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Review

Hormone multifunctionalities: a theory of endocrine signaling, command and control

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Abstract

A theory is presented outlining how organisms can function and benefit from multifunctionality of hormones in order to enhance greatly the information-carrying potential of endocrine signaling. Hormones are produced continuously as micropulses, and intermittently as larger pulses. It is generally believed that micropulses generate fluctuating basal hormone concentrations, which may consistently elicit particular responses among diverse variables. Evidence is discussed suggesting that in contrast to the hormone micropulses, the larger endogenous hormone pulses may elicit responses which may differ from one pulse to another and may therefore serve different physiological functions. In this paper we postulate that an endogenous hormone pulse is a specific form of a multisignal message that serves a certain physiological function. Different pulses of a hormone may be signals of diverse multisignal messages that serve different functions. A multisignal message may elicit congruous responses by selectively enhancing some actions and suppressing other actions of the component signals. Various roles of signals of multisignal messages are discussed, as well as processes that may be involved in the diversity and selectivity of actions of different pulses of a hormone. Hormones also are converted into other hormones; we analyze how precursor and derived hormones may function independently of each other, and how precursor hormones may give rise to permissive effects. Mechanisms involved in therapeutic and adverse effects of hormone administrations are analyzed, and a strategy is suggested for developing more selective hormonal therapies.

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1. Introduction

It is generally recognized that any one hormone elicits several diverse responses in different organs and tissues, as well as in individual cells. Actions that serve a single physiological function, we will call *congruous or pleiotropic* actions. Actions that serve unrelated physiological functions we will designate *disparate or incongruous* actions.

However, disparate actions of hormones have complicated the assessment of their physiological functions (Yates and Maran, 1974). In this paper we propose a theory of the mode of functioning of organisms with hormones that have diverse physiological functions. Because hormones are used as therapeutic agents, we discuss also how they may produce both beneficial and adverse effects, and propose a strategy for developing more selective hormonal therapies.

2. Pulses, micropulses, and negative pulses of hormones

Hormones circulate in blood plasma at small, basal concentrations, elicited by a steady production of hormone micropulses (Boyle et al., 1997; Carnes et al., 1988, 1993; Fehm et al., 1984; Gudmundsson and Carnes, 1997; Holl et al., 1991; Ookhtens et al., 1974). At variable intervals, larger hormone pulses are generated (Bäckström et al., 1982; Boyle et al., 1997; Brabant et al., 1992; Carnes et al., 1992, 1993; Frantz, 1979; Gudmundsson and Carnes, 1997; Holl et al., 1991; Judd, 1979; Krieger, 1979; Krieger and Allen, 1975; Licinio et al., 1994; Ookhtens et al., 1974; Rebar and Yen, 1979; Seif and Robinson, 1979), elicited by diverse endogenous and exogenous signals; these pulses are themselves signals of physiological control systems. Hormone micropulses are produced continuously, even during the production of the larger pulses (Greenspan et al., 1986; Carnes et al., 1988, 1993; Brabant et al., 1992).

Some hormones are released steadily at high rates, and for brief periods their rates of release may be greatly decreased. Martínez de la Escalera and Weiner (1992) have shown that the steady large concentrations of dopamine in the hypothalamic-pituitary portal system lead to occupation of most dopamine D₂ receptors of pituitary lactotrophs. As a result, prolactin secretion by the lactotrophs is inhibited. These authors have shown that a brief reduction in dopamine concentration leads to a rapid dissociation of dopamine from its receptors, which increases the release of prolactin by the lactotrophs. Prolactin secretion in response to TRH pulses is also increased (Martínez de la Escalera and Weiner, 1992). Thus, such brief reductions in the plasma concentration of dopamine can be considered negative dopamine pulses.

Under the term *hormone pulse*, we will encompass both moderate and large transient increases in hormone concentrations, as well as negative hormone pulses. Hormone micropulses and the corresponding changes in basal hormone concentrations appear to function independently of the larger hormone pulses, and will be discussed separately.

3. Kinetics of hormone pulses

The studies of [Dallman and Yates \(1969\)](#) on the kinetics of corticosterone plasma concentration, show that an i.v. step infusion of corticosterone produces initially a rapid increase in plasma corticosterone concentration that cannot be described by a single exponential function; this is followed by a slower exponential increase that leads to a steady concentration. When the infusion is stopped, corticosterone concentration decreases exponentially with a time-constant similar to that of the late rising phase. The initial rapid increase in hormone concentration can be considered a feedforward process ([Houk, 1988](#)), generated by a reduction in the disposal rate of the hormone by the distribution-binding-metabolism elements ([Dallman and Yates, 1969](#)).

When a hormone pulse is elicited by an endogenous signal, e.g. a cortisol pulse elicited by an ACTH pulse, the feedforward process may be considerably larger. [Urquhart and Li \(1968\)](#) and [Urquhart \(1969, 1970\)](#) have shown in adrenal glands perfused in situ, that a *stepwise increase in ACTH concentration elicits an overshoot in the cortisol secretory response*, after which the secretion rate declines slowly towards a steady-state value. Furthermore, a *stepwise decrease in ACTH concentration reduces the cortisol secretion rate rapidly*. Thus, the initial overshoot, and the rapid reduction in cortisol secretion rates in response to an ACTH pulse, indicate feedforward processes in both the rising and declining phases of the *secretory response*. Not only the secretion rates of cortisol but also its disposal rates in response to an ACTH pulse present feedforward processes. ACTH has been shown to decrease glucocorticoid *disposal rates* ([Berliner et al., 1961](#); [de Moor et al., 1961](#); [Dougherty and Berliner, 1958](#); [Kusama et al., 1970](#)). This effect may add to the decreased glucocorticoid disposal rate observed by [Dallman and Yates \(1969\)](#) during the initial part of an exogenous glucocorticoid administration. Together, the feedforward processes of hormone secretion and disposal rates, would increase the efficacy and decrease the duration of hormone pulses.

Formally similar feedforward processes (also called autocatalytic or positive feedback effects in other contexts) have long been known to occur in electrical pulses of nerve axons. During the initial part of the rising phase of an action potential, depolarization of the cell membrane increases sodium conductance across the membrane; this increases sodium influx, which further depolarizes the cell membrane ([Hodgkin and Huxley, 1952](#)).

4. Unidirectional rate-sensitivities of hormone-responsive cells

Evidence discussed by [Clynes \(1962\)](#) supports the notion that biological control systems have unidirectional rate-sensitivities; if they are sensitive to rates of increase of a variable, they are either insensitive or less sensitive to rates of decrease of the same variable, and vice versa. [Dallman and Yates \(1969\)](#) have shown that the negative-feedback path of corticosterone has a pronounced

rate-sensitivity to increases, but not to decreases, in the plasma concentration of corticosterone. Pituitary lactotrophs appear to be sensitive only to the rate of decrease of dopamine concentration. Unidirectional rate-sensitivities of hormone-responsive cells prevent suppression of the response to the rising phase of a hormone pulse by the declining phase. [Martínez de la Escalera and Weiner \(1992\)](#) have shown that effects of a negative dopamine pulse prevail beyond the duration of the pulse.

5. The two cybernetic types of hormone pulses

A hormone with plasma concentrations subject to negative feedback control may give rise to two cybernetic types of pulses: those produced in response to a transient change in the setpoint of its controlling system, and those that are independent of its setpoint. The latter pulses correspond to feedforward strategies ([Houk, 1988](#)). [Yates et al. \(1961\)](#) have shown that the production of a corticosterone pulse elicited by a laparotomy or a moderate i.v. pulse injection of histamine, can be suppressed by an i.v. injection of corticosterone that mimics the endogenous corticosterone pulse. These observations indicate that the endogenous corticosterone pulses are a response to a transient increase in the setpoint of the corticosterone controlling system. In contrast, as has been shown also by [Yates et al. \(1969\)](#), the corticosterone pulse elicited by a larger i.v. pulse injection of histamine, cannot be suppressed by an i.v. injection of corticosterone that mimics the endogenous corticosterone pulse. Thus, this large corticosterone pulse is a feedforward process. As indicated by [Houk \(1988\)](#), feedforward processes increase the speed of response of controlling systems, and are subject only to slower control processes, the adaptive controls.

6. Actions of hormone micropulses

Regardless of their small magnitude, micropulses of a hormone probably produce small, basal actions that serve the diverse physiological functions of the hormone. The small intervals between micropulses, and unidirectional rate-sensitivities of hormone receptors, may lead to summation of their minute actions. Effects of changes in basal hormone concentrations, which are elicited by changes in the magnitude and frequency of hormone micropulses, will be addressed in section 17, after discussing the conversion of hormones into other hormones.

7. Actions of endogenous hormone pulses

Knowledge that pulses of a hormone elicit pulses of other hormones provides an important tool for studying the functions of the hormone. Based on their observational studies, [Gallagher et al. \(1973\)](#), [Krieger and Allen \(1975\)](#), [Sherman et al. \(1984\)](#), [Linkowski et al. \(1985\)](#) and [Krishnan et al. \(1988\)](#) have concluded that only some ACTH pulses elicit cortisol pulses. Also, [Judd et al. \(1974\)](#) and [Liptrap et al. \(1986\)](#) have observed that only some luteinizing hormone (LH) pulses elicit testosterone pulses. Pulses of ACTH and LH that do not elicit cortisol and testosterone pulses, respectively, are likely to produce other responses, which remain to be

identified. Even assuming that some hormone pulses elicit no responses, an unlikely assumption, it would not detract from the notion that different pulses of a hormone have different physiological roles.

If the pulse of a hormone would affect two or more unrelated physiological functions, correction of disturbances in one function might produce disturbances in other unrelated functions. This might generate a chain reaction in which the number of disturbed physiological functions would increase exponentially, with probably lethal consequences.

As actions elicited by hormone micropulses differ from those elicited by larger hormone pulses; one would expect hormone micropulses and larger hormone pulses to be controlled independently of each other. This notion agrees with the suggestion of [McKenna et al. \(1999\)](#) and [Heinlein and Chang \(2002\)](#) that coregulators (coactivators and corepressors), which interact with nuclear receptors, and enhance or reduce transactivation of target genes, do not significantly affect basal transcription rates.

