EMBO reports

viewpoint

One hundred years of hormones

A new name sparked multidisciplinary research in endocrinology, which shed light on chemical communication in multicellular organisms

Jamshed R. Tata

In June 1905, Ernest Starling, a professor of physiology at University College London, UK, first used the word 'hormone' in one of four Croonian Lectures—'On the chemical correlation of the functions of the body'—delivered at the Royal College of Physicians in London. Starling defined the word, derived from the Greek meaning 'to arouse or excite', as "the chemical messengers which speeding from cell to cell along the blood stream, may coordinate the activities and growth of different parts of the body" (Starling, 1905). Starling (Fig 1) was a brilliant experimentalist, and these prestigious lectures were in recognition of his work—much of it in collaboration with his brother-in-law William Bayliss—on the effects of innervations and pancreatic secretion on the intestine.

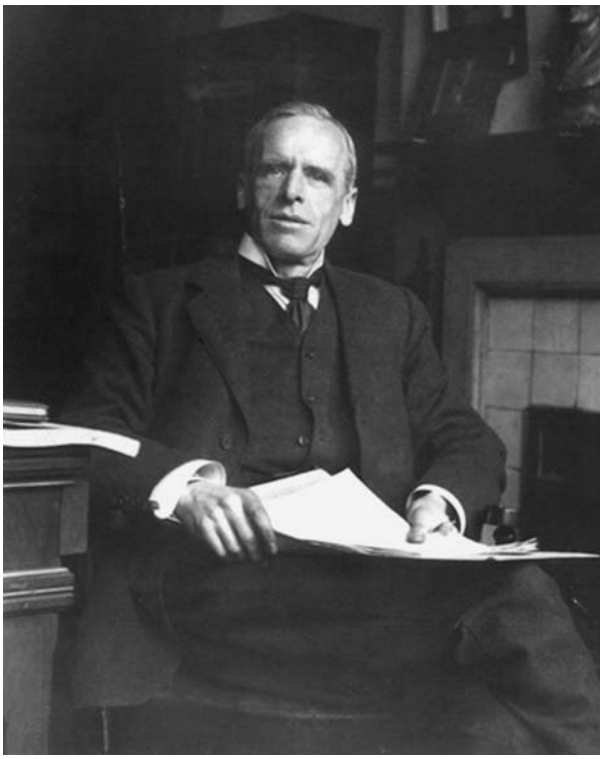

Fig 1 | Ernest Starling, a few years after he coined the word 'hormone'. Picture with permission from the Starling family.

Since Starling coined the word, the concept of hormones has spawned immense interest in a wide range of research fields, ranging from chemistry to molecular biology to epidemiology (Baulieu & Kelly, 1990; Turner & Bagnara, 1971). In addition to purely scientific advances, the study of hormones has led to enormous benefits to human health, social and economic progress, such as contraception, *in vitro* fertilization (IVF) and recombinant human hormones. More recently, the topic of hormones and hormonally regulated metabolism and development has also found interest among public health experts and the larger public, after concerned scientists in the USA hypothesized that various man-made chemicals could interfere with the hormonal system to cause a wide range of diseases and disorders.

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The nature and work of chemical messengers in the body had already attracted the interest of scientists before Starling. Experimental work by pioneers such as Arnold Adolphe Berthold in Germany and Claude Bernard in France, in the middle of the nineteenth century, established the concept that some sort of chemical communication takes place between different organs in an animal. Later in the same century, several physicians described the successful treatment of patients with certain disorders by administering extracts of animal endocrine tissues, such as the thyroid, adrenal glands and pancreas; they subsequently showed that these disorders were due to hormonal deficiencies.

Nevertheless, the history of science has repeatedly shown how the introduction of a new word can act as a catalyst for research—just consider the words 'radioactivity', 'chromosome', 'antibiotic', 'apoptosis' and, of course, 'molecular biology'. When Starling first introduced 'hormone' a hundred years ago, virtually nothing was known about the nature of hormones or chemical messengers. Biochemistry was then still in its infancy, but it soon became obvious to many physiologists that a chemical approach was needed to understand the nature and actions of hormones.

