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# GLUCOCORTICOID RECEPTORS

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**Summary**—Glucocorticoid hormones are secreted uniquely from the zona fasciculata of the adrenal cortex, with marked circadian variation in basal levels and acute elevation in response to stress Glucocorticoid receptors are almost ubiquitously distributed, and mediate a wide range of tissue-specific responses, in addition to classical, [$^3$H]dexamethasone-binding GR (Type II receptors) there is excellent evidence that Type I sites (MR) act as mineralocorticoid receptors in some tissues but high affinity glucocorticoid receptors in others Particular issues to be addressed in the presentation include (i) the extent to which glucocorticoid receptor occupancy is modulated by extracellular (plasma-binding enzymes) or intracellular (proto-oncogenes) factors, (ii) whether or not there are specific response elements for Type I and II receptors, (iii) putative physiological roles for Type I, high affinity glucocorticoid receptors, (iv) evidence for glucocorticoid receptors other than classical GR and "MR" In summary, glucocorticoid receptors appear to be a final common pathway mediating and/or modulating circadian rhythms and stress responses Cell- and tissue-specificity of response to a whole-body signal is determined by local pre-receptor, receptor and genomic differences On the basis of previous studies on glucocorticoid secretion, and recent information on glucocorticoid action, it would at last appear possible to begin to construct a coherent physiology for glucocorticoid hormones

Glucocorticoid receptors are a complex subject, with three clearly defined receptors and clear evidence for glucocorticoid actions via mechanisms distinct from these defined receptors It is possible in a review article such as this to list the properties of the known receptors and to describe "non-receptor" glucocorticoid effects, essentially *in vacuo* Such a presentation, however, runs the risk of being descriptive rather than analytic, and of being less likely to afford physiological insights than one in which the biology of signal as well as receptor is addressed More than half a century after the first description and isolation of glucocorticoid hormones we still lack a coherent physiology of their roles in development, metabolism and the response to stress Such a physiology will only come from consideration of both signals and receptors, and it is with this in mind that the present brief overview is written

The secretion of physiological glucocorticoids (cortisol in most species, corticosterone in rats and mice) from the zona fasciculata of the adrenal cortex is under the predominant control of ACTH secreted from the anterior pituitary gland The mechanism whereby rats and mice express 17-hydroxylase activity in the gonad but not in the adrenal cortex has yet to be established, the implications of secreting a less elaborated glucocorticoid are yet to be explored In this context it is worth remarking that a variety of glucocorticoid-binding proteins in the rat—Type I and II receptors, plasma corticosteroid-binding globulin, the metabolizing enzyme 11$\beta$OH steroid dehydrogenase (11-HSD)—show much lower affinity for cortisol than corticosterone, in contrast with the equivalent human binding species

Although ACTH is widely accepted as the predominant regulator of glucocorticoid secretion from the adrenal cortex, other factors (e g angiotensin, $\gamma$-MSH) have been shown to have effects These are often at concentrations higher than commonly seen *in vivo*, so that a physiological role in the modulation of cortisol levels by secretagogues other than ACTH remains to be established Similarly open to question are physiological roles for factors other than corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) as stimuli for pro-opiomelanocortin (POMC)synthesis and ACTH release, and for glucocorticoids as inhibitors A range of candidate factors—including catecholamines, NPY, ANP, angiotensin, interleukin 1 and nitric oxide—has been studied, and roles as

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*Address for correspondence Baker Medical Research Institute, P O Box 348, Prahran 3181, Victoria, Australia hypothalamic or paracrine modulators postulated, the relative importance of any influence they have on ACTH synthesis and secretion *in vivo*, and under what physiological circumstances, remains to be explored

