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Appetite Control

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Preface

The marked and continuing increase in the prevalence of obesity during few decades is one of the most remarkable characteristics of Western civilization. It profoundly affects the society not only with its consequences for public health but also with its economical and sociological/cultural aspects. As has been demonstrated by artifacts such as the Venus of Willendorf as well as by historical reports, obesity occurred in almost all societies as a rare condition among the rich and privileged. However, in the last decades of the twentieth century, a marked increase in its prevalence commenced in the USA, in Europe, and subsequently, also in parts of Asia, reaching epidemic proportions. There is little doubt that this increase reflects the influence of an "adipogenic" environment: the unlimited availability of food in combination with the development of particularly palatable, less satiating foods (the so-called fast food), together with a mechanization of all tasks, causing an inactive, sedentary lifestyle. So far, all efforts to halt this epidemic by changes in diet and lifestyle had little success: Triglycerides lost during an intervention are rapidly regained once the individual returns to the previous food choice and eating behavior, and few individuals manage to continue their intervention indefinitely. This observation appears to reflect the influence of a powerful biological system that controls not only energy balance, i.e., caloric intake, but also food choice and nutritional preferences.

It is obvious that such a biological system controlling energy balance can comprise targets for a pharmacological intervention. Consequently, considerable efforts have been made in the past to elucidate the molecular basis of this system, to identify potential targets for intervention, and to discover agents inhibiting food intake by a reduction of appetite. As this volume will summarize, these efforts have led to a broad understanding of the mechanisms controlling food intake, to the identification of numerous targets for intervention, and also to several agents with appetite-inhibiting potency. However, so far, none of these agents have met the high safety standards required for the chronic treatment of obesity. Agents such as sibutramine and rimonabant that were in use for some time have been withdrawn because of unacceptable side effects. Thus, this volume cannot describe established and accepted therapeutics. Rather, its aim is to summarize the state of knowledge of

potential target proteins and mechanism in order to point out promising directions of future research. Thereby, the volume addresses pharmacologists, physiologists, neuroendocrinologists, and all other scientists who are interested in the field of obesity research.

The first part of the volume presents a comprehensive description of the central mechanisms controlling food intake, and thereby energy balance, in the mammalian organism. During the last two decades, research in this area has produced a remarkable wealth of information and has characterized the function of numerous peptides and their receptors in a neuroendocrine network of appetite control. Chapters covering leptin, neuropeptide Y, MSH, AGRP, NMU, the orexins and neuromedins, and their respective receptors highlight this plethora of information. In addition, the central effects of insulin in modulating this network are covered in the first section. An often overlooked aspect of the obesity problem is its analogy with addictive behavior. Thus, the concluding chapter of the first section covers the role of reward systems in appetite control. It has been believed that dysfunction of the neuroendocrine circuitry leads to obesity, e.g., by alterations such as "leptin resistance," but so far, no fully convincing, comprehensive molecular mechanism has been proposed. Thus, the question as to why individuals are sensitive or resistant to the "adipogenic" environment remains to be answered.

The circuits controlling food intake depend on peripheral signals from sensors that monitor the availability of nutrients. Solid evidence has been accumulated, indicating that the gastrointestinal tract plays a major role in generating these signals. Therefore, the second section of the volume includes chapters covering the peptides ghrelin, GLP-1, CCK, PYY, PP, and amylin, as well as their receptors. More recently, it has become apparent that the intestinal tract plays an even more important role because its microbiota appears to modulate energy balance and, consequently, adiposity. Although the underlying mechanisms are largely unknown, it was appropriate to add a chapter covering these novel aspects to the second section of the volume.

Three separate chapters describing the sensing of nutrients are included in the third section of the volume. The availability of glucose is assessed by a complex system of glucosensors in the CNS; at low glucose levels, these neurons trigger the sensation of hunger. The consumption of fat is also monitored, but the underlying molecular mechanisms are less well known. The current status of knowledge is described in the second chapter of the third section, with particular focus on the fatty acid transporter CD36. The molecular mechanisms of chemosensation of glucose, fatty acids, and amino acids in the intestinal mucosa are described in the third chapter of the section. These processes are controlled by nutrient-binding receptors, transporters, or ion channels that trigger the secretion of intestinal hormones. Interestingly, receptors recognizing sweet taste have been found recently in the intestinal mucosa, as is also described in the final chapter of the section.

The current status of antiobesity drugs is described in the fourth section of the volume. In contrast to the plethora of mechanistic information described in the first three sections of the volume, at present, there are no antiobesity drugs available for the therapy of morbid obesity. This situation is not due to a lack of effective agents

but to the presence of serious side effects which cannot be tolerated under conditions of a chronic therapy. The section describes the agents that have been in use and later withdrawn (reuptake inhibitors of catecholamines, e.g., sibutramine; cannabinoid antagonists, e.g., rimonabant) or have been investigated in clinical trials (HT-receptor antagonists, e.g., lorcaserine; MCH-receptor antagonists; antiepileptics, e.g., topiramate, zonisamide). Efforts are still being made to develop strategies minimizing the side effects of existing agents, for instance, by reduced dosage in drug combinations. An interesting strategy to prevent the psychiatric side effects of cannabinoid antagonists is the design of peripherally restricted derivatives. In addition, bombesin-3-receptor agonists, a more recently identified, promising group of appetite-inhibiting agents, are covered in a separate chapter.

I am deeply grateful to the authors of the volume who have contributed excellent, informative, and comprehensive chapters to this volume. All authors are distinguished experts in their fields and have contributed important original data to our understanding of appetite control. They have quite different scientific backgrounds, and, together, they represent all relevant disciplines. Thereby, the topics are presented from different points of view, not exclusively from that of pharmacology. Thus, I believe that they have written a timely and unique overview on one of the most important areas of current research. I do hope that this volume will contribute to generate novel ideas, findings, and solutions to the pressing problem of obesity.

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