION <i>T.I.Zhytkevich</i>	252
CHANGES IN HEMOGLOBIN-OXYGEN AFFINITY DURING FEVER <i>V.V.Zinchuk & M.V.Borisiuk</i>	256
Author index	262