What has been established is a clear species difference for CRF and AVP in terms of role as predominant ACTH secretagogue In the rat CRF increases POMC synthesis and ACTH secretion, whereas AVP appears not to alter transcription and acts primarily as a synergistic factor with CRF in terms of release, in the sheep exactly the opposite is the case [1] What has also been established is the extraordinary complexity of glucocorticoid feedback on POMC synthesis and ACTH release Sites of glucocorticoid action which have been demonstrated include the hippocampus, with high concentrations of both Type I and II glucocorticoid receptors, and recently defined relays to the hypothalamus [2], the hypothalamus, where synthesis and release of CRF and/or AVP is influenced by glucocorticoid levels [3], the median eminence, where glucocorticoid-regulated metabolism appears to regulate levels accessing the portal circulation [4], and the pituitary itself, where glucocorticoids negatively regulate both POMC gene transcription and ACTH release Equally complex appear to be the time dimensions over which this negative control is exerted, from seconds/minutes—presumably by non-genomic mechanisms—to many hours Given that essentially all cells appear to contain Type II glucocorticoid receptor, this complexity of glucocorticoid negative feedback control is likely to increase rather than decrease if other factors—particularly negative regulators—are established as having physiological roles in the control of ACTH secretion

What even the established complexity clearly admits is that ACTH secretion responds to two distinct, superimposable signals, those of circadian variation and stress Secretion of glucocorticoids is pulsatile, reflecting pulsatile secretion of ACTH, and in turn of CRF and AVP [5] Though the implications of such pulsatility are essentially unexplored in terms of metamessage, over a 24 h period glucocorticoids show a clearly circadian variation, reflecting ACTH secretion, with a nadir during sleep and a peak around the time of beginning activity, furthermore, the more carefully the study is done to avoid superimposed stress, the more different are peak and nadir values of circulating glucocorticoids, up to a 70- to 100-fold difference [6] Peak values for plasma glucocorticoids are commonly moderately rather than maximally elevated, and are also commonly transient, in contrast, glucocorticoid synthesis and release in response to stress may generate very high levels over a considerable time period

Just as glucocorticoids are secreted in two modes—circadian and in response to stress—they clearly interact with two classes of well-characterized members of the steroid/thyroid/retinoic acid/orphan receptor family of nuclear transactivating factors, the Type I (mineralocorticoid) and Type II (classical glucocorticoid) receptors Type I receptors have high ($K_d$ $\leqslant 1$ nM at 4°C) and equal affinity for aldosterone, deoxycorticosterone and corticosterone [7] The human mineralocorticoid receptor has been cloned from human kidney cDNA, and shows equivalent affinity for cortisol as for aldosterone, corticosterone and deoxycorticosterone [8] Its homologue in the rat has been cloned and sequenced from rat hippocampal cDNA, underlining the commonality of Type I receptors in diverse tissues in the body In the kidney it is aldosterone-selective, and thus able to act as a mineralocorticoid receptor, in the hippocampus it is clearly not aldosterone-selective, so that it is overwhelmingly occupied by the much higher circulating levels of glucocorticoids

The mechanism whereby the same receptor can respond to two different ligands in different tissues in the body appears to involve, at least in large part, the operating of the enzyme 11-HSD [9, 10] This enzyme, as its name implies, acts on C-11 hydroxylated steroids, such as cortisol and corticosterone, and converts them to receptor-inactive 11-keto analogues (cortisone and 11-dehydrocorticosterone) Aldosterone is not metabolized in a similar fashion, the unique, highly reactive aldehyde group at C-18 cyclizes with the C-11 hydroxyl in the aldosterone molecule to yield an 11,18 hemiketal, which is resistant to enzymatic attack High levels of enzyme activity have been found in the kidney and parotid, very modest levels in the colon, and very low levels in hippocampus, blockade of the enzyme by the administration of carbenoxolone [9] or glycyrrhetinic acid [10] is followed by a marked increase in glucocorticoid binding to these otherwise aldosterone-selective Type I receptors in physiological mineralocorticoid target tissues such as kidney, parotid and colon

There are, however, several caveats that should be clearly stated before too readily accepting the activity of 11-HSD as the unique determinant of Type I receptor selectivity, and of its activity as being uniquely such a selectivity-conferring mechanism. First, though to date only a single species of 11-HSD has been cloned—from rat liver [11], and by extension in the human [12]—there is cogent though indirect evidence for more than one enzyme responsible for such activity [13–15]. The hepatic species [11, 12] is expressed at high levels in liver, lung, testis and renal proximal tubule, none of which are currently considered physiological aldosterone target tissues, but is absent from renal cortical collecting tubules, parotid and colon. This species has thus been termed 11-HSD1, to distinguish it from the activity demonstrated in aldosterone target tissues (11-HSD2).