8. Further indications of the multiplicity of hormone functions

Different types, subtypes or isoforms of receptors of a hormone may mediate diverse, and even opposing actions. As shown by [García-Sáinz et al. \(1980, 2000\)](#), [García-Sáinz and Fain \(1982\)](#), [Fain and García-Sáinz \(1980, 1983\)](#), [Burns et al. \(1881\)](#), [Wright and Simpson \(1981, 1982\)](#), [Lafontan and Berlan \(1995\)](#), and [Bousquet-Mélou et al. \(1995\)](#) activation of β -adrenergic receptors of adipocytes by epinephrine stimulates lipolysis, whereas activation of α -adrenergic receptors has the opposite effect. Also, as pointed out by [McDonnell et al. \(2000\)](#), the two subtypes of nuclear estrogen receptors, as well as the two isoforms of progesterone receptors appear to have two distinct roles.

The notion that different endogenous pulses of a hormone elicit different actions and thus have different functions, leads to the following question: what factors determine the diversity and selectivity of actions of different pulses of a hormone? This question will be addressed in the following sections.

9. Diversity of elicitors of different pulses of a hormone

Different pulses of a hormone may be elicited by diverse signals or sets of signals. Observational studies by [Doell et al. \(1981\)](#), [Wood et al. \(1982\)](#), [Wilkinson et al. \(1982\)](#), [Dempsher and Gann \(1983\)](#), [Fehm et al. \(1983\)](#), [Sherman et al. \(1984\)](#), and [Krishnan et al. \(1988\)](#), show that only some cortisol pulses are elicited by ACTH pulses. Also observational studies by [Asher et al. \(1989\)](#) and [Monfort et al. \(1993\)](#), show that only some testosterone pulses are elicited by LH pulses. Thus, such cortisol and testosterone pulses that are not elicited by ACTH and LH pulses, respectively, are elicited by other signals that remain to be identified.

In addition to ACTH, the following hormones and other signals may increase cortisol secretion: corticotropin-releasing hormone (CRH) ([Andreis et al., 1991b, 1992](#); [Neri et al., 1991](#)), vasoactive intestinal peptide (VIP) ([Bloom et al., 1987](#); [Mazzocchi et al., 1998b](#)), galanin ([Mazzocchi et al., 1998a](#)), interleukin-1 (IL-1) ([Andreis et al., 1991a](#); [Ehrhart-Bornstein et al., 1998](#); [Gwosdow, 1995](#);

Neri et al., 1991; O'Connell et al., 1994), epinephrine, norepinephrine, and sympathetic nerve activity (Charlton, 1990; Edwards and Jones, 1987; England and Gann, 1989). Thus, such signals might elicit cortisol pulses. The observations of Waterman and Simpson (1989) on the multifactorial nature of the regulation of steroid hydroxylase gene expressions are consistent with this notion.

Also ACTH secretion may be increased, possibly as pulses, by diverse signals, such as CRH, arginine-vasopressin (AVP), lysine-vasopressin (LVP), oxytocin, cholecystokinin-octapeptide, angiotensin II, thymulin, serotonin, prostaglandins, nitric oxide, epinephrine, norepinephrine, IL-1 β , and IL-6 (Axelrod and Reisine, 1984; Buckingham et al., 1992; Gaillard et al., 1981; Hadley et al., 1997; Plotsky et al., 1989; Ur and Grossman, 1994). Such signals might elicit ACTH pulses. (The response produced by a hormone pulse might be determined in part by the signal or set of signals that elicit the hormone pulse, but details have not been worked out.)

Some hypothalamic neurons contain and release a single hormone, such as CRH, AVP, LVP, oxytocin, or cholecystokinin-octapeptide. Each of these hormones may stimulate pituitary ACTH secretion. Other hypothalamic neurons contain and co-release two hormones, such as CRH and one of the following hormones: AVP, LVP, oxytocin and cholecystokinin-octapeptide (Buckingham et al., 1992; Fuxe et al., 1991; Ur and Grossman, 1994). The release or co-release of these hormones might generate ACTH pulses.

Cortisol pulses elicited by different sets of signals, such as pulses of CRH+ACTH, AVP+ACTH, CRH+AVP+ACTH, or sets of signals that do not include ACTH pulses, might produce different responses. Thus, the diversity of responses elicited by different pulses of a hormone might result in part from the diversity of signals that elicit different pulses of the hormone. Evans et al. (1996) have shown complex interactions of CRH, cortisol, and pulses of AVP, on ACTH secretion in pituitary cell suspensions.

10. Hormone pulses, signals of multisignal messages

As diverse signals may elicit different pulses of a hormone, and assuming that these may produce diverse responses, we advance the hypothesis that *an endogenous hormone pulse is an expression of a multisignal message*. Different pulses of a hormone may be signals of diverse multisignal messages that *produce different patterns of congruous actions, and thus have different physiological roles*. The component signals of a multisignal message may be pulses of hormones, neurotransmitters, neuropeptides, cytokines, growth factors, paracrine and autocrine factors, as well as other signals. We propose that the various components of the multisignal message act in concert, permitting and enhancing actions of the component signals that are congruous with its role, and suppressing other actions.

11. Roles of different components of multisignal messages

11.1. Stimulation of some functions and inhibition of other functions of effector tissues

Probably most known actions of hormones are multifunctional. ACTH may stimulate cortisol and corticosterone secretion by adrenal cortical cells, and stimulate lipolysis in adipocytes. As

observed by Bornstein and co-authors (Bornstein et al., 1997), leptin, a hormone produced by adipocytes, inhibits not only the corticosterone secretory response to ACTH, but also basal corticosterone secretion. As shown by Morimoto et al. (1998), insulin inhibits not only ACTH- or norepinephrine-induced lipolysis in adipocytes, but also basal lipolysis. Stimulation of an effector tissue may elicit a hormone pulse. Both the hormone pulse elicitor and the elicited hormone pulse may be part of the same multisignal message.

11.2. *Permissive roles*

A signal has a permissive role when its presence is necessary for a different hormone or agent to produce a certain response, but the response does not track or depend upon variations in the level of the permissive agent. Cortisol, 17α -hydroxyprogesterone, and tetrahydrocortexolone inhibit angiogenesis only in the presence of heparin or a heparin fragment, the permissive signals (Crum et al., 1985). In contrast, the anti-angiogenic action of 2-methoxyestradiol does not require the presence of heparin or the heparin fragment (Fotsis et al., 1994). Different mechanisms may be involved in different permissive effects of hormones. We shall discuss below permissive roles of hormones that are precursors of other hormones.

11.3. *Enhancement of responses to other signals*

Giordano and Sayers (1971), Sayers et al. (1971), and Morita et al. (1984) have shown that a factor present in plasma increases in vitro the corticosterone secretory response to ACTH. Ackerman et al. (1981) have observed that 2-hydroxyestrone, 2-hydroxyestradiol and 2-methoxyestradiol, three physiological biotransformation products of estradiol, enhance in vitro epinephrine-induced lipolytic activity of adipocytes. Under the conditions studied, the estrogen biotransformation products per se had no lipolytic activity; thus, these compounds might be components of multisignal messages that enhance the lipolytic activity of epinephrine.

11.4. *Suppression of responses to other signals*

A factor also present in plasma, has been shown to decrease in vitro the corticosterone secretory response to ACTH (Fehm et al., 1973; Giordano and Sayers, 1971; Sayers et al., 1971). According to the concepts discussed above, signals that suppress the corticosterone secretory response to ACTH, may enhance other ACTH actions, whereas signals that enhance the corticosterone secretory response to ACTH may suppress other ACTH actions.

Cartier et al. (2001) have shown that nitric oxide produced by the adrenal chromaffin cells, suppresses corticosterone and aldosterone secretory responses to ACTH, angiotensin II, and endothelin I, but does not decrease basal production of corticosterone and aldosterone. Thus, nitric oxide may be a paracrine component of diverse multisignal messages that would suppress the corticosterone secretory responses to ACTH, angiotensin II, and endothelin I.

Briefly, a signal, e.g., a hormone pulse may be a signal of a multisignal message, if it does not affect the basal activity of an effector tissue, but enhances or suppresses its response to another signal.

Dissociation between changes in plasma bioactive and immunoreactive hormone concentrations, have been observed for ACTH by [Besser et al. \(1971\)](#), [Engeland et al. \(1989\)](#), and [Brabant et al. \(1992\)](#). These observations are consistent with the notion that some actions of a hormone are enhanced by other signals, whereas other actions are suppressed. Thus, estimates of hormone plasma concentrations based on bioassays may be affected considerably by other signals, whereas estimates based on radioimmunoassays probably are not.

12. Time relationships between signals of a multisignal message

Not only the composition of a multisignal message, but also the time relationships between its component signals, may determine which responses are elicited. [Shipston and Antoni \(1992\)](#) have shown that a brief CRH pulse applied in vitro to the pituitary at the beginning of a corticosterone pulse, transiently suppresses the inhibitory effect of the corticosterone pulse on pituitary ACTH release. No such suppression is produced when the CRH pulse is applied later, nor with an AVP pulse applied at any time during the corticosterone pulse.

13. Processes that may participate in determining the diversity and selectivity of actions of different pulses of a hormone

13.1. Selective increases in blood flow and hormone translocation to effector organs

[Urquhart \(1965\)](#), [L'Age et al. \(1970\)](#), [Hinson et al. \(1986\)](#), and [Vinson and Hinson \(1992\)](#) have shown that, even at constant ACTH plasma concentrations, increases in adrenal infusion rates may increase cortisol secretion rates. [Benton, Loring and Yates](#) have observed spontaneous transitions from steady to oscillatory blood flow into the adrenal gland (see [Yates and Poston, 1986](#)).

[Van Oers et al. \(1992\)](#) have shown in adrenal glands perfused in situ, that associations of CRF and ACTH induce increases in adrenal perfusion rates and corticosterone secretion rates; under the same conditions, neither CRF nor ACTH alone increased adrenal perfusion rates.

