Over the last 5 years, we have witnessed a significant increase in interest in food intake, currently acting as an external biological clock synchronizer (zeitgeber) not associated with daylight. Nonetheless, over the last 15 years many compounds affecting appetite and release of body energy resources have been described. However, it was only the research conducted during the last several years that has shown that activity and intensity of some of these factors is impacted by the biological clock, and its biochemical signal in the form of melatonin functionally interacts with proteins involved in the regulation of the organism energy balance. Many hormones involved in maintenance of the appropriate energy homeostasis of the body demonstrate circadian and annual changes in activity. One of these is leptin, originally - as well as currently - of interest primarily due to the role that this hormone may play in helping us understand the causes of obesity in mammals. High concentrations of leptin observed in some obese subjects are most likely associated with the loss of the natural appetite-reducing (anorexic) properties of this hormone. Brain - specifically, satiety center - insensitivity to high levels of circulating leptin is one of the factors causing metabolic disorders, including onset of obesity, and to understand the mechanisms involved in the phenomenon of leptin resistance would contribute not only to prevention, but also to development of an adequate therapy for treating these disorders. Research undertaken by our team since 2004 has identified that resistance to leptin occurs in animals exhibiting seasonality of reproduction, including sheep. These animals demonstrate annual changes in reproductive cycle, appetite and body weight. Increase in food intake and body weight during long days is associated with high concentration of peripheral leptin and low concentration of leptin in cerebrospinal fluid. Importantly, this phenomenon is characterized by a strongly reduced sensitivity of hypothalamic neurons to leptin action over this period. During short days, on the other hand, a natural sensitivity of neurons to leptin is observed, as recorded when leptin was administered directly into the third ventricle of the brain in sheep. For leptin to be "able" to inform the brain about the amount of food consumed and the weight of accumulated fat, it must penetrate into the brain, crossing the blood-brain barrier and the blood-cerebrospinal fluid barrier as well. Recent studies indicate that inhibited penetration of leptin across the brain barriers is the cause of resistance to the hormone activity, due to its very low concentration in the brain. The main goal of the proposed research is to determine whether leptin deficiency in the brain is the result of impeded penetration of leptin through brain barriers. The proposed study is also a continuation of research into distortions of the signal transduction from leptin to its receptor, a mechanism which may possibly involve resistin. We should also consider that transport across brain barriers may depend on the nutritional status of the individual, namely whether it is sated or hungry, and in the case of analyzing the role of biological clock in our lives - it may also be associated with photoperiod. The experiments will be carried out on sheep fed and fasted for 72 hours in two photo-periods - respectively during the period of shortening and lengthening days. As continuity of the previous studies the experiments will investigate the role of resistin in the development of insensitivity (resistance) to leptin in the brain, which until now was considered to be related to the phenomenon of insulin resistance. Above all, however, the main purpose of the planned experiments it to determine the causes of disturbances in the transport of leptin across the blood-brain barrier and the blood-cerebrospinal fluid barrier, taking into account the nutritional status of the organism and the length of day. The research animal model used - sheep - will permit to track the changes in permeability of brain barriers to the experimental factor, namely leptin, with particular emphasis on the impact of photoperiod. The final goal of the project is to use in the experiments the leptin analogue - the so-called MTS-leptin, a protein molecule modified to quickly cross the brain barriers, regardless of the dependence on the nutritional status or time of year. The research results will not only deepen the knowledge of the phenomenon of leptin resistance, and therefore be a further step in understanding the involvement of different factors in disruptions of leptin signal transduction to its receptor in the brain, but will predominantly allow for testing of hypotheses related to the variable permeability of brain barriers to proteins acting on centers located in the hypothalamus that are transported across these barriers. "Leakages" across brain barriers are observed in many disease states, e.g. in neurodegenerative diseases - such as Parkinson's or Alzheimer's disease, in multiple sclerosis as well as epilepsy, therefore understanding the determinants of the tightness of hypothalamus barriers and their permeability for the transported factors depending on the nutritional status or time of year will be both an interesting observation and a starting point for further research. The effective treatment of brain-related diseases is severely hampered by the presence of BBB. Moreover, identification of the role and significance of factors involved in the mechanism of leptin transport to the hypothalamus and their receptors in choroid plexus (vascular endothelial growth factor VEGF isoforms 120 and 164 and its receptors VEGFR1 and VEGFR2) will expand our knowledge about the strong influence of photoperiod on life processes in seasonal animals, as exemplified by sheep. These animals were underestimated so far but are now increasingly appreciated as a possible experimental model for understanding the etiology of many diseases, as they have similar body weight to humans and demonstrate similarity of reproductive processes in many respects. They are also animals with unique characteristics, such as biannual reversible sensitivity of the hypothalamus to leptin signal, or close linking of their life processes with the external environment.