Given that 11-HSD1 appears to be expressed in what would normally be considered classical glucocorticoid target tissues, its role would appear to be to fractionate circulating glucocorticoid signal in different target tissues, so that depending on the extent of 11-HSD activity in a particular tissue it will be more or less responsive to a common level of circulating glucocorticoids. The best experimental evidence for this is currently in the testis, where the appearance of 11-HSD activity coincides with a marked increase in testicular androgen biosynthesis, known to be suppressed by glucocorticoids [16].

There are similarly open questions in terms of 11-HSD2. Though in kidney extracts there are multiple mRNA species [17], these are clearly variants of HSD1 recognized with an hepatic cDNA probe. Though there are yet no sequence data available for the activity termed 11-HSD2, it has been convincingly demonstrated cytochemically in rat [14] and more recently pig (Provencher *et al.*, unpublished) cortical collecting tubules. On the other hand, only very modest levels of 11-HSD activity have been demonstrated in colon, where there are very high levels of Type I receptors which are particularly aldosterone-selective *in vivo*. For this tissue, then, additional and/or alternate specificity-conferring mechanisms have been postulated [18]; similarly yet to be addressed are the mechanisms excluding progesterone and deoxycorticosterone, both of which are fully reduced at C-11, from Type I receptors in mineralocorticoid target tissues.

Type I receptors, which recognize aldosterone and the physiological glucocorticoids equivalently, will normally be occupied by glucocorticoids unless they are excluded. For Type II or classical glucocorticoid receptors such ambiguity at the receptor level does not appear to be an equivalent problem. Type II receptors appear essentially ubiquitous, are commonly labelled with $[^3H]$dexamethasone, and were the first members of the extended steroid receptor superfamily to be cloned and sequenced [19]. Type II receptors have a considerably lower affinity for corticosterone and cortisol than do Type I receptors, so that their occupancy profile over the range of physiological glucocorticoid concentrations is clearly different. On the other hand, the N-terminal region of the Type I receptor is only 5–10% as efficient in transcriptional terms as the equivalent domain in the Type II receptor, leading to the suggestion that in concert the two receptors may provide an extended dynamic range over which glucocorticoids can affect target cells.

For both Type I and II receptors our current models of mechanism of action are similar but not identical. One area in which the two receptors appear to differ are their localization in the absence of ligand; for Type I receptors the localization is predominantly nuclear, whereas Type II receptors appear to be both cytoplasmic and nuclear, though the extent of the partitioning is a matter of some debate. Secondly, Type II receptors have recently been shown to be profoundly altered—in terms of steroid binding, and thus of activation by binding to protooncogene products (c-*fos*, c-*jun*) in some but not all cell lines studied [20–22].

An area of current ambiguity is that of the identity or otherwise of the hormone response element (HRE) for Type I and II receptors. The nucleotide sequence involved is a palindromic pentadecamer (GAACAnnnTGTTC), which experimentally at least can serve as a response element for Type I (MRE), II (GRE), androgen and progestin receptors. A two nucleotide change (GGTCAnnnTGACC) turns the motif into a response element recognizing activated oestrogen and vitamin D receptors, and omission of the three linking indifferent nucleotides (GGTCATGACC) a thyroid and retinoic acid response element.