13.2. Concerted changes in the activities of hormone-converting enzymes

Some hormones circulate in blood as precursors that are converted by the effector tissues into active compounds, generating autocrine, paracrine, and endocrine actions. Thyroxine (T_4) is converted into 3,5,3'-triiodothyronine (T_3) and 3,3',5'-triiodothyronine (retro- T_3) ([Reed, 2001](#)). Testosterone is converted into 5 α -dihydrotestosterone, 5 β -dihydrotestosterone and estradiol ([Horton, 1995](#)). A multisignal message that increases the plasma concentration of the precursor, may increase the activity of one or several converting-enzymes, and in a concerted manner, decrease the activities of other converting-enzymes. From the experiments of [Carmichael and Belanger \(1984\)](#) it can be inferred that LH may increase not only testosterone secretion, but also prostatic 5 α -reductase activity. Thus, production and actions of 5 α -dihydrotestosterone would be enhanced; enzymes that convert testosterone into estradiol might be inhibited.

Conversely, Slater et al. (2001) have shown that ovarian hyperstimulation in women using a gonadotropin-releasing hormone agonist and human gonadotropins, increase androgen metabolism mediated by aromatase, and decrease androgen metabolism mediated by 5-alpha-reductase.

13.3. Selective activation of each receptor type, subtype, and isoform

As indicated above, different types, subtypes or isoforms of receptors of a hormone may mediate different, and even opposing responses. Probably different receptor types, subtypes, and isoforms may be activated selectively by pulses of a hormone that are signals of different multisignal messages.

As is well known from many studies, hormone receptors may be localized in plasma membranes, in the cytosol, or in the nucleus, and some, when occupied by their ligand may move to a new location (Power et al., 1991a, b; Campbell and Watson, 2001; Chen et al., 1999a, b; Clarke et al., 2000; Diba et al., 2001; Gametchu et al., 1991a, b, 1993, 1999; Norfleet et al., 1999, 2000; Pappas et al., 1995; Powell et al., 1999; Sackey et al., 1997; Thomas et al., 1993; Watson et al., 1995, 1999a, b, 2002; Watson and Gametchu, 1999, 2001).

13.4. Selective changes in receptors, which may activate and suppress different signaling pathways

As indicated by Bockaert and Pin (1999), receptors may undergo various types of changes, such as phosphorylations, homo- and heterodimerizations, and binding to proteins other than G proteins, like arrestins, and PDZ domain-containing proteins. The functional significance of these changes are being actively investigated.

13.5. Selective activation and suppression of different nuclear transcription processes

Several types of co-activators and co-repressors have been uncovered, which enhance or suppress a cellular response to a hormone (Heinlein and Chang, 2002; Horwitz et al., 1996; Jenster et al., 1997; Lemon and Tjian, 2000; McDonnell, 2000; McKenna et al., 1998, 1999, 2000). A multisignal message might affect selectively, and in a concerted manner, co-activators and co-repressors, thereby enhancing some cellular responses and suppressing other responses.

13.6. Selective RNA splicing

As has been discussed by Lou and Gagel (2001), a single hormone-responsive gene may generate hundreds of different mRNA molecules, which may generate hundreds of different proteins and peptides. The selective inclusion and exclusion of different RNA exons determines which mRNA molecules are generated, and consequently which proteins and peptides are synthesized. The proteins and peptides may have disparate or even antagonistic actions. In addition to the developmental stage of a cell, the composition of multisignal messages might determine how RNAs are spliced, thus generating proteins and peptides with congruous cellular actions.

13.7. Selective protein transformations

A protein synthesized by a cell may be cleaved in diverse ways, and also may be transformed otherwise. Pro-opiomelanocortin (POMC) may give rise to ACTH, N-terminal peptide, β -lipoprotein, β -endorphin, γ -melanocyte stimulating hormone, and ACTH phosphate (Lowry, 1984; Torpy and Jackson, 2001). The products of such cleavages or of other transformations might depend on the composition of the multisignal messages that stimulate POMC biosynthesis.

14. Importance of observational studies for uncovering multisignal messages

There have been few observational studies for assessing the actions of endogenous hormone pulses. However, regardless of their limited number and scope, observational studies of hormone pulses have generated significant information that is not obtainable from experimental studies. One cannot emphasize strongly enough the importance of uncovering the compositions and actions of the diverse multisignal messages of which a hormone is a component signal. In addition to experimental studies, it requires numerous observational studies with greatly increased scopes. However, one must be aware of certain difficulties: (1) Some signals may be pulses of hormones that have not yet been uncovered. (2) Signals reaching different organs may differ, owing to the selective actions of multisignal messages on blood flow and hormone translocations to different organs, as well as on local biotransformations of hormones. (3) Furthermore, autocrine and paracrine signals may be local components of multisignal messages (Cartier et al., 2001; Ehrhart-Bornstein et al., 1998; Hinson, 1990; Simpson et al., 1996). In an editorial comment on the impact of genomics and proteomics in endocrinology, Thompson (2002) has discussed current limitations of these technologies, and has suggested future lines of improvements. These technologies, when further developed, might be useful in observational studies, for identifying the composition of multisignal messages, as well as the corresponding cellular responses.

15. Conversion of hormones into other hormones

15.1. *Protohormones and metahormones*

As well as being signals of various multisignal messages, hormones are also converted into other multifunctional hormones (Baird et al., 1968; Longcope et al., 1969; Winkel et al., 1980). We shall use the terms *protohormone* and *metahormone*, to designate the relationship between a precursor hormone and a hormone derived from it. The terms “protohormone” and “metahormone” differ from the terms “prohormone” and “hormone metabolite”, as the latter terms do not refer always to hormones, whereas the former do. Metahormones are converted into second-generation metahormones, and these into further generations of metahormones. The following conversions of hormones into other hormones have been documented (Mellon and Griffin, 2002; Robel et al., 1991; White, 2001; Winkel et al., 1980): pregnenolone into progesterone and testosterone; progesterone into deoxycorticosterone and cortisol; deoxycorticosterone into corticosterone;

corticosterone into aldosterone; testosterone into 5α -dihydrotestosterone, 5β -dihydrotestosterone, and estradiol; estradiol into 2-methoxyestradiol. Probably many unknown metahormones are derived from currently known hormones.

Numerous receptors with unknown cognate ligands have been uncovered lately (Enmark and Gustafsson, 1996; Lala and Heyman, 2000; O'Malley and Conneely, 1992; Zeng et al., 1994). Some of these so-called “orphan receptors” might be receptors of as yet unknown metahormones derived from known hormones. The search for the cognate ligands of these receptors that is being pursued in many laboratories (Cooney et al., 2001; Zeng et al., 1994), may uncover many novel metahormones.

15.2. Relationships between protohormone and metahormone actions

Actions of a metahormone may complement, antagonize, or be unrelated to actions of the corresponding protohormone. Protohormone and metahormone pulses with actions that complement each other may be signals of the same multisignal message. Two or more metahormones derived from the same protohormone also may have complementary actions. For example, 5α -dihydrotestosterone and 5β -dihydrotestosterone, two metahormones derived from testosterone, increase erythropoiesis; the former, by increasing the secretion of erythropoietin by the kidney; the latter, by recruiting inactive erythroid stem cells into an erythropoietin-responsive phase (Goldberg and Kessler, 1995).

Some actions produced by the exogenous administration of a hormone, may result from increased production of the corresponding metahormones. For example, mammary growth, produced in human males by the administration of testosterone (Glass, 2001; Wu et al., 1996), may result from increased plasma concentrations and actions of estradiol (Matsumoto, 2001), one of the metahormones derived from testosterone. Also, the increased erythrocyte production elicited by the administration of testosterone, may result from increased production and actions of 5α - and 5β -dihydrotestosterone.

16. Independence of protohormone and metahormone pulses

16.1. Production of protohormone pulses without eliciting metahormone pulses

As indicated above, *exogenous* administrations of a protohormone may increase the production rates and actions of the corresponding metahormones. However, *endogenous* protohormone pulses may not elicit pulses of the corresponding metahormones; other components of the multisignal message may suppress increases in metahormone production rates. Thus, an ACTH pulse that elicits a cortisol pulse might prevent the production of pulses of cortisol metahormones. Only if both the protohormone and metahormone pulses are components of the same multisignal message, would the metahormone pulse not be suppressed.

16.2. Production of metahormone pulses without affecting protohormone plasma concentrations

Some metahormones are synthesized mainly from protohormone produced locally in the same tissue; e.g. cortisol is synthesized by the adrenal cortex from pregnenolone and progesterone

produced in the same organ (White, 2001). In such cases, large metahormone pulses can be elicited without affecting the plasma concentration of the protohormone.

Other metahormones are synthesized mainly from protohormone circulating in the blood, e.g. estradiol production from plasma testosterone in the human male (Baird et al., 1968; Longcope et al., 1969), and deoxycorticosterone production from plasma progesterone (Winkel et al., 1980). In such cases, a metahormone pulse might decrease the plasma concentration of the respective protohormone, and disturb protohormone-controlled variables. Large ratios of protohormone/metahormone plasma concentrations and production rates would reduce such undesirable decreases in protohormone plasma concentrations to insignificant values. Approximately two-thirds of plasma estradiol in men is derived from plasma testosterone (Baird et al., 1968). The molar ratios in men of basal testosterone/estradiol plasma concentrations (Attanasio and Gupta, 1980) and blood production rates (Longcope et al., 1969) are approximately 220 and 165, respectively. Thus, a thousand-fold increase of estradiol blood production rate would reduce testosterone plasma concentration by approximately only 2%.

16.3. Permissive effects of protohormones

One type of permissive effects of protohormones may be inferred from the above-indicated data. Metahormone pulses or sustained changes in basal metahormone plasma concentrations may be elicited even with small protohormone plasma concentrations. However, in the absence of the protohormone, no metahormone pulses or sustained changes in metahormone plasma concentrations can occur.

17. Effects of changes in basal hormone concentrations

Basal hormone concentrations may undergo significant changes. Whereas the effect of a hormone pulse that elicits a pulse of another hormone may be identified readily, the effects of changes in basal hormone concentrations are not easily discernible. Signals associated with changes in the basal concentration of a hormone may determine the response to such changes. Sapolsky et al. (2000) have pointed out that increases in basal plasma concentrations of epinephrine, ACTH, and glucocorticoid hormones, may occur during different phases of a stress response. Thus, the effects of a change in the basal concentration of a hormone, like cortisol, may differ at different phases of a stress response.

