Chapter 11

METABOLIC ACTIONS OF GHRELIN

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Abstract: Ghrelin is mainly expressed in the stomach, followed by lower parts of the gastrointestinal tract. Ghrelin secretion is mainly influenced by changes in energy balance and glucose homeostasis, followed by alterations of endocrine axes. Ghrelin therefore seems to be an interface between energy homeostasis, glucose metabolism and physiological processes regulated by the classical endocrine axes that e.g., control growth. Ghrelin most likely defends fat mass to ensure survival and to provide the calories that are needed for growth hormone to act on growth and repair. The possibility of using a ghrelin antagonist for the treatment of obesity initiated a hunt for such a valuable agent. It will not be long before antagonists are disclosed and tested for the treatment of obesity.

Key words: body weight, food intake, stomach, insulin, metabolism

1. INTRODUCTION

Apart from a potent growth hormone (GH)-releasing action, ghrelin has many other actions including stimulation of the lactotroph and corticotroph, influence on the pituitary gonadal axis, stimulation of appetite, control of energy balance, influence on sleep and behavior, control of gastric motility and acid secretion, influence on pancreatic exocrine and endocrine function as well as on glucose metabolism. Moreover, many growth hormone secretagogues (GHS) and/or ghrelin have cardiovascular actions and modulate proliferation of neoplastic cells, as well as of the immune system. In this chapter we will discuss the metabolic actions of this fascinating new hormone.
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PERIPHERAL ACTIONS OF SYNTHETIC AND NATURAL GHS

The first synthesized GHS were non-natural peptides, which were designed rather than isolated by Bowers and Momany in the late 1970s. They were met-enkephalin derivatives devoid of any opioid activity (1,2). Growth Hormone Releasing Peptide-6 was the first hexapeptide to actively release GH in vivo. A well known member of the non-peptidyl GHS family is spiroindoline L-163,191 (MK-0677) (3-11). MK-0677 has been shown to possess a high bioavailability and it is able to enhance 24-hour GH secretion after single oral administration (3-11). Studies focusing on the distribution of the identified GHS receptors (GHS-R) showed a particular concentration of these receptors in the hypothalamus-pituitary area, but specific binding sites have also been found in other brain areas and peripheral, endocrine and nonendocrine animal and human tissues (12-17). Indeed this distribution of the GHS-R does explain the GH-releasing effect of GHS, but also their other endocrine and nonendocrine biological activities (Figure 11-1 and 11-2) (3;18-31).