In physiological terms the data are conflicting. Arguing for a common MRE/GRE are studies on cultured cortical collecting tubules, in which $Na^+$ and $K^+$ fluxes between two chambers separated by a cultured cell monolayer are equivalently stimulated by aldosterone, dexamethasone and the "pure" glucocorticoid RU28362, which does not bind to Type I receptors [23] Against a necessarily shared response element are studies on hippocampal slices, where selective activation of Type I and II receptors has been shown to produce distinct effects on electrophysiological indices [24] Resolution of this conundrum will be assisted by the identification of genes which are aldosterone-responsive in physiological mineralocorticoid target tissues

Both Type I and II receptors are classical, intracellular, ligand-activated nuclear transcription factors Recently, membrane receptors for adrenal steroids have been identified in two distinct systems In very recent studies, human peripheral monocyte membranes have been shown to bind [$^{125}$I]aldosterone, with high affinity and specificity clearly distinct from that of the intracellular sites, notably a much lower affinity for glucocorticoids than for aldosterone [25] Previously, classical intracellular Type I receptors have been demonstrated in monocytes [26], and *in vitro* effects of aldosterone administration on monocyte $Na^+$ and $K^+$ flux documented [27], although some discrepancies were noted between receptor and effector studies In terms both of affinity and the profile of agonist and antagonist effects of various steroids, the recently described membrane binding sites for aldosterone may thus be more reasonably implicated in mediating effects on ion flux than the classical intracellular Type I sites

For glucocorticoids, a similar high affinity membrane receptor has been demonstrated in the nervous system of the amphibian *Ticarda* [28] These sites have nanomolar affinity for corticosterone, and for cortisol an order of magnitude less, for aldosterone and dexamethasone, and a series of "neurosteroids", their affinity is very much less, again clearly distinguishing them from classic intracellular receptors for adrenal steroids In *Ticarda* corticosterone administration to the male of the species is followed by a very rapid abrogation of mounting of females, and an excellent correlation has been demonstrated between relative affinity for the membrane bound corticosterone receptors and ability to inhibit mounting and the clasp reflex

In addition to these high affinity membrane-bound receptors, there is compelling but to date indirect evidence for physiological receptors with low affinity for corticosterone, in the adrenal medulla The first evidence for such a mechanism came from studies over 25 years ago [29], which showed that hypophysectomy was followed by a fall in adrenal phenylethanolamine *N*-methyl transferase (PNMT EC 2 1 1 28) activity, a fall which was restored by the administration of much higher than replacement doses of glucocorticoids [30] Subsequently, the PNMT gene has been cloned and shown to have a canonical GRE in the 5′ untranslated region, which responds to dexamethasone by a $\sim$10-fold increase in transcription, an increase abrogated when the GRE is mutagenized [31]

On the other hand, mechanisms in addition to this classical glucocorticoid regulation of gene expression are clearly operant in control of PNMT activity The much higher than replacement doses of corticosteroid required to restore PNMT activity post-hypophysectomy is evidence for this, more recently, this has been confirmed and extended by studies in which adrenal PNMT activity and levels of PNMT mRNA were measured in intact rats chronically treated for 1 week with a range of doses of dexamethasone or the highly selective Type II glucocorticoid RU28362 [32]

Under such conditions dexamethasone appears 3–5 times as potent as RU28362, as gauged by progressive decreases in thymus and adrenal weights with progressive increases in doses of administered steroid In parallel, both steroids produced a $\geqslant$10-fold increase in the levels of PNMT mRNA, consistent with the *in vitro* transfection studies previously cited When, however, PNMT activity in the contralateral adrenal was determined by the standard radioenzymatic assay, a clear distinction between the effects of dexamethasone and RU28362 was seen With RU28362, an initial fall in PNMT activity was seen over the dose range 1–30 $\mu$g/day with plateau levels at higher doses With dexamethasone a slightly steeper initial fall in activity to a nadir at 30 $\mu$g/day was followed by a progressive increase with higher doses, so that at 1 mg/day dexamethasone values identical to those seen in vehicle-treated control rats were seen