18. Biological significance of hormone multifunctionalities

The richness of behavior of organisms, at all their levels of organization, requires numerous hormone functions serving many controlling systems. If each hormone were synthesized *de novo*, and performed one role only, the machinery needed for the production of hormones would be unwieldy. Hormone multifunctionalities greatly reduce the number of hormones needed for the functioning of an organism, and consequently, also the biosynthetic machinery of hormones. The conversion of a multifunctional hormone into other multifunctional hormones by means of few

reactions, reduces the biosynthetic machinery of hormones even further. The combination of signals, whether discrete (endocrine, paracrine, and autocrine pulses), or sustained (changes in basal concentrations of endocrine, paracrine and autocrine factors), as well as selective changes in blood supply to different organs, enables organisms to produce numerous selective reactions.

19. Effects of hormone administrations

The therapeutic use of hormones makes it important to understand not only the diverse physiological roles of each hormone, but also the various processes underlying the effects of exogenous hormone administrations. In contrast to endogenous hormone pulses, which elicit diverse patterns of congruous actions, exogenous administrations of a hormone elicit a constant pattern of disparate actions. For example, ACTH administrations consistently enhance the following processes: secretion of cortisol, corticosterone, aldosterone (Giordano and Sayers, 1971; Hinson et al., 1986; Sayers et al., 1971; van Oers et al., 1992), androgens, estrogens (Baird et al., 1969; Parker and Odell, 1980), and interleukin-6 (IL-6) (Judd and MacLeod, 1992) by the adrenal cortex; it also enhances glucose-induced insulin secretion (Gagliardino et al., 1995), glucose and amino acid transport into muscle cells (Lebovitz et al., 1965), lipolysis in adipocytes (Scow et al., 1965; White and Engel, 1958), melanin synthesis in melanocytes (Torpy and Jackson, 2001), learning, and consolidation of memory (de Wied and Jolles, 1982), and also inhibits urea production. Such disparate actions can be attributed to the fact that the administered hormone is not a part of a multisignal message. The same explanation may be valid for the observation by Smith and O'Malley (1999) that transcriptional activities of estrogen receptors are not affected by co-repressors when estradiol is administered.

The effects of the administration of a hormone, depend, among other factors, on the status of the organism receiving the hormone. We will describe briefly three conditions that may influence the response.

19.1. *In the absence of the hormone*

Multiple disturbances are produced in the absence of a hormone, for lack of the hormone and of the metahormones of all generations. Exogenous hormone administrations correct the hormone deficiencies quite effectively, despite the non-physiological rates and routes of hormone administrations. Stimulator-inhibitor signals, permissive signals, and enhancer-suppressor signals normally associated with the endogenous hormone pulses, or with changes in basal hormone concentrations, may diminish the effects of imperfections in hormone administrations. Deficiencies resulting from lack of the metahormones of all generations are corrected even more effectively, because metahormone production rates and actions are governed by the needs of the organism.

19.2. *During insufficient production of the hormone*

In patients with Addison's disease, who secrete glucocorticoids and probably derived metahormones at insufficient rates, administration of physiological glucocorticoid hormones

tends to correct the hormonal deficiencies. Also patients in severe stress produce glucocorticoid hormones at insufficient rates; the exogenous administration of glucocorticoid hormones increases the survival rates of such patients (Munck et al., 1984; Munck and N aray-Fejes-T oth, 1992; Munck and N aray-Fejes-T oth, 1994). As Munck et al. have pointed out, various effects of glucocorticoid administrations in unstressed organisms would be detrimental during stress. However, these authors have suggested that such effects might be beneficial by neutralizing possible harmful overreactions of the organism. As indicated above, Hafezi-Moghadam et al. (Hafezi-Moghadam et al., 2002) have shown that glucocorticoids have a protective action on the cardiovascular system, which is mediated by non-transcriptional activation of nitric oxide synthase. Based on the theory of hormone multifunctionalities presented here, we believe that the diverse signals generated during different phases of the stress response, selectively suppress detrimental actions of glucocorticoid hormones and of the corresponding metahormones, and enhance actions that promote survival.

Patients in severe stress from metastatic neoplasia, frequently receive more active synthetic glucocorticoid derivatives like dexamethasone (Gums and Smith, 1999). These compounds have the advantages of a longer half-life and a lack of mineralocorticoid activity. However, their prolonged use might lead to some hormone deficiencies, as the biotransformation products of these synthetic compounds may not substitute all metahormones derived from physiological glucocorticoid hormones.

19.3. During adequate production of the hormone

When a hormone is produced at adequate rates, the exogenous administration of the hormone may elicit three types of effects: (1) Disparate actions that serve the various functions of the hormone. (2) Disparate actions of the metahormones derived from the administered hormone. (3) Effects that result from suppressing the production and actions of other hormones and their metahormones.

Administration in vivo of cortisol, for example, may elicit the following types of effects: (1) Actions of cortisol per se, corresponding to its various functions. (2) Actions of cortisol metahormones, which remain to be uncovered. Both the increase in cortisol plasma concentration and the consequent decrease in ACTH plasma concentration would enhance production and actions of cortisol metahormones. (3) Decreased or suppressed production and actions of the following hormones and the respective metahormones: ACTH, deoxycorticosterone, corticosterone, aldosterone, adrenal androgens, estrogens, and IL-6. Thus, the effects of the exogenous administration of the hormone would reflect physiological functions of several hormones; some effects would reflect increased production and actions of various hormones, whereas other effects would reflect decreased or suppressed production and actions of other hormones.

19.4. Pharmacological effects

Effects of a hormone produced only when the hormone is administered at rates greatly exceeding physiological production rates, are considered pharmacological effects. As indicated by Munck et al. (1984), the physiological significance of pharmacological effects has not been clarified. According to the concepts discussed above, pharmacological effects might result from

either of the following two processes: (1) Increases in the concentrations and actions of further generations of metahormones produced by large increases in the plasma concentrations of protohormones and of earlier generations of metahormones. (2) Suppression of the production and actions of other hormones. Thus, a pharmacological effect of a hormone may reflect an enhanced or suppressed physiological action of another hormone.

19.5. Ingle's permissive effects

As stated above, there are probably many types of permissive effects of hormones involving different mechanisms. The permissive effect described by Ingle (1954) can be summarized as follows: (1) Administration of a glucocorticoid hormone, like cortisol or corticosterone, stimulates protein catabolism in a dose-related manner; this effect corresponds to a *stimulator role*. (2) A noxious stimulus, e.g. a bone fracture, increases plasma concentrations of glucocorticoid hormones and stimulates protein catabolism. The magnitude of the catabolic response depends on the intensity of the stimulus; a multiple fracture enhances protein catabolism more than a single fracture. (3) In adrenalectomized animals, which lack glucocorticoid hormones, noxious stimuli do not enhance protein catabolism. (4) In adrenalectomized animals, administration of small doses of cortisol or corticosterone, which maintain a "eucorticoid state", restores the protein catabolic response to noxious stimuli.

Thus, with respect to protein catabolism, glucocorticoid hormones have both a *stimulator effect* and a *permissive effect*. Either of the following two mechanisms might elicit such dual effects.

1. Protein catabolism is stimulated by glucocorticoid hormones per se. According to this hypothesis, Ingle's observations could be explained as follows: (a) Administration of glucocorticoids to intact animals increases glucocorticoid plasma concentrations and protein catabolic actions. (b) Noxious stimuli increase the secretion of glucocorticoid hormones, which enhances protein catabolism. (c) In adrenalectomized animals, in the absence of glucocorticoids, no protein catabolic action occurs. (d) In adrenalectomized animals receiving small maintenance doses of glucocorticoids, signals generated by noxious stimuli might enhance the protein catabolic actions of even the small concentrations of glucocorticoids. If this hypothesis were correct, it might be possible to produce protein catabolic actions by glucocorticoid hormone administrations in vitro.
2. Protein catabolism is stimulated not by glucocorticoid hormones per se, but by glucocorticoid metahormones. According to this hypothesis, Ingle's observations could be explained as follows: (a) Administration of glucocorticoids increases plasma concentrations and actions of glucocorticoid metahormones that enhance protein catabolism. (b) Noxious stimuli increase the production and actions of glucocorticoid metahormones that enhance protein catabolism. (c) Without glucocorticoids, no glucocorticoid metahormones can be produced, and consequently, in adrenalectomized animals, noxious stimuli do not enhance protein catabolism. (d) Administration of small doses of glucocorticoid hormones to adrenalectomized animals restores the production of glucocorticoid metahormones. Large ratios of protohormone/metahormone plasma concentrations make it possible, even with small plasma concentrations of glucocorticoid hormones, to increase greatly plasma concentrations and actions of glucocorticoid metahormones that enhance protein catabolism. Signals elicited by noxious

stimuli might further enhance the protein catabolic action of the glucocorticoid metahormones. If, as we believe, this is the correct hypothesis, glucocorticoid metahormones that stimulate protein catabolism might be extracted and isolated from appropriate tissues.

20. A strategy for developing more selective hormonal therapies

In recent years, compounds like tamoxifen and raloxifen, which antagonize the actions of estradiol on the mammary gland, have been shown to retain some actions of estrogens in other organs or tissues, like the increase in mineral bone density. These observations have generated great interest in developing other selective estrogen receptor modulators (SERMs) (McDonnell, 1999; Smith and O'Malley, 1999).

Here we propose a different strategy for developing more selective hormonal therapies. Administrations of hormones that increase the hormone plasma concentrations above normal values produce both beneficial and adverse effects. To prevent the adverse effects, it is important to understand the mechanisms involved in the beneficial as well as in the adverse effects. As discussed above, the administration of a hormone may produce three types of effects: (1) Effects from increased concentrations and actions of the administered hormone. (2) Effects from increased concentrations and actions of metahormones derived from the administered hormone. (3) Effects from decreased production and actions of other hormones. One may infer the type of each effect, by studying, in addition to the effects of administrations of the hormone, *the composition and actions of the various multisignal messages of which the hormone is a part*. With this knowledge, hormonal therapies might be improved greatly.

