# Formation of Systemic Structural Trace in Rat Kidneys after Cold Adaptation

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We studied the adaptive response of rats to cold exposure. It was found that the development of the adaptive response and formation of systemic structural trace in the kidneys occurred within 1 month after the start of adaptation. Activation of proliferative processes in the kidneys was accompanied by an increase in intracellular calcium concentration.

**Key Words:** *adaptation; cold; rectal temperature; kidneys; calcium*

The exposure of a multicellular organism to stress factors is followed by the conflict between increasing demands of the organism and inability of cells to satisfy these demands. This conflict may be resolved through activation of the adaptive response, which is accompanied by the formation of the systemic structural trace. This state is provided by energy and plastic reserves of the organism [6]. It remains unclear which stimulus triggers the formation of the systemic structural trace under the influence of stress factors.

Here we studied the mechanism and period of the development of the adaptive response in rats under cold conditions.

## MATERIALS AND METHODS

Experiments were performed on 52 male Wistar rats weighing 160-250 g. Control animals were maintained at 22±2°C with free access to water and food. Experimental rats were adapted to cold in a cold chamber for 6±1 h (6 times a week) without immobilization and then were kept with controls. Core temperature was estimated by rectal temperature with a TPEM-1 electric thermometer. A sensor was introduced into the rectum (4 cm). DNA content in the renal cortex was estimated spectrophotometrically by a modified method of Schmidt and Tannhauser [7,10]. Protein content in the renal cortex was measured spectrophotometrically [10]. The cell fraction was isolated from the renal cortex as described elsewhere [5]. Intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_{in}$) was measured using Fura-2AM fluorescent probe (2.5 μM) [4] on an Aminco Bowman Series 2 spectrofluorometer (Thermo Spectronic) at 25°C. Each sample contained 3 million washed cells of the renal cortex.

The results were analyzed using Origin 5.0 and Statistica 7.0 softwares. The significance of differences was evaluated by nonparametric Mann—Whitney test.

## RESULTS

The ability to maintain a constant level of core temperature under cold conditions serves as a criterion of adaptive mechanism, which protects the organism from cooling. Before adaptation, rectal temperature of rats was 38.6±0.1°C. After 1-h cold exposure, rectal temperature decreased by 1.40±0.03°C. This parameter returned to normal by the end of the 4th week (Table 1). Thus, the adaptive mechanism of thermoregulation in rats was completely formed over 1 month.

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**TABLE 1.** Body Weight, Rectal Temperature, and Functional Activity of Rat Kidneys during Cold Adaptation

| Parameter | Control | Adaptation time | | | | |
|---|---|---|---|---|---|---|
| | | 1 h | 3 h | 20 h | 2 weeks | 4 weeks |
| Rectal temperature, °C | 38.6±0.1 (*n*=20) | 37.2±0.1** (*n*=20) | 37.4±0.2** (*n*=20) | 37.8±0.2** (*n*=20) | 38.1±0.2* (*n*=20) | 38.6±0.1 (*n*=20) |
| DNA/protein×$10^{-3}$ | 2.2±0.6 (*n*=10) | 2.9±0.6 (*n*=9) | 4.0±0.6* (*n*=10) | 4.2±0.9* (*n*=10) | 2.2±0.6 (*n*=9) | 3.2±0.7 (*n*=10) |
| Relative weight of the kidneys, % | 0.69±0.02 (*n*=20) | 0.68±0.02 (*n*=10) | 0.69±0.02 (*n*=10) | 0.69±0.02 (*n*=10) | 0.78±0.02* (*n*=16) | 0.80±0.03* (*n*=16) |
| Water content in renal tissue, % | 73.0±0.8 (*n*=10) | 74.1±0.9 (*n*=10) | 74.2±0.8 (*n*=10) | 73.0±0.7 (*n*=10) | 74.1±0.9 (*n*=8) | 75.2±0.9 (*n*=8) |
| Body weight, g | 160±10 (*n*=20) | 159±9 (*n*=10) | 161±12 (*n*=10) | 160±15 (*n*=10) | 210±14** (*n*=16) | 250±17** (*n*=16) |
| $[Ca^{2+}]_{in}$, nM | 55.5±13.5 (*n*=10) | 190.5±75.0** (*n*=10) | 49.8±5.1 (*n*=9) | — | 89.4±16.2 (*n*=10) | 60.3±10.8 (*n*=9) |

**Note.** *$p<0.05$ and **$p<0.01$ compared to the control.

Body temperature is maintained due to modulation of metabolic activity of various organs and tissues. For instance, cold exposure is accompanied by a rapid change in functional activity of the kidneys, which leads to an increase in the excretion of water and $Na^+$ cations by the kidneys [3]. These processes disturb ion homeostasis [9] and, probably, stimulate the formation of the systemic structural trace, leading to an increase in the weight of the kidneys. For example, the relative weight of the kidneys in rats increased by 16% during adaptation. Body weight of animals also increased under these conditions (Table 1). Hence, the increase in the relative weight of the kidneys did not result from a decrease in body weight in adapted rats. The increase in the weight of the kidneys was related to an increase in dry tissue weight, since water content remained unchanged at various periods of adaptation (Table 1). It remained unclear which mechanism mediated the increase in the weight of the kidneys during cold adaptation (hypertrophy or hyperplasia).

The DNA/protein ratio was calculated to estimate proliferative activity in the kidneys. This index reflects mitotic activity [1], since the intracellular DNA/protein ratio increases during the S-phase of the cell cycle [2]. The DNA/protein ratio increased by 2 times over the first 3 h of cold exposure (Table 1). These data indicate that the increase in the weight of the kidneys during cold exposure is associated with activation of proliferative processes. Adaptation is accompanied by stimulation of cell division, but the mechanism responsible for activation of cell proliferation during cold stress remains unknown. $[Ca^{2+}]_{in}$ is one of the major intracellular messengers, which triggers cascade reactions activating cell cycle and cell division. Published data show that long-term increase in cytosolic $Ca^{2+}$ concentration stimulates cell division [8]. In our experiments, activation of mitotic activity in the kidneys persists over a long time (judging from DNA/protein ratio), while $[Ca^{2+}]_{in}$ sharply increased only in the initial period after stress exposure and returned to normal in the follow-up period (Table 1). It can be hypothesized that $Ca^{2+}$ ions only trigger cell division under cold conditions.

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