We interpret these findings as follows The initial fall in PNMT activity with both glucocorticoids reflects suppression of the hypothalamo–pituitary drive to the adrenal, as indicated by the fall of adrenal weight to plateau levels with 100 $\mu$g–1 mg of either steroid Under such circumstances endogenous secretion of corticosterone, upon which PNMT activity normally depends, falls progressively, this fall in corticosterone is thus measured in a fall in PNMT activity At higher doses of dexamethasone, the "restorative" action of high dose dexamethasone or corticosterone previously noted [29, 30] progressively comes into play That this effect is via other than classical Type II glucocorticoid receptors is clearly seen from the inability of otherwise equivalent doses of RU28362 to elevate PNMT activity, given that RU28362 is a potent and highly selective Type II receptor agonist Given the doses of corticosterone or dexamethasone required to restore the effect in the surgically [29, 30] or chemically [32] hypophysectomized rat, the receptor via which such an effect is mediated clearly is of relatively low affinity, consistent with the very high levels of free corticosterone in the portal blood perfusing the adrenal medulla Whether or not this low affinity corticosterone receptor is a membrane or intracellular receptor awaits determination, as does the mechanism whereby it modulates PNMT activity independent of the classical Type II receptor mediated effects on PNMT gene transcription

In summary, glucocorticoids appear to act through at least two classes of relatively high affinity intracellular receptors (Type I and II) In some tissues Type I receptors are aldosterone selective, at least in part reflecting the activity of one species of the enzyme 11-HSD in cells which are physiological targets for aldosterone action In other cells and tissues 11-HSD activity appears to modulate Type II (classical GR) occupancy and activation by glucocorticoids, thus fractionating individual target tissue response to a common circulating level of steroid In addition, there has recently been demonstrated a high affinity membrane receptor specific for physiological glucocorticoids in neural tissue from the amphibian *Ticarda*, and there is compelling albeit indirect evidence for a low affinity receptor recognizing corticosterone and dexamethasone but not RU28362 in the rat adrenal medulla It therefore appears highly likely that in future we will recognize not only classical GR as mediators of the physiological actions of glucocorticoid hormones, but a range of other high and low affinity receptors, membrane and intracellular, acting via both genomic and non-genomic mechanisms

## REFERENCES

1 Liu J -P , Robinson P J , Funder J W and Engler D The biosynthesis and secretion of adrenocorticotropin by the ovine anterior pituitary is predominantly regulated by arginine vasopressin (AVP) *J Biol Chem* **265** (1990) 14,136–14,142

2 Patel P D , Kwak S P , Herman J P , Young, E Y , Akil H and Watson S J Functional heterogeneity of Type I and Type II corticosteroid receptor expression in rat hippocampus In *Stress and Reproduction, Serono Symposia Publications* (Edited by K E Sheppard, J H Boublik and J W Funder) Raven Press, New York, Vol 86 (1992) pp 1–17

3 Canny B J , Funder J W and Clarke I J Glucocorticoids regulate ovine hypophysial portal levels of corticotropin-releasing factor and arginine vasopressin in a stress specific manner *Endocrinology* **125** (1989) 2532–2539

4 Smith A I , Engler D , Fullerton M J , Pham T , Wallace C , Morgan F J , Clarke I J and Funder J W Post-translational processing of corticotropin-releasing factor in the ovine tuberoinfundibular system and pituitary *N Y Acad Sci* **512** (1987) 24–47

5 Engler D , Pham T , Fullerton M , Ooi G , Funder J W and Clarke I J Studies of the secretion of corticotropin-releasing factor and arginine vasopressin into the hypophysial portal circulation of the conscious sheep I Effect of an audiovisual stimulus and insulin-induced hypoglycaemia *Neuroendocrinology* **49** (1989) 367–381

6 Moldow R L and Fischman A J Circadian rhythm of corticotropin releasing factor-like immunoreactivity in rat hypothalamus *Peptides* **5** (1984) 1213–1215

7 Krozowski Z S and Funder J W Renal mineralocorticoid receptors and hippocampal corticosterone binding species have identical intrinsic steroid specificity *Proc Natn Acad Sci U S A* **80** (1983) 6056–6060