In the first half of the twentieth century, researchers thus concentrated their efforts on identifying the source of these internal messengers, with the result that many hormones have been named after the gland or organ from which they are secreted, such as thyroid or adrenal. This system of nomenclature was not always perfect, because distinct hormones can be secreted by the same gland,

as, for example, with the pituitary and the pancreas. Scientists also succeeded in deciphering the chemical nature of hormones and, less than 20 years after Starling had coined the word 'hormone', Edward Calvin Kendall at the Mayo Clinic in Rochester, NY, USA, purified and determined the structures of cortisone (a steroid) and thyroxine (an iodoamino acid). In 1926, Sir Charles R. Harington in London performed the first chemical synthesis of a hormone, thyroxine. His breakthrough work was soon followed by the characterization of the nature and activity of the pancreatic hormone insulin—a protein—by Sir Frederick Grant Banting and Charles Herberg Best. In the 1920s and 1930s, Adolf Butenandt, Tadeus Reichstein and Edward Adelbert Doisy discovered and characterized various steroid hormones, including oestrogen, testosterone and progesterone. Butenandt, Doisy, Kendall, Banting and Reichstein were all later awarded Nobel Prizes, which illustrates the growing importance of this emerging research field. This increasing knowledge of physiological actions also led to many hormones being named according to their actions, such as growth hormone and prolactin. However, this nomenclature can still be unsatisfactory as various hormones exert different actions in different target tissues or organisms at varying developmental stages.

It soon became obvious from the effects of endocrine extracts in heterologous tissues that internal secretions were conserved across species (Fig 2). A particularly dramatic example is the discovery by Friedrich Gudernatsch in 1912 that extracts of horse thyroid tissue can induce precociously the complete metamorphosis of frog tadpoles into adults. The availability of synthetic thyroid hormone further established the extraordinary multiplicity of responses to this hormone. Another example of how a given hormone has been put to different uses through evolution is prolactin, which has important and diverse actions in fish, amphibians, birds and mammals.

Soon, another major principle of endocrinology emerged, that of the interplay and feedback between the central nervous and endocrine systems. Most of the external physical signals—such as photoperiodicity and temperature—are transmitted to the central nervous system, where neurotransmitters act on specific target neurons, which in turn produce neurohormones and set up a cascade of endocrine secretions (Fig 3). Hormones

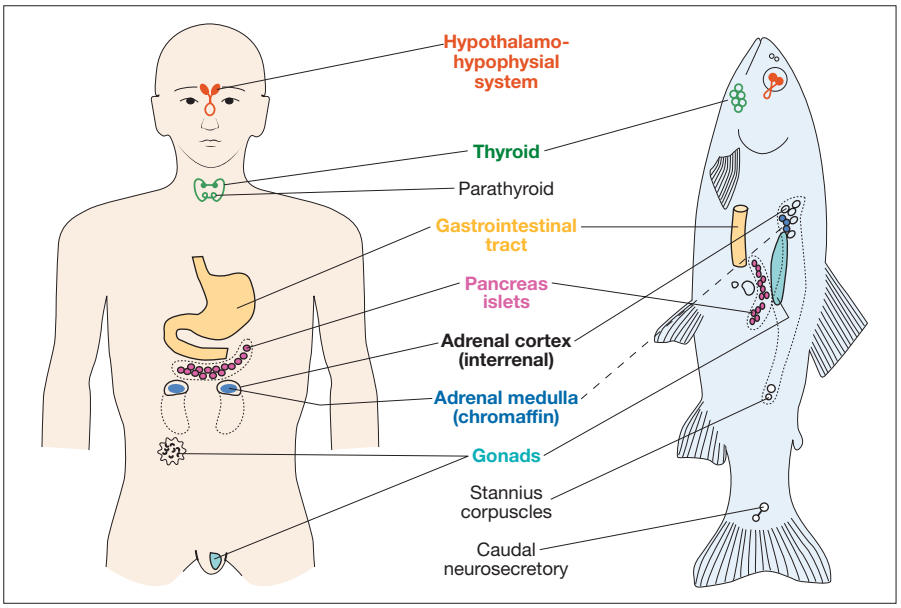

Fig 2 | Conservation of endocrine glands in two evolutionarily distant vertebrates, which produce similar hormones but whose actions may vary according to the species and target tissue (Gorbman & Bern, 1962).