A therapeutic effect of the hormone itself could be produced selectively by reproducing the multisignal message that elicits only that effect. If the therapeutic effect attributable to a novel metahormone, it may lead to its isolation, identification, synthesis, and therapeutic use. Administration of the metahormone is likely to produce fewer adverse effects than administration of the corresponding protohormone. Identification and reproduction of the multisignal message that selectively produces the therapeutic effect of the novel metahormone would reduce adverse effects even further. A therapeutic effect produced by the suppression of another hormone can be achieved, probably with fewer adverse effects, using hormone antibodies or selective hormone antagonists. Adverse effects produced by the suppression of hormones can be decreased or prevented by the concomitant administration of the suppressed hormones.

21. Concluding remarks

In this paper we advance the theory that each hormone has several functions that are performed in various ways: (1) Micropulses elicited steadily at high frequencies produce small basal actions serving the diverse functions of the hormone. (2) Larger pulses, elicited at variable intervals, are postulated to be part of multisignal messages that produce selectively actions serving a single physiological function. Different pulses of the hormone may be part of diverse multisignal messages that elicit different responses, serving different physiological functions. (3) In addition, a

hormone may serve as precursor in the biosynthesis of many multifunctional hormones, and may therefore have many different permissive roles.

Functions of hormones may be uncovered using both experimental and observational studies, and identifying the composition and actions of the diverse multisignalr messages of which the hormone is a part. Studies of the pharmacological actions of a hormone, identification of its biotransformation products and their actions, may lead to uncovering novel metahormones. Knowledge gained by all such studies will enhance our understanding of endocrine physiology and will lead to improvements in the use of hormones in Medicine.

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References

- Ackerman, G.E., MacDonald, P.C., Gudelsky, G., Mendelson, C.R., Simpson, E.R., 1981. Potentiation of epinephrine-induced lipolysis by catechol estrogens and their methoxy derivatives. *Endocrinology* 109, 2084–2088.
- Andreis, P.G., Neri, G., Belloni, A.S., Mazzocchi, G., Kasprzak, A., Nussdorfer, G.G., 1991a. Interleukin-1 beta enhances corticosterone secretion by acting directly on the rat adrenal gland. *Endocrinology* 129, 53–57.
- Andreis, P.G., Neri, G., Nussdorfer, G.G., 1991b. Corticotropin-releasing hormone (CRH) directly stimulates corticosterone secretion by the rat adrenal gland. *Endocrinology* 128, 1198–1200.
- Andreis, P.G., Neri, G., Mazzocchi, G., Musajo, F., Nussdorfer, G.G., 1992. Direct secretagogue effect of corticotropin-releasing factor on the rat adrenal cortex: involvement of the zona medullaris. *Endocrinology* 131, 69–72.
- Asher, G.W., Peterson, A.J., Bass, J.J., 1989. Seasonal pattern of LH and testosterone secretion in adult male fallow deer, *Dama dama*. *J Reprod Fertil* 85, 657–665.
- Attanasio, A., Gupta, D., 1980. Simultaneous radioimmunoassay of estrogens and androgens in plasma of prepubertal children. In: Gupta, D. (Ed.), *Radioimmunoassay of Steroid Hormones*. Verlag Chemie, Weinheim, pp. 117–126.
- Axelrod, J., Reisine, T.D., 1984. Stress hormones: their interaction and regulation. *Science* 224, 451–459.
- Bäckström, C.T., McNeilly, A.S., Leask, R.M., Baird, D.T., 1982. Pulsatile secretion of LH, FSH, prolactin, oestradiol and progesterone during the human menstrual cycle. *Clin Endocrinol* 17, 29–42.
- Baird, D.T., Horton, R., Longcope, C., Tait, J.F., 1968. Steroid prehormones. *Perspect Biol Med* 11, 384–421.
- Baird, D.T., Uno, A., Melby, J.C., 1969. Adrenal secretion of androgens and oestrogens. *J Endocrinol* 45, 135–136.
- Berliner, D.L., Keller, N., Dougherty, T.F., 1961. Tissue retention of cortisol and metabolites induced by ACTH: an extra-adrenal effect. *Endocrinology* 68, 621–632.
- Besser, G.M., Orth, D.N., Nicholson, W.E., Byyny, R.L., Abe, K., Woodham, J.P., 1971. Dissociation of the disappearances of bioactive and radioimmunoreactive ACTH from plasma in man. *J Clin Endocrinol Metab* 32, 595–603.
- Bloom, S.R., Edwards, A.V., Jones, C.T., 1987. Adrenal cortical responses to vasoactive intestinal peptide in conscious hypophysectomized calves. *J. Physiol.* 391, 441–450.
- Bockaert, J., Pin, J.P., 1999. Molecular tinkering of G protein-coupled receptors: An evolutionary success. *EMBO J.* 18, 1723–1729.

- Bornstein, S.R., Uhlmann, K., Haidan, A., Ehrhart-Bornstein, M., Scherbaum, W.A., 1997. Evidence for a novel peripheral action of leptin as a metabolic signal to the adrenal gland: Leptin inhibits cortisol release directly. *Diabetes* 46, 1235–1238.
- Bousquet-Mélou, A., Galitzky, J., Lafontan, M., Berlan, M., 1995. Control of lipolysis in intra-abdominal fat cells of nonhuman primates: comparison with humans. *J Lipid Res* 36, 451–461.
- Boyle, L.L., Brownfield, M.S., Lent, S.J., Goodman, B., Hill, H.Vo., Litwin, J., Carnes, M., 1997. Intensive venous sampling of adrenocorticotrophic hormone in rats with sham or paraventricular nucleus lesion. *J Endocrinol* 153, 159–167.
- Brabant, G., Prank, K., Schöfl, C., 1992. Pulsatile patterns in hormone secretion. *Trends Endocrinol Metab* 3, 183–190.
- Buckingham, J.C., Smith, T., Loxley, H.D., 1992. The control of ACTH secretion. In: James, V.H.T. (Ed.), *The Adrenal Gland*. Raven Press, New York, pp. 131–158.
- Burns, T.W., Langley, P.E., Terry, B.E., Bylund, D.E., Hoffman, B.B., Tharp, M.D., Lefkowitz, R.J., García-Sáinz, J.A., Fain, J.N., 1881. Pharmacological characterizations of adrenergic receptors in human adipocytes. *J Clin Invest* 67, 467–475.
- Campbell, C.H., Watson, C.S., 2001. A comparison of membrane vs. intracellular estrogen receptor alpha in GH(3)/B6 pituitary tumor cells using a quantitative plate immunoassay. *Steroids* 66, 727–736.
- Carmichael, R., Belanger, A., 1984. Study of the direct effect of LHRH agonist on testicular 17-hydroxylase and 5 α -reductase activities in non-hypophysectomized adult rats treated with an anti-luteinizing hormone serum. *Steroids* 43, 1–12.
- Carnes, M., Kalin, N.H., Lent, S.J., Barksdale, C.M., Brownfield, M.S., 1988. Pulsatile ACTH secretion: variation with time of day and relationship to cortisol. *Peptides* 9, 325–331.
- Carnes, M., Brownfield, M.S., Lent, S.J., Nichols, K., Schuler, L., 1992. Pulsatile ACTH and cortisol in goats: effects of insulin-induced hypoglycemia and dexamethasone. *Neuroendocrinology* 55, 97–104.
- Carnes, M., Goodman, B.M., Lent, S.J., Vo, H., 1993. High intensity venous sampling reveals subtle alterations in plasma adrenocorticotropin patterns in old rats. *Endocrinology* 133, 608–616.
- Cartier, F., Do-Rego, J.L., Remy-Jouet, I., Fournier, A., Vaudry, H., DeLarue, C., 2001. Evidence for the involvement of nitric oxide in the control of steroid secretion by the frog adrenal gland. *J Steroid Biochem Mol Biol* 77, 251–259.
- Charlton, B.G., 1990. Adrenal cortical innervation and glucocorticoid secretion. *J Endocrinol* 126, 5–8.
- Chen, F., Watson, C.S., Gametchu, B., 1999a. Association of the glucocorticoid receptor alternatively spliced transcript 1A with the presence of the high molecular weight membrane glucocorticoid receptor in mouse lymphoma cells. *J Cell Biochem* 74, 430–446.
- Chen, F., Watson, C.S., Gametchu, B., 1999b. Multiple glucocorticoid receptor transcripts in membrane glucocorticoid receptor-enriched S-49 mouse lymphoma cells. *J Cell Biochem* 74, 418–429.
- Clarke, C.H., Norfleet, A.M., Clarke, M.S., Watson, C.S., Cunningham, K.A., Thomas, M.L., 2000. Perimembrane localization of the estrogen receptor alpha protein in neuronal processes of cultured hippocampal neurons. *Neuroendocrinology* 71, 34–42.
- Clynes, M., 1962. The non-linear biological dynamics of unidirectional rate sensitivity illustrated by analog computer analysis, pupillary reflex to light and sound, and heart rate behavior. *Ann NY Acad Sci* 98, 806–845.
- Cooney, A.J., Lee, C.T., Lin, S.-C., Tsai, S.Y., Tsai, M.-J., 2001. Physiological function of the orphans GCNF and COUP-TF. *Trends Endocrinol Metab* 12, 247–251.
- Crum, R., Szabo, S., Folkman, J., 1985. A new class of steroids inhibits angiogenesis in the presence of heparin or a heparin fragment. *Science* 230, 1375–1378.
- Dallman, M.F., Yates, F.E., 1969. Dynamic asymmetries in the corticosteroid feedback path and distribution-metabolism-binding elements of the adrenocortical system. *Ann NY Acad Sci* 156, 696–721.
- de Moor, P., Hendrikx, A., Hinnekens, M., 1961. Extra-adrenal influence of corticotropin (ACTH) on cortisol metabolism. *J Clinl Endocrinol Metab* 21, 106–109.
- Dempsher, D.P., Gann, D.S., 1983. Increased cortisol secretion after small hemorrhage is not attributable to changes in adrenocorticotropin. *Endocrinology* 113, 86–93.
- de Wied, D., Jolles, J., 1982. Neuropeptides derived from pro-opiocortin: behavioral, physiological, and neurochemical effects. *Physio. Rev* 62, 976–1059.

