A wide variety of biologically active polypeptides encompassing hormones, neuropeptides, and other molecules such as gramins (chromogranin A and B) are initially synthesized as large inactive precursors, packaged into the granules of the regulated secretory pathway, processed to biologically active products, and finally released in a calcium-dependent manner upon stimulation. To release the biologically active products, the precursors must undergo limited proteolysis at pairs of basic residues by specific enzymes, named convertases.

Three mammalian convertases, prohormone convertases 1 (PC1) (1) and 2 (PC2) (2) and furin, have been identified to date (3, 4). PC1 and PC2 differentially cleave pro-opiomelanocortin (POMC) (5) and proinsulin (6), whereas furin is a specific proteinase capable of activating the β-subunit of pro-transforming growth factor (pro-TGFβ) (7), von Willebrand factor (8), and viral glycoproteins (9).

It has now become apparent that mutations of the genes encoding for convertases, leading to impaired prohormone processing, can cause specific endocrine disorders, as in the case described by Jackson et al. (10). The proband was a 43-year-old woman with extreme childhood obesity (weight at the age of three 3, 36 kg; weight and body mass index at presentation, 89·2 kg and 34.4 kg/m² respectively), abnormal glucose tolerance, post-prandial hypoglycemia, hypogonadotropic hypogonadism, and hypocortisolism. Her hormonal state was characterized by increased plasma proinsulin and POMC concentrations, associated with very low insulin concentrations. These findings were suggestive of a defective prohormone-processing by PC1. Indeed, it has been demonstrated that insulin is normally produced by the action of two prohormone-cleaving enzymes on the proinsulin molecule (6, 11). One of these, PC1, cleaves proinsulin between the 32 and the 33 positions, and the other, PC2, cleaves proinsulin between the 65 and the 66 positions, and the resulting intermediate products are trimmed of their terminal lysines or arginines by the action of ubiquitous carboxypeptidase H (CPH), also known as carboxypeptidase E (CPE). Nevertheless, the major pathway involved in proinsulin cleavage is related to PC1, which is essential for initiating the sequential processing.

In addition to this role, PC1 seems to be involved in the production of corticotropin from POMC in the corticotropes. In particular, PC1 cleaves POMC into corticotropin and β-lipotropin (5). In addition, PC2 has some activity at various POMC cleavage sites, producing β-endorphin, N-terminally extended corticotropin containing the joining peptide, and α melanocyte stimulating hormone (αMSH) (5).

In the proband, the high plasma concentrations of proinsulin and 65–66 split proinsulin and the low to undetectable concentrations of 32–33 split proinsulin and insulin were consistent with a PC1 activity defect. Moreover, the moderate increase in corticotropin precursors, together with the nearly normal adrenal production of glucocorticoids, also suggested a PC1 defect. However, the mild hypoadrenalism observed in the patient seems to indicate that PC1 is more crucial for the processing of the proinsulin than that of POMC. On the basis of the above findings, PC1 gene was sequenced and a compound heterozygosity for deleterious mutations was found. In particular, Gly–Arg183 missense mutation and A to C transversion at position +4 of the intron-5 donor splice site, which causes skipping of exon 5, loss of 26 residues and a frameshift resulting in the creation of a premature stop codon were demonstrated. These genetic alterations prevent processing on PC1 and lead to its retention in the endoplasmic reticulum (ER). Mutant PC1 is thus unable to leave the ER and enter the high calcium concentration and low pH within the granules of the regulated secretory pathway – conditions that are essential for PC1 enzymatic activity. The high plasma concentrations of proinsulin, its partial insulin-like action and its long biological half-life can account for the impaired glucose tolerance and the post-prandial hypoglycemia observed in the patient. Impaired processing of POMC probably underlies her hypocortisolism. Other abnormalities found in the proband, such as the hypogonadotropic hypogonadism and the obesity, could be due to an impaired PC1 activity. In the former case, an impairment of the processing of hypothalamic hormones and neuropeptides related to gonadotropin-releasing hormone secretion could be involved.

As far as the obesity is concerned, serum leptin concentrations were normal for the body mass index of
the patient, thus excluding involvement of defects in leptin, which cause obesity in rodents (12).

The potential relevance of such obesity associated with other endocrine disorders has recently been highlighted by the discovery of the molecular basis for the fat/fat mouse phenotype (13). This is characterised by obesity, hyperglycemia, and impaired fertility associated with abnormalities of proinsulin and POMC processing, which result from a mutation in the gene for CPE. This enzyme localises to the Golgi apparatus and acts distally to PC1 as an exopeptidase which is capable of removing basic residues from the C-terminal of peptide hormones subsequent to cleavage from the prohormone by convertases (14, 15).

Although the genetic defect resides on different genes, the similarity between these human and fat/fat mouse phenotypes is intriguing, because PC1 and CPE cooperate in the prohormone processing. Products of the gene encoding human PC2, a proprotein convertase, which result from a mutation in the gene for CPE. This enzyme localises to the Golgi apparatus and acts distally to PC1 as an exopeptidase which is capable of removing basic residues from the C-terminal of peptide hormones subsequent to cleavage from the prohormone by convertases (14, 15).

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