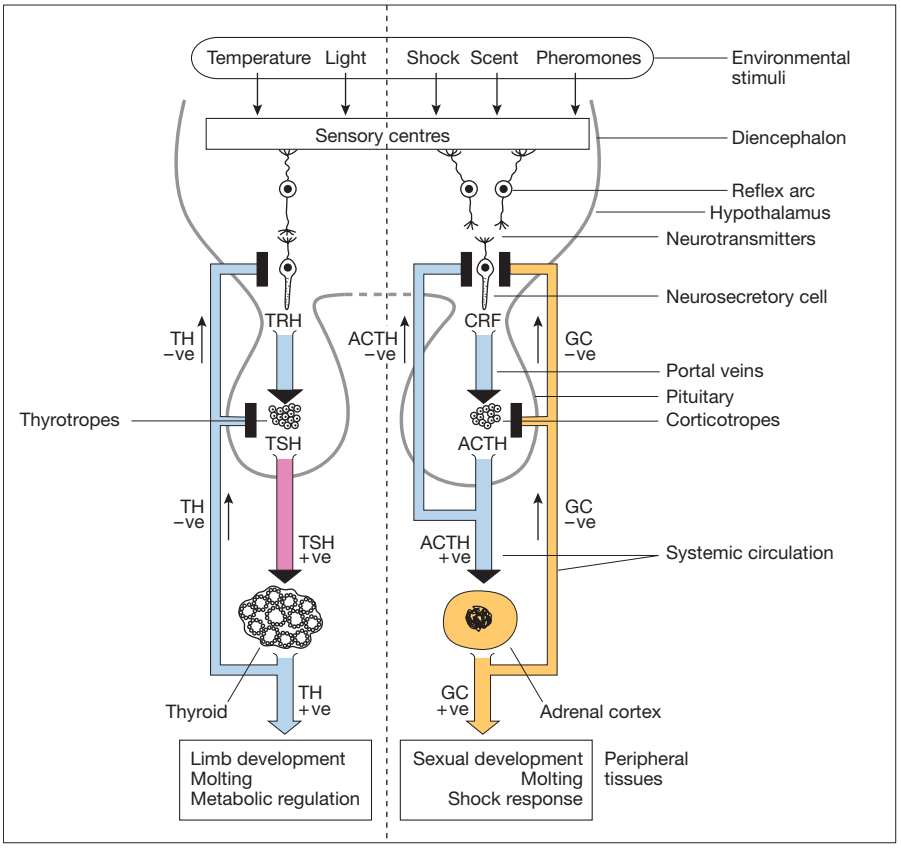

Fig 3 | Two examples of how information received in the central nervous system is converted to chemical signals by endocrine cascades leading to important physiological regulatory functions. The upward and downward arrows indicate negative (–ve) and positive (+ve) feedback loops, respectively. TSH-releasing hormone (TRH) and corticotrophic-releasing factor (CRF) are produced by the hypothalamus and act on the pituitary to produce thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (ACTH), which regulate the activities of the thyroid and adrenal glands, respectively. GC, glucocorticoids; TH, thyroid hormone.