- Diba, F., Watson, C.S., Gametchu, B., 2001. 5'UTR sequences of the glucocorticoid receptor 1A transcript encode a peptide associated with translational regulation of the glucocorticoid receptor. *J Cell Biochem* 81, 149–161.
- Doell, R.G., Dallman, M.F., Clayton, R.B., Gray, G.D., Levine, S., 1981. Dissociation of adrenal corticosteroid production from ACTH in water-restricted female rats. *Am J Physiol* 241, R21–R24.
- Dougherty, T.F., Berliner, D.L., 1958. The effect of stress and ACTH on the metabolism of hydrocortisone in the liver. In: *Symposium on Liver Function* ed. American Institute of Biological Sciences, Washington, D.C, pp. 416–417.
- Edwards, A.V., Jones, C.T., 1987. The effect of splanchnic nerve stimulation on adrenocortical activity in conscious calves. *J Physiol* 382, 385–396.
- Ehrhart-Bornstein, M., Hinson, J.P., Bornstein, S.R., Scherbaum, W.A., Vinson, G.P., 1998. Intraadrenal interactions in the regulation of adrenocortical steroidogenesis. *Endocr Rev* 19, 101–143.
- Engeland, W.C., Gann, D.S., 1989. Splanchnic nerve stimulation modulates steroid secretion in hypophysectomized dogs. *Neuroendocrinology* 50, 124–131.
- Engeland, W.C., Miller, P., Gann, D.S., 1989. Dissociation between changes in plasma bioactive and immunoreactive adrenocorticotropin after hemorrhage in awake dogs. *Endocrinology* 124, 2978–2985.
- Enmark, E., Gustafsson, J.A., 1996. Orphan nuclear receptor—the first eight years. *Mol Endocrinol* 10, 1293–1307.
- Evans, M.J., Mulligan, R.S., Livesey, J.H., Donald, R.A., 1996. The integrative control of adrenocorticotrophin secretion: a critical role for corticotrophin-releasing hormone. *J Endocrinol* 148, 475–483.
- Fain, J.N., García-Sáinz, J.A., 1980. Role of phosphatidylinositol turnover in α_1 and adenylate cyclase inhibition in α_2 effects of catecholamines. *Life Sci* 26, 1183–1194.
- Fain, J.N., García-Sáinz, J.A., 1983. Adrenergic regulation of adipocyte metabolism. *J Lipid Res* 24, 945–966.
- Fehm, H.L., Voigt, K.H., Lang, R., Özyol, M.B., Pfeiffer, E.F., 1973. Influence of plasma on ACTH stimulated corticosterone production of isolated adrenal cells. *FEBS Lett* 36, 109–112.
- Fehm, H.L., Holl, R., Klein, E., Voigt, K.H., 1983. The meal-related peak in plasma cortisol is not mediated by radioimmunoassayable ACTH. *Clin Physiol Biochem* 1, 329–333.
- Fehm, H.L., Klein, E., Holl, R., Voigt, K.H., 1984. Evidence for extrapituitary mechanisms mediating the morning peak of plasma cortisol in man. *J Clin Endocrinol Metab* 58, 410–414.
- Fotsis, T., Zhang, Y., Pepper, M.S., Adlercreutz, H., Montesano, R., Nawroth, P.P., Schwelgerer, L., 1994. The endogenous oestrogen metabolite 2-methoxyoestradiol inhibits angiogenesis and suppresses tumour growth. *Nature* 368, 237–239.
- Frantz, A.G., 1979. Rhythms in prolactin secretion. In: *Krieger, D.T. (Ed.), Endocrine Rhythms*. Raven Press, New York, pp. 175–186.
- Fuxe, K., Agnati, L.F., Zoli, M., Biagini, G., Cintra, A., Eneroth, P., 1991. Regulatory peptides in the neuroendocrine system: aspects of the communicational and computational processes in peptidergic neurons and their steroidal regulation. In: *Motta, M. (Ed.), Brain Endocrinology*. Raven Press, New York, pp. 31–69.
- Gagliardino, J.J., Borelli, M.I., Boschero, A.C., Rojas, E., Atwater, I., 1995. Modulatory mechanisms of ACTH on insulin secretion: effect on cytosolic Ca^{2+} membrane potential and Ca^{2+} -atpase activity. *Arch Physiol Biochem* 103, 73–78.
- Gaillard, R.C., Grossman, A., Gillies, G., Rees, L.H., Besser, G.M., 1981. Angiotensin II stimulates the release of ACTH from dispersed rat anterior pituitary cells. *Clin Endocrinol* 15, 573–578.
- Gallagher, T.F., Yoshida, K., Roffwarg, H.D., Fukushima, D.K., Weitzman, E.D., Hellman, L., 1973. ACTH and cortisol secretory patterns in man. *J Clin Endocrinol Metab* 36, 1058–1068.
- Gametchu, B., Watson, C.S., Pasko, D., 1991a. Size and steroid-binding characterization of membrane-associated glucocorticoid receptor in S-49 lymphoma cells. *Steroids* 56, 402–410.
- Gametchu, B., Watson, C.S., Shih, C.C., Dashew, B., 1991b. Studies on the arrangement of glucocorticoid receptors in the plasma membrane of S-49 lymphoma cells. *Steroids* 56, 411–419.
- Gametchu, B., Watson, C.S., Wu, S., 1993. Use of receptor antibodies to demonstrate membrane glucocorticoid receptors in cells from human leukemic patients. *FASEB J* 7, 1283–1292.
- Gametchu, B., Chen, F., Sackey, F., Powell, C., Watson, C.S., 1999. Plasma membrane-resident glucocorticoid receptors in rodent lymphoma and human leukemia models. *Steroids* 64, 107–119.
- García-Sáinz, J.A., Fain, J.N., 1982. Regulation of adipose tissue metabolism by catecholamines: Roles of α_1 , α_2 , and beta-adrenoceptors. *Trends Pharmacol Sci.* 3, 201–203.

- García-Sáinz, J.A., Hoffman, B.B., Li, S.-Y., Lefkowitz, R.J., Fain, J.N., 1980. Role of α_1 adrenoceptors in the turnover of phosphatidylinositol and of α_2 adrenoceptors in the regulation of cyclic AMP accumulation in hamster adipocytes. *Life Sci.* 27, 953–961.
- García-Sáinz, J.A., Vázquez-Prado, J., Medina, L.d.C., 2000. α_1 -adrenoceptors: function and phosphorylation. *Europ J Pharmacol* 389, 1–12.
- Giordano, N.D., Sayers, G., 1971. Isolated adrenal cells: assay of ACTH in rat serum. *Proc Soc Exper Biol Med* 136, 623–626.
- Glass, A.R., 2001. Gynecomastia. In: Becker, K.L. (Ed.), *Principles and Practice of Endocrinology and Metabolism*. Lippincott Williams & Wilkins, Philadelphia, pp. 1200–1206.
- Goldberg, S.L., Kessler, C.M., 1995. Hematologic Endocrinology. In: Becker, K.L. (Ed.), *Principles and Practice of Endocrinology and Metabolism*. Lippincott, Philadelphia, pp. 1776–1784.
- Greenspan, S.L., Klibanski, A., Schoenfeld, D., Ridgway, E.C., 1986. Pulsatile secretion of thyrotropin in man. *J Clin Endocrinol Metab* 63, 661–668.
- Gudmundsson, A., Carnes, M., 1997. Pulsatile adrenocorticotrophic hormone: An overview. *Biol Psychiatry* 41, 342–365.
- Gums, J.G., Smith, J.D., 1999. Adrenal gland disorders. In: DiPiro, J.Y., Talbert, R.L., Yee, G.C., Matzke, G.R., Wells, B.G., Posey, L.M. (Eds.), *Pharmacotherapy*. Appleton & Lange, Stanford, Connecticut, pp. 1265–1280.
- Gwosdow, A.R., 1995. Mechanisms of interleukin-1 induced hormone secretion from the rat adrenal gland. *Endocrine Res* 21, 25–37.
- Hadley, A.J., Rantle, C.M., Buckingham, J.C., 1997. Thymulin stimulates corticotrophin release and cyclic nucleotide formation in the rat anterior pituitary gland. *Neuroimmunomodulation* 4, 62–69.
- Hafezi-Moghadam, A., Simoncini, T., Yang, E., Limbourg, F.P., Plumier, J.C., Rebsamen, M.C., Hsich, C.M., Chui, D.S., Thomas, K.L., Prorocj, A.J., Laubach, V.E., Moskowitz, M.A., French, B.A., Ley, K., Lian, J.K., 2002. Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase. *Nat Med* 8, 453–455.
- Heinlein, C.A., Chang, C., 2002. Androgen receptor (AR) coregulators: an overview. *Endocr Rev* 23, 175–200.
- Hinson, J.P., 1990. Paracrine control of adrenocortical function: a new role for the medulla? *J Endocrinol* 124, 7–9.
- Hinson, J.P., Vinson, G.P., Whitehouse, B.J., 1986. The relationship between perfusion medium flow rate and steroid secretion in the isolated perfused rat adrenal gland in situ. *J Endocrinol* 11, 391–396.
- Hodgkin, A.L., Huxley, A.F., 1952. The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*. *J Physiol* 116, 497–506.
- Holl, R.W., Hartman, M.L., Veldhuis, J.D., Taylor, W.M., Thorner, M.O., 1991. Thirty-second sampling of plasma growth hormone in man: correlation with sleep stages. *J Clin Endocrinol Metab* 72, 854–861.
- Horton, R., 1995. Testicular steroid transport, metabolism and effects. In: Becker, K.L. (Ed.), *Principles and Practice of Endocrinology and Metabolism*. Lippincott, Philadelphia, pp. 1042–1047.
- Horwitz, K.H., Jackson, T.A., Bain, D.L., Richer, J.K., Takimoto, G.S., Tung, L., 1996. Nuclear receptor coactivators and corepressors. *Mol Endocrinol* 10, 1167–1177.
- Houk, J.C., 1988. Control strategies in physiological systems. *FASEB J* 2, 97–107.
- Ingle, D.J., 1954. Permissive actions of hormones. *Acta Endocrinol (Copenh)* 17, 1272–1274.
- Jenster, G., Spencer, T., Burcin, M., Tsai, S.-Y., Tsai, M.-J., O'Malley, B.W., 1997. Steroid receptor induction of gene transcription—a two step model. *Proc Natl Acad Sci USA* 94, 7879–7884.
- Judd, A.M., MacLeod, R.M., 1992. Adrenocorticotropin increases interleukin-6 release from rat adrenal zona glomerulosa cells. *Endocrinology* 130, 1245–1254.
- Judd, H.L., 1979. Biorhythms of gonadotropins and testicular hormone secretion. In: Krieger, D.T. (Ed.), *Endocrine Rhythms*. Raven Press, New York, pp. 299–324.
- Judd, H.L., Parker, D.C., Rakoff, J.S., Hopper, B.R., Yen, S.S., 1974. Elucidation of mechanism(s) of nocturnal rise of testosterone in men. *J Clin Endocrinol Metab* 38, 134–141.
- Krieger, D.T., 1979. Rhythms in CRF, ACTH, and corticosteroids. In: Krieger, D.T. (Ed.), *Endocrine Rhythms*. Raven Press, New York, pp. 123–142.
- Krieger, D.T., Allen, W., 1975. Relationship of bioassayable and immunoassayable plasma ACTH and cortisol concentrations in normal subjects and in patients with Cushing's disease. *J Clin Endocrinol Metab* 40, 675–687.

