20 YEARS OF LEPTIN

What we know and what the future holds

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This special issue of *Journal of Endocrinology* celebrates the 20th anniversary of the discovery of leptin, a hormone produced by adipose tissue, which provides critical signals to the organism regarding the status of its energy stores. The discovery of leptin not only revolutionised our understanding of endocrine physiology but has also resulted in a registered medicinal product which is already improving the health of patients with serious metabolic diseases. In this issue, we have gathered together a group of essays by some of the world leaders in leptin research, including an overview by Dr Jeffrey Friedman who, in his seminal article in December 1994, described the adipocyte-derived hormone, the lack of which was responsible for the severe obesity in *ob/ob* mice and suggested that it should be named leptin.

Key Words

- ▶ leptin
- ▶ adipocyte
- ▶ metabolism
- ▶ physiology

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I can recall, as if it was yesterday, my first sight of the 1st December 1994 copy of *Nature* with its now iconic cover image of an *ob/ob* mouse outweighing its two WT siblings (Zhang *et al.* 1994). I devoured the accompanying article with a growing sense of nuchal pilo-erection! Although I had been training as a clinical endocrinologist for almost a decade and had started research in type 2 diabetes, I had only very recently become aware of the long history of mechanistic research in obesity, reaching back to the hypothalamic lesioning experiments of Hetherington & Ranson (1940), the work of Kennedy on evaluating the response of rodents to fasting and overfeeding (Kennedy 1966), the classic parabiosis work of Hervey, which provided the first evidence for a circulating factor affecting body fat stores (Cummings & Hervey 1959), the descriptions of the *ob/ob* (Ingalls *et al.* 1950) and *db/db* (Hummel *et al.* 1966) mice by Snell, Coleman

and colleagues at the Jackson Labs where Coleman subsequently undertook the renowned parabiosis experiments (Coleman 1973), establishing that the *ob/ob* mouse lacked a circulating factor to which the *db/db* mouse was resistant.

Given the limited technical resources available at the time, the identification of that circulating factor through positional genetic methods in the mouse was a tour de force requiring prodigious vision, courage, dedication and skill. I am delighted therefore that, in putting together this volume celebrating the discovery of leptin 20 years ago, Jeff Friedman has contributed a personal piece reflecting on the process of leptin's discovery and adumbrating the questions that remain (Friedman 2014).

The identification of the leptin receptor (Tartaglia *et al.* 1995) and its disruption in the *db/db* mouse (Chen *et al.* 1996, Chua *et al.* 1996) were major landmarks, and

Jan Tavernier, whose laboratory has contributed much invaluable information about the relationships between structure and function of the leptin receptor, provides a scholarly overview of this aspect of leptin action (Peelman *et al.* 2014). Martin Myers has been at the forefront of using murine genetic manipulation to explore the physiological consequences of the perturbation of leptin signalling within the brain and provides an invaluable overview of the broader biology of leptin signalling (Allison & Myers 2014). The fall in circulating leptin levels upon starvation initiates a set of homeostatic responses far wider than those simply concerned with appetite and energy expenditure (Ahima *et al.* 1996). Among these are its profound effects on the reproductive system. Farid Chehab and Christos Mantzoros, who have made seminal contributions to this aspect of the field, in rodent models and humans respectively, provide thoughtful and insightful summaries of the current state-of-the-art of leptin and reproduction (Chebab 2014, Chou & Mantzoros 2014).

Leptin has recently been approved as a licensed, prescription medicine in both Japan and in the USA. It is therefore highly appropriate that our special issue should have a major focus on studies in humans. Sadaf Farooqi and I provide a perspective summarising the discovery of human genetic disorders of leptin secretion and action including our experience of witnessing, first-hand and for the first time, the dramatic effects of restoring leptin to humans who congenitally lacked the hormone (Farooqi & O'Rahilly 2014).

When leptin was first discovered, there was some understandable excitement about the possibility that it might be a widely applicable panacea for human obesity. To date, this has not proved to be the case, as obesity appears to be generally associated with reduced responsiveness to leptin. Alex DePaoli has been intimately involved with leptin as a potential therapeutic from the earliest stage of its evolution and brings his unique insights to this volume (DePaoli 2014). Rosenbaum & Leibel (2014) have undertaken some of the most challenging but insightful studies of the human physiology of leptin and its potential relationship with weight regain after weight loss. In elegant studies of weight-reduced humans, they have shown that preventing the decrement in leptin induced by weight loss can abrogate some of the 'energy-saving' responses to weight loss. A deeper understanding of those effects of leptin may eventually result in a broadening of the therapeutic impact of this fascinating peptide.

There are many intriguing elements of leptin's biology and or pharmacology that we have not been able to cover

in this volume. The examples include the effects of leptin on insulin sensitivity, blood pressure and the immune system. In the short space of 20 years, leptin has moved from the research journal to the canonical undergraduate physiology textbook as well as from the academic laboratory to the clinic. There is still much to do to illuminate the role of this fascinating adipose-derived hormone in biological functions and to optimise its use to benefit human health. The 30th anniversary issue will, I am sure, be a fascinating read.

Declaration of interest

I declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this editorial.

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