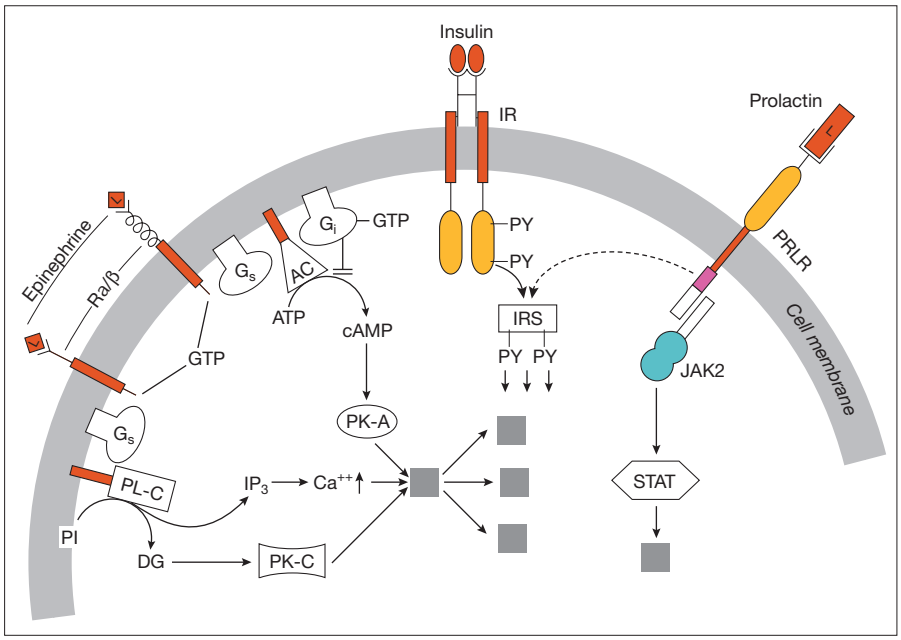

Fig 4 | A simplified diagram to illustrate 'second messenger' and protein phosphorylation pathways associated with target-cell membrane receptors for three hormones: epinephrine (adrenaline), insulin and prolactin. AC, adenylyl cyclase; cAMP, cyclic AMP; DG, diacylglycerol; Gs and Gi, stimulatory and inhibitory G proteins; IP_3, inositide trisphosphate; IRS, insulin receptor substrate; JAK, Janus kinase; PI, phosphatidyl inositol; PK-A and PK-C, phosphokinases A and C; PL-C, phospholipase C; PY, phosphotyrosine; Rα/Rβ, IR and PRLR, receptors for epinephrine, insulin and prolactin, respectively; STAT, signal transduction and transcription factor. The grey squares indicate different protein targets for phosphorylation by different pathways, depending on hormonal signal, species and tissue.

can thus be considered as intermediaries in the transfer of information from the environment to the organism. Their overall purpose is to coordinate and integrate the activities of metabolic and developmental processes in diverse target cells in response to environmental signals. By the 1950s, important associations between the neural and hormonal signalling pathways were established for a variety of hypothalamic 'releasing' hormones or factors, such as thyrotropin releasing hormone (TRH), corticotropin releasing factor (CRF), luteinizing hormone releasing hormone (LHRH) and prolactin-inhibiting factor (PIF), each of which acts on different, specialized cells of the pituitary gland to regulate the production of thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), luteinizing hormone/follicle-stimulating hormone (LH/FSH) and prolactin, respectively. It is an interesting fact that some neurotransmitters, such as serotonin, are also signalling molecules in plants, while many animal hormones are found in primitive organisms and have obviously been put to different uses throughout evolution (Gorbman & Bern, 1962; Barrington 1964).

> The … observation—that all steroid and thyroid hormones administered *in vivo*, affect the protein-synthesizing machinery *in vitro* soon shifted the focus to transcriptional control

Initial studies on the mechanism of hormone action sought to uncover a unique mode of action for all hormones and vitamins, which often involved adding a given hormone or active principle to isolated tissues, cell homogenates or subcellular preparations. The study of direct hormone–enzyme interactions became easier in the 1930s and 1940s with the availability of purified enzymes. For a few years, it was thought that hormones induced allosteric or conformational changes in proteins, such as the effects of insulin on hexokinase. The very high concentrations of hormones needed to elicit a direct effect on a given enzyme rendered these studies ineffective, and this approach was not compatible with the high degree of tissue specificity shown by hormones. By the end of the 1950s, there was little enthusiasm for the idea of direct hormone–enzyme interactions as the basis for a common mode of action (Tata, 1986, 1998).

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By the early 1940s, Rachmiel Levine had proposed that insulin controlled sugar metabolism by regulating its transport into the cell, which led several years later to the concept that protein and smaller peptide signals interact with the cell membrane. The discovery of cyclic AMP (cAMP) by Earl Sutherland in 1956 as a 'second messenger' of adrenaline and glucagon, followed by the discovery that adenylyl cyclase, the enzyme that synthesizes cAMP, was located in the plasma membrane, further consolidated the view that the cell membrane was a major site of action for many hormones (Sutherland, 1972; Beavo & Brunton, 2002). With the discovery of other secondary signalling molecules, such as inositol trisphosphate, G proteins and oncogenes, and the advent of gene cloning and sequencing technologies, it soon became possible to identify and characterize several membrane hormone receptors. Binding of the ligand to these receptors initiates a cascade of protein phosphorylation and dephosphorylation in the cytoplasm, which eventually leads to the physiological action of the hormone (Fig 4; Parker & Pawson, 1996; Hunter, 1997).