- Krishnan, K.R.R., Ritchie, J.C., Manepalli, A.N., Venkataraman, S., France, R.D., Nemeroff, C.B., Carroll, B.J., 1988. What is the relationship between plasma ACTH and plasma cortisol in normal humans and depressed patients? In: Schatzberg, A.F., Nemeroff, C.B. (Eds.), *The Hypothalamic-Pituitary-Adrenal Axis. Physiology, Pathophysiology, and Psychiatric Implications*. Raven Press, New York, pp. 115–131.
- Kusama, M., Abe, O., Sakauchi, N., Takatani, O., Mayama, T., Demura, R., Kumaoka, S., 1970. Extra-adrenal action of adrenocorticotropin on cortisol metabolism. *J Clin Endocrinol Metab* 30, 778–784.
- Lafontan, M., Berlan, M., 1995. Fat cell α_2 -adrenoceptors: the regulation of fat cell function and lipolysis. *Endocr Rev* 16, 716–738.
- L'Age, M., González-Luque, A., Yates, F.E., 1970. Adrenal blood flow dependence of cortisol secretion rate in unanesthetized dogs. *Am J Physiol* 219, 281–287.
- Lala, D.S., Heyman, R.A., 2000. Orphan nuclear receptors. In: Conn, P.M., Means, A.R. (Eds.), *Principles of Molecular Regulation*. Humana Press, Totowa, New Jersey, pp. 363–384.
- Lebovitz, H.E., Bryant, K., Frohman, L.A., 1965. Acute effects of corticotropin and related peptides on carbohydrate and lipid metabolism. *Ann NY Acad Sci* 131, 274–287.
- Lemon, B., Tjian, R., 2000. Orchestrated response: a symphony of transcription factors for gene control. *Gen Dev* 14, 2551–2569.
- Licinio, J., Wong, M.L., Altemus, M., Bongiorno, P.B., Bernat, A., Brabant, G., Tamarkin, L., Gold, P.W., 1994. Pulsatility of 24-h concentrations of circulating interleukin-1-alpha in healthy women: analysis of integrated basal levels, discrete pulse properties, and correlation with simultaneous interleukin-2 concentrations. *Neuroimmunomodulation* 1, 242–250.
- Linkowski, P.L., Mendlewicz, J., Leclercq, R., Brasseur, M., Hubain, P., Golstein, J., Copinschi, G., van Cauter, E., 1985. The 24-h profile of adrenocorticotropin and cortisol in major depressive illness. *J Clin Endocrinol Metab* 61, 429–438.
- Liptrap, R.M., Doble, E., Cheng, K.W., 1986. Plasma concentration profiles of gonadotrophins and testosterone in the adult boar. *Can J Vet Res* 50, 427–432.
- Longcope, C., Kato, T., Horton, R., 1969. Conversion of blood androgens to estrogens in normal adult men and women. *J Clin Invest* 48, 2191–2201.
- Lou, H., Gagel, R.F., 2001. Alternative ribonucleic acid processing in endocrine systems. *Endocr Rev* 22, 205–225.
- Lowry, P.J., 1984. Pro-opiomelanocortin: the multiple adrenal hormone precursor. *Bioscience Rep* 4, 467–482.
- Martinez de la Escalera, G., Weiner, R.I., 1992. Dissociation of dopamine from its receptor as a signal in the pleiotropic hypothalamic regulation of prolactin secretion. *Endocr Rev* 13, 241–255.
- Matsumoto, A.M., 2001. Clinical use and abuse of androgens and antiandrogens. In: Becker, K.L. (Ed.), *Principles and Practice of Endocrinology and Metabolism*. Lippincott Williams & Wilkins, Philadelphia, pp. 1181–1200.
- Mazzocchi, G., Rebuffat, P., Gottardo, G., Malendowicz, L.K., Nussdorfer, G., 1998a. Galanin stimulates glucocorticoid secretion in rats through a receptor-dependent activation of the adenylate cyclase/protein kinase A-dependent signaling pathway. *Peptides* 19, 891–895.
- Mazzocchi, G., Rebuffat, P., Gottardo, L., Nussdorfer, G.G., 1998b. Vasoactive intestinal peptide stimulates rat adrenal glucocorticoid secretion, through an ACTH receptor-dependent activation of the adenylate cyclase signaling pathway. *Horm Metab Res* 30, 241–243.
- McDonnell, D.P., 1999. The molecular pharmacology of SERMs. *Trends Endocrinol Metab* 10, 301–311.
- McDonnell, D.P., 2000. The mechanism of action of steroid hormone receptors. In: Conn, P.M., Means, A.R. (Eds.), *Principles of Molecular Regulation*. Humana Press, Totowa, New Jersey, pp. 351–361.
- McKenna, N.J., Nawaz, Z., Tsai, S.Y., Tsai, M.-J., O'Malley, B.W., 1998. Distinct steady state nuclear hormone receptor complexes exist in vivo. *Proc Natl Acad Sci USA* 95, 11697–11702.
- McKenna, N.J., Lanz, R.B., O'Malley, B.W., 1999. Nuclear receptor coregulators: cellular and molecular biology. *Endocr Rev* 20, 321–344.
- McKenna, N.J., Nawaz, Z., Tsai, S.Y., Tsai, M.-J., 2000. Coactivators and corepressors. In: Conn, P.M., Means, A.R. (Eds.), *Principles of Molecular Regulation*. Humana Press, Totowa, New Jersey, pp. 385–394.
- Mellon, S.H., Griffin, L.D., 2002. Neurosteroids: biochemistry and clinical significance. *Trends Endocrinol Metab* 13, 35–43.

- Monfort, S.L., Brown, J.L., Wood, T.C., Wemmer, C., Vargas, A., Williamson, L.R., Wildt, D.E., 1993. Seasonal patterns of basal and GnRH-induced LH, FSH and testosterone secretion in Eld's deer stags (*Cervus eldi thamin*). *J Reprod Fertil* 98, 481–488.
- Morimoto, C., Tsujita, T., Okuda, H., 1998. Antilipolytic actions of insulin on basal and hormone-induced lipolysis in rat adipocytes. *J Lipid Res* 39, 957–962.
- Morita, Y., Shimizu, K., Obata, T., 1984. Potentiating activity of rat serum extract on ACTH-induced corticosteroidogenesis in isolated rat adrenal cells. *Endocrinol Jpn* 31, 217–225.
- Munck, A., Guyre, P.M., Holbrook, N.J., 1984. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev* 5, 25–44.
- Munck, A., Náray-Fejes-Tóth, A., 1992. The ups and downs of glucocorticoid physiology. Permissive and suppressive effects revisited. *Mol Cell Endocrinol* 90, C1–C4.
- Munck, A., Náray-Fejes-Tóth, A., 1994. Glucocorticoids and stress: permissive and suppressive actions. *Ann NY Acad Sci* 746, 115–130.
- Neri, G., Andreis, P.G., Nussdorfer, G.G., 1991. Comparison of ACTH and corticotropin-releasing hormone effects on rat adrenal steroidogenesis in vitro. *Endocrinology* 129, 53–57.
- Norfleet, A.M., Thomas, M.L., Gametchu, B., Watson, C.S., 1999. Estrogen receptor-alpha detected on the plasma membrane of aldehyde-fixed GH3/B6/F10 rat pituitary tumor cells by enzyme-linked immunocytochemistry. *Endocrinology* 140, 3805–3814.
- Norfleet, A.M., Clarke, C.H., Gametchu, B., Watson, C.S., 2000. Antibodies to the estrogen receptor-alpha modulate rapid prolactin release from rat pituitary tumor cells through plasma membrane estrogen receptors. *FASEB J* 14, 157–165.
- O'Connell, N.A., Kumar, A., Chatzipanteli, K., Mohan, A., Agarwal, R.K., Head, C., Bornstein, S.R., Abou-Samra, A.B., Gwosdow, A.R., 1994. Interleukin-1 regulates corticosterone secretion from the rat adrenal gland through a catecholamine-dependent and prostaglandin E₂-independent mechanism. *Endocrinology* 135, 460–467.
- O'Malley, B.W., Conneely, O.M., 1992. Orphan receptors: In search of a unifying hypothesis for activation. *Mol Endocrinol* 6, 1359–1361.
- Ookhtens, M., Marsh, D.J., Smith, S.W., Bergman, R.N., Yates, F.E., 1974. Fluctuations of plasma glucose and insulin in conscious dogs receiving glucose infusions. *Am J Physiol* 226, 910–919.
- Pappas, T.C., Gametchu, B., Watson, C.S., 1995. Membrane estrogen receptors identified by multiple antibody labeling and impeded-ligand binding. *FASEB J* 9, 404–410.
- Parker, L.N., Odell, W.D., 1980. Control of adrenal androgen secretion. *Endocr Rev* 1, 392–410.
- Plotsky, P.M., Cunningham Jr., E.T., Widmaier, E.P., 1989. Catecholaminergic modulation of corticotropin-releasing factor and adrenocorticotropin secretion. *Endocr Rev* 10, 437–458.
- Powell, C.E., Watson, C.S., Gametchu, B., 1999. Immunoaffinity isolation of native membrane glucocorticoid receptor from S 49⁺ lymphoma cells: biochemical characterization and interaction with Hsp 70 and Hsp 90. *Endocrine* 10, 271–280.
- Power, R.F., Lydon, J.P., Conneely, O.M., O'Malley, B.W., 1991a. Dopamine activation of an orphan of the steroid receptor superfamily. *Science* 252, 1546–1548.
- Power, R.F., Mani, S.K., Codina, J., Conneely, O.M., O'Malley, B.W., 1991b. Dopaminergic and ligand-independent activation of the steroid hormone receptors. *Science* 254, 1636–1639.
- Rebar, R.W., Yen, S.S.C., 1979. Endocrine rhythms in gonadotropins and ovarian steroids with reference to reproductive processes. In: Krieger, D.T. (Ed.), *Endocrine Rhythms*. Raven Press, New York, pp. 259–298.
- Reed, H.L., 2001. Thyroid physiology: synthesis and release, iodine metabolism, binding and transport. In: Becker, K.L. (Ed.), *Principles and Practice of Endocrinology and Metabolism*. Lippincott Williams & Wilkins, Philadelphia, pp. 314–321.
- Robel, P., Akwa, Y., Corpéchet, C., Hu, Z.-Y., Jung-Testas, I., Kabbadj, K., Le Goascogne, C., Morfin, R., Vourc'h, C., Young, J., Baulieu, E.-E., 1991. Neurosteroids: biosynthesis and function of pregnenolone and dehydroepiandrosterone in the brain. In: Motta, M. (Ed.), *Brain Endocrinology*. Raven Press, New York, pp. 105–132.
- Sackey, F.N., Watson, C.S., Gametchu, B., 1997. Cell cycle regulation of membrane glucocorticoid receptor in CRCEM human ALL cells: correlation to apoptosis. *Am J Physiol* 273, E571–E583.

- Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev* 21, 55–89.
- Sayers, G., Swallow, R.L., Giordano, N.D., 1971. An improved technique for the preparation of isolated rat adrenal cells. *Endocrinology* 88, 1063–1068.
- Scow, R.O., Sticker, F.A., Pick, T.Y., Clary, T.R., 1965. Effect of ACTH on FFA release and diglyceride content in perfused rat adipose tissue. *Ann NY Acad Sci* 131, 288–301.
- Seif, S.M., Robinson, A.G., 1979. Rhythms of the posterior pituitary. In: Krieger, D.T. (Ed.), *Endocrine Rhythms*. Raven Press, New York, pp. 187–201.
- Sherman, B.M., Schlechte, J.A., Pfohl, B.M., 1984. Dissociation of plasma cortisol and ACTH responses to dexamethasone in healthy subjects. *Horm Res* 20, 157–165.
- Shipston, M.J., Antoni, F.A., 1992. Inactivation of early glucocorticoid feedback by corticotropin-releasing factor in vitro. *Endocrinology* 130, 2213–2218.
- Simpson, E.R., Bulun, S.E., Nichols, J.E., Zhao, Y., 1996. Estrogen biosynthesis in adipose tissue: regulation by paracrine and autocrine mechanisms. *J Endocrinol* 150 (Suppl.), S51–S57.
- Slater, C.C., Chang, L., Stanczyk, F.Z., Paulson, R.L., 2001. Altered balance between the 5 alpha-reductase and aromatase pathways of androgen metabolism during controlled ovarian hyperstimulation with human menopausal gonadotropins. *J. Assist Reprod Genet* 18, 527–533.
- Smith, C.L., O'Malley, B.W., 1999. Evolving concepts of selective estrogen receptor action: from basic science to clinical applications. *Trends Endocrinol Metab* 10, 299–300.
- Thomas, M.L., Xu, X., Norfleet, A.M., Watson, C.S., 1993. The presence of functional estrogen receptors in intestinal epithelial cells. *Endocrinology* 132, 426–430.
- Thompson, E.B., 2002. Editorial: the impact of genomics and proteomics on endocrinology. *Endocr Rev* 23, 366–368.
- Torpy, D.J., Jackson, R.V., 2001. Adrenocorticotropin: physiology and clinical aspects. In: Becker, K.L. (Ed.), *Principles and Practice of Endocrinology and Metabolism*. Lippincott Williams & Wilkins, Philadelphia, pp. 153–159.
- Ur, E., Grossman, A., 1994. The neuroregulation of corticotropin secretion. In: Imura, H. (Ed.), *The Pituitary Gland*. Raven Press, New York, pp. 309–330.
- Urquhart, J., 1965. Adrenal blood flow and the adrenocortical response to corticotropin. *Am J Physiol* 209, 1162–1168.
- Urquhart, J., 1969. Dynamic testing and modeling of adrenocortical secretory function. *Ann NY Acad Sci* 156, 756–778.
- Urquhart, J., 1970. Fourteenth bowditch lecture. Blood-borne signals. The measuring and modelling of humoral communication and control. *Physiologist* 13, 7–41.
- Urquhart, J., Li, C.C., 1968. The dynamics of adrenocortical secretion. *Am J Physiol* 214, 73–85.
- van Oers, J.W., Hinson, J.P., Binnekade, R., Tilders, F.J., 1992. Physiological role of corticotropin-releasing factor in the control of adrenocorticotropin-mediated corticosterone release from the rat adrenal gland. *Endocrinology* 130, 282–288.
- Vinson, G.P., Hinson, J.P., 1992. Blood flow and hormone secretion in the adrenal gland. In: James, V.H.T. (Ed.), *The Adrenal Gland*. Raven Press, New York, pp. 71–86.
- Waterman, M.R., Simpson, E.R., 1989. Regulation of steroid hydroxylase gene expression is multifactorial in nature. *Recent Prog Horm Res* 45, 533–566.
- Watson, C.S., Gametchu, B., 1999. Membrane-initiated steroid actions and the proteins that mediate them. *Proc Soc Exper Biol Med* 220, 9–19.
- Watson, C.S., Gametchu, B., 2001. Membrane estrogen and glucocorticoid receptors—implications for hormonal control of immune function and autoimmunity. *Internat. J Immunopharmacol* 1, 1049–1063.
- Watson, C.S., Pappas, T.C., Gametchu, B., 1995. The other estrogen receptor in the plasma membrane: implications for the actions of environmental estrogens. *Environ Health Perspect* 103 (Suppl.), 41–50.
- Watson, C.S., Campbell, C.H., Gametchu, B., 1999a. Membrane oestrogen receptors on rat pituitary immune cells: Immuno-identification and responses to oestradiol and xenoestrogens. *Exp Physiol* 84, 1013–1022.
- Watson, C.S., Norfleet, A.M., Pappas, T.C., Gametchu, B., 1999b. Rapid actions of estrogens to GH3/B6 pituitary cells via a plasma membrane version of estrogen receptor-alpha. *Steroids* 64, 5–13.

- Watson, C.S., Campbell, C.H., Gametchu, B., 2002. The dynamic and elusive membrane estrogen receptor-alpha. *Steroids* 67, 429–437.
- White, J.E., Engel, F.L., 1958. Lipolytic action of corticotropin on rat adipose tissue in vitro. *J Clin Invest* 37, 1556–1563.
- White, P.C., 2001. Synthesis and metabolism of corticosteroids. In: Becker, K.L. (Ed.), *Principles and Practice of Endocrinology and Metabolism*. Lippincott Williams & Wilkins, Philadelphia, pp. 704–714.
- Wilkinson, C.W., Shinsako, J., Dallman, M.F., 1982. Rapid decreases in adrenal and plasma corticosterone concentrations after drinking are not mediated by changes in plasma adrenocorticotropin concentration. *Endocrinology* 110, 1599–1606.
- Winkel, C.A., Milewich, L., Parker Jr., R., Gant, N.F., Simpson, E.R., MacDonald, P.C., 1980. Conversion of plasma progesterone to deoxycorticosterone in men, nonpregnant and pregnant women, and adrenalectomized subjects. Evidence for steroid hydroxylase activity in nonadrenal tissues. *J Clin Invest* 66, 803–812.
- Wood, C.E., Shinsako, J., Keil, L.C., Ramsay, D.J., Dallman, M.F., 1982. Apparent dissociation of adrenocorticotropin and corticosteroid responses to 15 ml/kg hemorrhage in conscious dogs. *Endocrinology* 110, 1416–1421.
- Wright, E.E., Simpson, E.R., 1981. Inhibition of the lipolytic action of beta-adrenergic agonists in human adipocytes by alpha-adrenergic agonists. *J Lipid Res* 22, 1265–1270.
- Wright, E.E., Simpson, E.R., 1982. Inhibition of adenylate cyclase activity in human fat cells by alpha-adrenergic agonists. *Horm Metab Res* 14, 475–479.
- Wu, F.C., Farley, T.M., Peregoudov, A., Waites, G.M., 1996. Effects of testosterone enanthate in normal men: world health organization task force on methods for the regulation of male fertility. *Fertil Steril* 65, 626–636.
- Yates, F.E., Maran, J.W., 1974. The physiology of the mammalian hypothalamo-adenohypophysial-adrenal glucocorticoid system — a new hypothesis. *Chronobiologia* 1 (Suppl. 1), 195–223.
- Yates, F.E., Poston, T., 1986. Rate-controlled delivery of endocrine agents: some paradoxical consequences of controlling the inputs. In: Struyker-Boudier, H.A.J. (Ed.), *Principles and Applications of Rate-Controlled Drug Administration and Action*. CRC Press, Boca Raton, pp. 247–272.
- Yates, F.E., Leeman, S.E., Glenister, D.W., Dallman, M.F., 1961. Interaction between plasma corticosterone concentration and adrenocorticotropin-releasing stimuli in the rat: evidence for the reset of an endocrine feedback control. *Endocrinology* 69, 67–80.
- Yates, F.E., Brennan, R.D., Urquhart, J., 1969. Application of control systems theory to physiology. Adrenal glucocorticoid control system. *Fed Proc* 28, 71–83.
- Zeng, Z., Allan, G.F., Thaller, C., Cooney, A.J., Tsai, S.Y., O'Malley, B.W., Tsai, M.J., 1994. Detection of potential ligands for nuclear receptors in cellular extracts. *Endocrinology* 135, 248–252.