Glycomics and Lipidopics

Extended Abstract

Different Effects of Ethanol and Activation of TRPM8 ION Channel on Metabolic Response to Cold

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Abstract:

The possible interrelation of ethanol and the membrane protein molecules such as TRP ion channels in the whole living organism has not been studied. In the present research we study the influence of ethanol (50%) and agonist of TRPM8 ion channel L-menthol (1% in 50% ethanol) application to abdominal skin on the thermoregulatory response to cooling in rats. We used two types of cooling with the different rates of skin temperature decrease - 0.1 °C/sec for rapid and 0.005°C/s for slow cooling. It was shown, that the effects of ethanol and activation of the cold-sensitive TRPM8 ion channel are mainly directed at different components of thermoregulatory metabolic response to cold. Menthol, as an agonist of the TRPM8 ion channel, besides the constrictor vascular response stimulates predominantly the emergency first phase of metabolic response which appears only at rapid cooling without any effect on the second phase of metabolic response to cooling. Ethanol inhibits the most powerful second phase of metabolic response to cold which is manifested at decreased deep body temperature and is associated with the development of not only non-shivering but also shivering thermogenesis. Effect of ethanol is accompanied by the acceleration of the deep body temperature fall. Ethanol does not prevent the effect of menthol on thermoregulatory blood vessel and emergency phase of metabolic response, and the activation of the cold-sensitive TRPM8 ion channel by menthol has no obvious influence on the effects of ethanol – inhibition being the most powerful thermogenic component of the metabolic response to cold. Ethanol while being introduced into the organism mainly through ingestion or skin application affects many functional systems. The basis for the influence of ethanol on the body functioning is its direct effect on the cell metabolic processes. Ethyl alcohol affects the cell membrane by separating fatty acid chains of phospholipids and changing membrane fluidity; it also alters the permeability of volt- and ligand-gated ion channels and directly alters the electrical potentials of neurolemma. Ambient temperature is one of the major factors affecting the living organism. The start thermal afferent information under the external cooling primarily is given by the peripheral skin thermo-afferents. In recent years there have been numerous studies concerning the cellular and molecular mechanisms of cold sensitivity. It is believed that thermosensitive TRP channels are the basis for temperature sensation[1]. Perception of cold in the physiologically relevant temperature range is performed with participation of the cold-sensitive ion channel TRPM8, which is activated by cooling in the range of 28-8ºC. Menthol is one of known agonists of the TRPM8 ion channel. The expression of the gene of the TRPM8 ion channel has been proved on the endings of sensory neurons, spinal ganglia and brain structures. Free endings of sensory neurons are the peripheral thermoreceptors (thermo-afferents). Thus the perception of cold and the afferent signal depend on the activity of cold-sensitive ion channels, which increase its permeability in response to the decrease in temperature. Afferent signal determines the character and sequence of various physiological responses initiation to some effect. Temperature thresholds for cold-defense responses, aimed at maintaining temperature homeostasis, characterize thermal afferent signal at external cold exposure. The study of the thermal afferent signal role that is formed under the effect of pharmacological modulation of the skin thermoreceptor activity is of particular interest. We have previously shown that pharmacological activation of cold-sensitive TRPM8 ion channels leads to the shift in temperature thresholds of responses to cooling[6]. What are the effects of ethanol on the temperature thresholds as well as the structure of thermoregulatory response of the whole organism to cold exposure is not currently known. Ethanol, being able quickly to penetrate the lipid-rich membrane, and causing the conformation of the protein molecules, can alter the function of ion channels. Currently, there are data that ethanol interacts with the molecules such as TRP ion channels[7, 8, 9]. So, it was shown *in vitro* on HEK293T cells that ethanol inhibits cold-sensitive TRPM8, but activates the warm-sensitive TRPV1 ion channel[7]. The possible interaction of ethanol and the TRPM8 ion channel in the whole living organism is not known. The obtained results prove that thermoregulatory response to cooling are largely modified by the preliminary application of the ethanol to skin. It can be assumed that the effect of ethanol in our experiments was caused mainly through the peripheral skin afferents. Previously we have shown that the modulation of the peripheral thermal inputs by various biologically active substances results in changes of the thermal thresholds and

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other parameters of thermoregulatory responses. As it was mentioned above, thermoregulatory responses to rapid and slow cooling are characterized by different components. In current experiments, the application of ethanol and solution of menthol in ethanol differently affects thermoregulatory metabolic response depending on the cooling rate. At rapid cooling, ethanol has no effect on the first phase of the metabolic response, which takes place only at rapid changes of the skin temperature, i.e. in the presence of the dynamic activity of the skin cold thermoreceptors. This suggests that ethanol does not influence the processes caused by the dynamic activity of the skin thermoreceptors. It should also be noted, that these responses are initiated when only skin temperature decreases before the fall of deep body temperature 6. On the contrary, according the above mentioned data, ethanol has clear inhibitory effect on the component of the metabolic response to rapid cooling, which normally develops when the deep body temperature falls. Thus, under the influence of ethanol, the second phase of the metabolic response to rapid cooling and shivering thermogenesis which accompanies this phase does not develop and is completely absent. At slow cooling, ethanol similar rapid cooling supresses the metabolic response and shivering does not develop. Inhibition in metabolic response to cold exposure is accompanied by the acceleration of the deep body temperature fall. Thus, at cooling with different rates, ethanol inhibits the most powerful thermogenic component of the metabolic response to cold which develops when the deep body temperature decreases, and has no influence on the earlier started responses which are initiated without considerable decrease in deep body temperature, but only at the rapid decrease in skin temperature. Moreover, on the background of ethanol, instead of increasing thermogenic metabolism during cooling, a significant decrease in oxygen consumption is observed. A number of researchers have also noted the hypothermic effect of the intrinsic administration of ethanol in thermoneutral conditions as well as its inhibitory effect mainly on thermogenesis and not on heat loss. Decrease of the main phase of the cold thermogenesis which we observed in our experiments, when applying ethanol to skin, may be due to inhibition of non-shivering thermogenesis in brown adipose tissue, and inhibition of muscle thermogenic activity (shivering). It is known that mitochondrial UCP1 in brown adipose tissue (BAT) is a key molecule for non-shivering thermogenesis. The data on the influence of ethanol on the level of noradrenaline and uncoupling in BAT give evidence for the possibility to change non-shivering thermogenesis by ethanol. So it was shown, that at room temperature, ethanol did not significantly alter the level of noradrenaline or UCP1 mRNA in BAT, whereas at cold exposure (+4ºC) the noradrenaline level in rats drinking ethanol was significantly lower than in control animals. Earlier, it was noted that drinking alcohol can delay the onset of shivering and reduce its duration, and this may also result in the decrease of thermogenesis.

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