At almost the same time as cAMP was discovered, Eugene Knox showed that glucocorticoids regulate hepatic metabolism by selectively enhancing the synthesis of the enzyme tyrosine aminotransferase (Knox *et al*, 1956). New methods to study cell-free protein synthesis and the availability of specific transcription

inhibitors allowed a more precise analysis of how growth and developmental hormones influenced protein synthesis in their respective target cells. The resulting observation—that all steroid and thyroid hormones administered *in vivo* affect the protein-synthesizing machinery *in vitro*—soon shifted the focus to transcriptional control (Tata, 1986). The first indication that hormonal signals regulate transcription rather than translation was provided in the early 1960s by studies showing that 'puffing'—an index of intense transcriptional activation—of polytenic chromosomes in the larval salivary glands of insects is regulated by the steroid moulting hormone ecdysone (Ashburner *et al*, 1974). The kinetics of nuclear RNA labelling further revealed that all steroid and thyroid hormones strongly influence the formation and turnover of messenger RNA. In the mid-1960s, several investigators were able to reproduce the transcriptional effects of steroid and thyroid hormones in cell-free transcription systems using isolated nuclei and nuclear extracts from target tissues (Tata, 1986, 1998). In the 1970s and 1980s, the laboratories of Pierre Chambon and Bert O'Malley described in detail how oestrogen tissue-specifically and selectively activates the genes for egg white protein—ovalbumin, conalbumin and ovomucoid—and yolk protein (O'Malley *et al*, 1978; LeMeur *et al*, 1981; Tata, 1998).

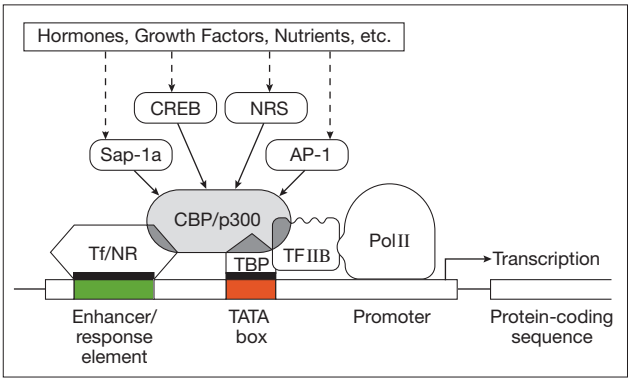

Fig 5 | Nuclear hormone receptors form complexes with other factors to regulate transcription. A bridging protein such as CBP/p300 would be in close contact with nuclear receptors and transcription factors (Tf) that recognize specific DNA sequences—TATA box binding protein (TBP) and transcription factor IIB (TFIIB), which would form a complex with RNA polymerase II (PolII). CBP/p300 is thought to form complexes with other transcription factors without involving DNA, such as CREB, AP1 and Sap1a. The activities of many of these components are modified by phosphorylation.

Although we know much about the details of the transcriptional machinery, it would be impossible to understand how hormones or other signals regulate gene expression without understanding their receptors. Hormone receptors have been commonly classified into two main groups: cell membrane receptors and nuclear receptors. Receptors for protein hormones and growth factors, such as insulin, epidermal growth factor, growth hormone and prolactin, as well as many neurotransmitters, are all located in the target-cell membrane; most of them are products of the oncogenes *v-erbB*, *v-ros* and *v-mpl*. Many membrane receptors are closely linked to adenylyl cyclase and G proteins, and, through these, to cytoplasmic protein phosphokinases, which transfer extracellular signals to the intracellular regulatory machinery (Parker & Pawson, 1996).

The first evidence for the existence of nuclear receptors came in 1961 from Elwood Jensen and colleagues, who tracked radioactively labelled oestradiol-17β in female sexual tissues and found that it forms a complex in the nucleus with a protein that fulfilled the criteria for a receptor (Jensen, 2004). The cloning of various receptors for oestrogen, glucocorticoids and thyroid hormone in the 1980s—in the laboratories of Chambon, Ronald Evans and Björn Vennström—showed that all nuclear receptors are cellular homologues of the oncogene *v-erbA* and function as ligand-activated zinc-finger transcription factors; this research later earned Chambon and Evans the prestigious Lasker prize. Today, more than 30 nuclear receptors encoded by this gene superfamily have been cloned and sequenced, and many are now available as pure recombinant proteins (Mangelsdorf *et al*, 1995; Benoit *et al*, 2004; Chambon, 2004), including several 'orphan' receptors for which the ligands have not yet been identified. What is most remarkable for these nuclear hormone receptors is their high degree of target-gene specificity, which is achieved by a precise spacing of nucleotide repeats in the target gene promoter's hormone response element (HRE), which interacts with the DNA-binding domain of the receptor.

