The aim of this work is to study the role played by melatonin in the control of energy metabolism. By using \textit{in vivo} and \textit{in vitro} experiments, in intact or pinealectomized young or old animals, treated or not with melatonin, we are proposing to study the metabolic function and gene expression in the white adipose tissue, skeletal muscular system and the pancreatic B cells and the apoptosis phenomenon induced by fatty acids. Moreover, we intend to study the action of melatonin in association or not with insulin and/or leptin on cellular metabolism and gene expression in specific hypothalamic nuclei or in neurons and/or glia cells maintained in culture. The central nervous system structures to be studied are those mainly involved in the control of energy metabolism and circadian rhythms.
SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Due to its special characteristics of production and secretion, melatonin is considered the darkness hormone. Its unique feature of being synthesized exclusively at night, regardless of the organism activity pattern and the fact that the duration of the daily secretory episode follows exactly the duration of the night confer to melatonin the very important role of timing the circadian and seasonal biological rhythms of the organism in order to adapt it to the regular daily and annual environmental fluctuations.

Therefore, it is not surprising that it is possible to find scientific data demonstrating the effect of melatonin on almost all physiological processes, such as sleep-wakefulness, reproduction, aging, immune and inflammatory responses, cardiovascular reactions, energy metabolism including insulin secretion and action on adipose tissue function and weight regulation, among others.

The aim of this project is to study the melatonin effects on the regulation of energy metabolism and its implication on diabetes and obesity control and aging.

Pinealectomized animals develop a diabetogenic syndrome characterized by insulin resistance and 50% reduction of GLUT4 in adipose and muscular tissue. This dramatic picture can be partially or totally restored by melatonin reposition or restricted feeding.

Melatonin, in addition, by acting through MT1 membrane receptors, is able to induce insulin receptor phosphorylation, at the same time as it mobilizes several intracellular transduction steps that are common to insulin signaling. Moreover, it was demonstrated that the absence of melatonin in pinealectomized animals impairs the temporal organization of several metabolic functions associated to the carbohydrate metabolism, such as daily insulin secretion, adaptation to starvation and exercise. The same melatonin timing action was demonstrated in vitro in adipocyte cultures synchronized to 24h cycle of melatonin administration. In this experimental condition, the expression of some clock genes, particularly Bmal1 and Clock, and the lipogenic and lipolytic functions were synchronized to a particular phase of the in vitro daily melatonin cycle. In addition, it was demonstrated that melatonin given to old animals is able to reduce the insulin resistance in several tissues and to reduce body weight.

As a corollary of the above described actions, it was demonstrated that insulin can act on in vitro pineal glands by potentiating the noradrenergic-induced melatonin synthesis, and regulating the activity of the enzymes tryptophan hydroxylase and N-acetyltransferase through post-transcriptional mechanisms.

Most importantly, it was demonstrated, by using the pineal microdialysis technique, that streptozotocin-diabetic rats show a 50% reduction in the nocturnal melatonin production, which contributes for aggravating the diabetic syndrome.

MAIN PUBLICATIONS


José CIPOLLA Neto

Instituto de Ciências Biomédicas
Universidade de São Paulo (USP)
Departamento de Fisiologia e Biofísica
Avenida Prof. Lineu Prestes,1524 – C. Universitaria
CEP 05508-000 – São Paulo, SP – Brasil
+55-11-3091-7466
cipolla@icb.usp.br