As Figure 5 shows, large proteins termed CBP (cAMP responsive element binding protein (CREB)-binding protein) and p300 are thought to form bridges between nuclear hormone receptors and other transcription factors. Other important elements of this complex are the p160 nuclear receptor coactivator and the 270-kDa nuclear receptor co-repressor (McKenna & O'Malley, 2002). The CBP/p300 complex integrates several signalling pathways in the cell nucleus and many more such modulators will probably be discovered in the near future, forming even more complex structures with nuclear receptors. The functions of many transcription factors and co-regulators of nuclear receptors that are involved in such integration are themselves regulated by protein phosphorylation (Wu *et al*, 2004), thus creating a wider network that links membrane and nuclear receptors into complex signal-transduction pathways (Fig 6). In this context, work from James Darnell's laboratory has highlighted the importance of protein phosphorylation in the control of gene expression—for example, as seen with the JAK/STAT signalling pathway and that of nuclear factors, such as CREB (Brivanlou & Darnell, 2002).

> … the knowledge of hormone action in reproductive endocrine physiology enabled IVF, which is an enormous blessing for many couples in the developed world who are unable to conceive

Recent work on how steroid and thyroid hormones modify the chromatin structure of their target genes has provided evidence that the HREs of the glucocorticoid receptor are highly organized in phased nucleosomes. The binding of the hormone to its nuclear receptor causes an alteration in the chromatin structure, such

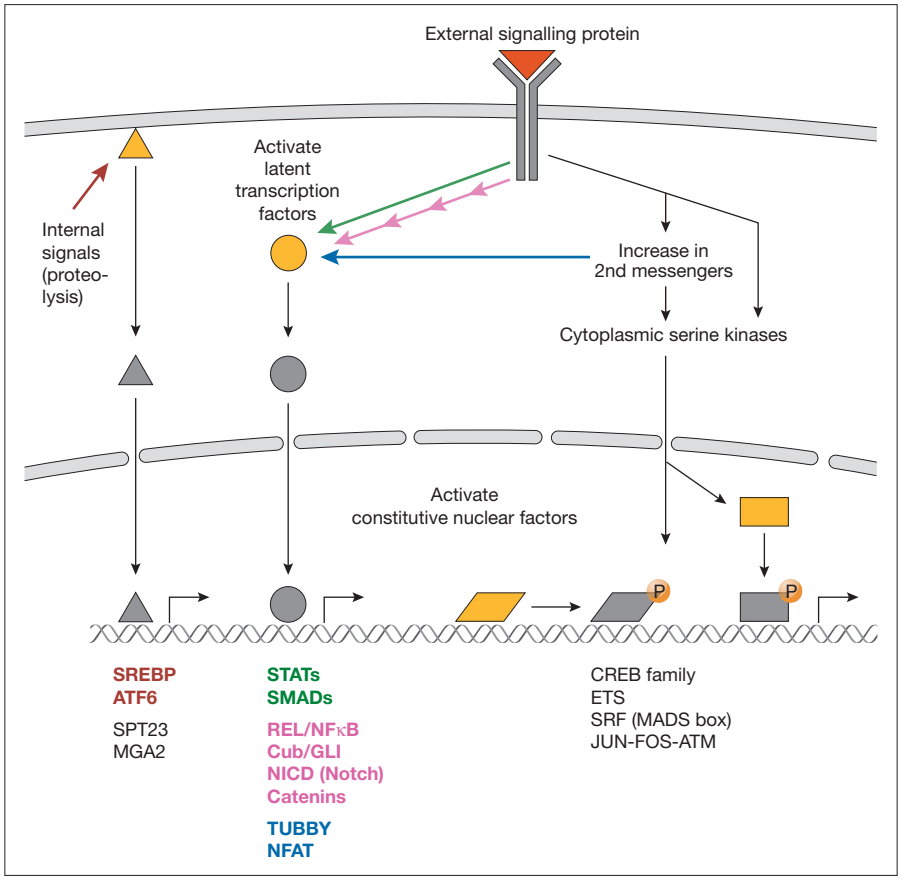

Fig 6 | Convergence of signalling through membrane and nuclear receptors. Latent intracellular regulatory factors can be activated (or inhibited) directly by phosphorylation (green), proteolysis (pink) or second messenger fluctuations (blue), as indicated by arrows of different colours. The activities of nuclear proteins, receptors and transcription factors can thus be modified by phosphorylation through plasma membrane receptors (Brivanlou & Darnell, 2002).

that it induces the incorporation of other transcription factors into chromatin, which eventually triggers the transcription of the hormone-regulated gene (Beato, 1996; Wolffe, 1992; Evans, 2004). So far, most conclusions drawn from chromatin experiments are based on indirect observations *in vitro*. The recent development of chromatin immunoprecipitation (ChIP; Sachs & Shi, 2000) is therefore a promising new technique. Raphael Métivier and George Reid in the laboratory of Frank Gannon have already used ChIP to show that the oestrogen receptor activates its target gene in a cyclical manner, in that the receptor–ligand complex is continuously removed by a protease and replaced by a new receptor (Métivier *et al*, 2003; Reid *et al*, 2003).

Hormone receptors now occupy a central role in our current concepts of signalling mechanisms. The fact that about 4,000 publications in the year 2004 were about nuclear hormone receptors alone illustrates this point well (B. O'Malley, personal communication). During the past 25 years, the application of gene cloning, cell transfection, transgenic and gene knock-out techniques, X-ray crystallography and nuclear magnetic resonance analysis of DNA–protein and protein–protein interactions have significantly advanced our understanding of the structure and function of receptors beyond all expectations. What is most striking is that, since Starling introduced the word 'hormone', our views on the structure and function of hormones have followed the progression of technology that is needed to understand biological processes in ever more detail. Starting with cellular physiological processes, such as respiration and glycolysis, our ideas have moved on to the interaction with enzymes and then to subcellular biochemical processes, such as oxidative phosphorylation and protein and RNA synthesis, followed by more recent advances in cell biology, immunology, structural biology and genomics.

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As fascinating as these rapid scientific advances from multidisciplinary research have been, it is also worth considering the impressive contributions to human and animal health, social progress and economic benefits made by the application of endocrinology. Just three examples suffice to illustrate this point. In the 1950s, Gregory Pincus led the development of the oral contraceptive—commonly known as 'the Pill'—based on the arrest of ovulation with derivatives of oestrogen and progesterone, followed two decades later by the antiprogestin RU486, often termed 'the morning-after Pill' (Pincus *et al*, 1958; Baulieu & Segal, 1985). This has had an enormous impact on society. According to many sociobiologists, the availability of chemical contraception has done more for the emancipation of women than any legislation. Unfortunately, its impact has been beneficial mostly to affluent, industrialized countries and not to the disadvantaged, developing world, where this advance is, of course, most needed.

Similarly, the knowledge of hormone action in reproductive endocrine physiology enabled IVF, which is an enormous blessing for many couples in the developed world who are unable to conceive. Since the birth of Louise Brown in 1978, the first 'test tube baby', in the hands of Patrick Steptoe and Robert Edwards in Manchester, UK, this technology has become routine, and hundreds of thousands of children have been born as a result (Edwards *et al*, 1984). In addition, the advent of recombinant DNA technology, and the lessons learned from the deaths of young patients from

Creutzfeldt–Jakob disease (CJD) who were treated with growth hormone obtained from human cadaver pituitaries, has accelerated the availability of pure human protein hormones. Recombinant human insulin, growth hormone, erythropoietin (EPO) and other protein hormones are now commonly used in clinical endocrinology, thus eliminating the problems of contaminants from animal or human sources (Baulieu & Kelly, 1990). Indeed, recombinant protein hormones are among the most profitable products of the biotechnology industry—the market for human EPO alone is worth over US$3 billion.

But, as with many other scientific and technological advances, the benefits are often accompanied by the recognition of undesirable or harmful effects for human well-being. This became evident as recently as 2003, when the US National Institutes of Health (NIH; Bethesda, MD, USA) and the British Medical Research Council (London, UK) halted two large trials on the risks and benefits of hormone replacement therapy (HRT) after they found that HRT increases the risks of breast cancer, dementia, stroke and cardiovascular disease, and recommended that postmenopausal women should stop taking hormones (Brower, 2003). From a scientific point of view, it is not surprising that hormones have a role in disease pathology, given that breast cancer, for instance, is treated with medications that manipulate oestrogen-regulated cell proliferation. These trials highlight the need for caution and more research when manipulating the human hormonal system for medical or lifestyle reasons.

Another public health aspect of hormones was suggested as early as 1962 when Rachel Carson described in her book *Silent Spring* how man-made chemicals, such as dioxins, dichlorodiphenyltrichloroethane (DDT) or polychlorinated biphenyls (PCBs), affect the fertility, reproductive success and behaviour of wild animals by interfering with their endocrine system. The first experimental support for human health problems came from the work of John McLachlan, who showed that treating women with diethylstilbesterol, a synthetic oestrogen agonist, during the 1950s and 1960s resulted in a marked increase in cancer among their daughters (Li *et al*, 2003), which was further

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supported by work from Fred vom Saal on the development of unborn mice (Palanza *et al*, 1999). Elsewhere, Richard Sharpe in the UK and Nils Skakkebaek in Denmark found decreasing sperm count and sperm motility among men in Denmark and Scotland who were born after the Second World War. In a hypothesis paper in the *Lancet*, they advanced the theory that environmental chemicals could be a cause for this decline in male fertility (Sharpe & Skakkebaek, 1993).

During the late 1980s and early 1990s, Theo Colborn, a US zoologist working for the World Wildlife Fund and the W. Alton Jones Foundation, eventually put together different observations from wildlife, laboratory work and the European studies on declining male fertility into what is now called the 'endocrine disruptor hypothesis' (Colborn *et al*, 1996). It claims that various chemicals that accumulate in the environment can act as hormone agonists or antagonists or can interfere with hormone synthesis and thus disrupt endocrine networks in animals and humans. The young and the unborn are particularly sensitive to such disruptions as prenatal and postnatal development depend on the correct levels and timing of crucial hormones. Exposing them to endocrine disruptors even at low doses could therefore cause diseases later in life, ranging from cancer or malformations to immunological and neurological disorders and infertility. Perhaps the most vulnerable wildlife are aquatic animals, such as fish, amphibia and corals, many species of which have already been lost, with unforeseeable damage to biodiversity. Endocrine disruptor screening programmes, now being performed by many national and international agencies in the USA, European Union and Japan, will reveal more knowledge on how hormones act on organisms and on early developmental processes. Whether these chemicals are indeed as grave a threat to public health as Colborn and other concerned scientists think is not yet clear, as many of the predicted human diseases and disorders have not significantly increased since humans introduced man-made chemicals into the environment. But the public debate again highlights the enormous challenge of understanding the whole complexity of hormone action and the ensuing need for research. It has also further expanded the fields of inquiry as many epidemiologists, clinicians, zoologists and risk assessment experts have joined the ranks of biochemists and molecular biologists in trying to understand hormones and their actions.

Looking at the advances in biological research and the ongoing debates about public health, it is not too difficult to predict that hormones and hormone receptors will remain an exciting and important field of basic research in the future. Further developments in the science of signalling mechanisms will depend heavily on emerging technologies, such as proteomics and structural biology, while receptor pathology and gene therapy will occupy an important niche in clinical practice and commercial exploitation. One may then ask: Will we ever understand how hormones act at the cellular level? The simple answer is: No. Hormone research will continue to reflect our knowledge of regulatory mechanisms at any given time. Conversely, many important advances in biochemistry, cell and molecular biology are the result of work on hormones. For example, cAMP was discovered as a result of Sutherland's investigations on the action of glucagon and adrenaline; neurohormones have enhanced our understanding of the interplay between neural and chemical communication networks; and work on hormone receptors has taught us a great deal about cellular oncogenes.

Amazing progress has been made in the life sciences in the one hundred years since Starling first used the word 'hormone'. Who would have predicted in 1905 what we now know about membrane structure, gene cloning, DNA sequencing and transgenic animals? For the next hundred years of hormone research, it is worth recalling what Niels Bohr said about predictions in science: "It is always so difficult to make predictions—especially about the future."

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