8 Arriza J L , Weinberger C , Cerelli G , Glaser T M , Handelin B L , Housman D E and Evans R M Cloning of human mineralocorticoid receptor complementary DNA structural and functional kinship with the glucocorticoid receptor *Science* **237** (1987) 268–275

9 Funder J W , Pearce P T , Smith R and Smith A I Mineralocorticoid action target-tissue specificity is enzyme, not receptor, mediated *Science* **242** (1988) 583–585

10 Edwards C R W , Stewart P M , Burt D , McIntyre M A , de Kloet E R , Brett L , Sutanto W S and Monder C Localization of 11$\beta$-hydroxysteroid dehydrogenase-tissue specific protector of the mineralocorticoid receptor *Lancet* **ii** (1986) 986

11 Agarwal A K , Monder C , Eckstein B and White P C Cloning and expression of rat cDNA encoding corticosteroid 11$\beta$-dehydrogenase *J Biol Chem* **264** (1989) 18,939–18,943

12 Tannin G M , Agarwal A K , Monder C , New M I and White P I The human gene for 11$\beta$-hydroxysteroid dehydrogenase *J Biol Chem* **266** (1991) 16,653–16,658

13 Funder J W 11$\beta$-Hydroxysteroid dehydrogenase and the meaning of life *Molec Cell Endocr* **68** (1990) C3–C5

14 Mercer W and Krozowski Z Localization of an 11$\beta$-hydroxysteroid dehydrogenase activity to the distal nephron evidence for the existence of two species of dehydrogenase in the rat kidney *Endocrinology* **130** (1992) 540–543

15 Duperrex H , Gaeggeler H -P , Kenouch S , Farman N and Rossier B C Expression of rat liver 11$\beta$-hydroxysteroid-dehydrogenase (11$\beta$-OHSD) in TBM cells, an aldosterone responsive cell line *Proc 24th A Meet USGEB/USSBE* (1992) Basel, Abstr

16 Phillips D M , Lakshmi V and Monder C Corticosteroid 11$\beta$-dehydrogenase in rat testis *Endocrinology* **125** (1989) 209–216

17 Krozowski Z , Stuchbery S , White P , Monder C and Funder J W Characterization of 11$\beta$-hydroxysteroid dehydrogenase gene expression identification of multiple unique forms of messenger ribonucleic acid in the rat kidney *Endocrinology* **127** (1990) 3009–3013

18 Funder J W A la recherche du temps perdu In *Aldosterone Fundamental Aspects* (Edited by J -P Bonvalet, N Farman, M Lombes and M -E Rafestin-Oblin) John Libbey, France (1991) pp 77–83

19 Hollenberg S M , Weinberger C , Ong E S , Cerelli G , Oro A , Lebo R , Thompson E B , Rosenfeld M G and Evans M Primary structure and expression of a functional human glucocorticoid receptor cDNA *Nature* **318** (1985) 635–641

20 Jonat C , Rahmsdorf H J , Park K -K , Cato A C B , Gebel S , Ponta H and Herrlich P Antitumor promotion and antiinflammation down-dulation of AP-1 (fos/jun) activity by glucocorticoid hormones *Cell* **62** (1990) 1189–1204

21 Yang-Yen H -F , Chambard J -C , Sun Y -L , Smeal T , Schmidt T J , Drouin J and Karin M Transcriptional interference between c-jun and the glucocorticoid receptor mutual inhibition of DNA binding due to direct protein–protein interaction *Cell* **62** (1990) 1205–1215

22 Schule R, Rangarajan P, Kliewer S, Ransone L J, Bolado J, Yang N, Verma I M and Evans R M Functional antagonism between oncoprotein c-jun and the glucocorticoid receptor *Cell* **62** (1990) 1217–1226

23 Naray-Fejes-Toth A and Fejes-Toth G Glucocorticoid receptors mediate mineralocorticoid-like effects in cultured collecting duct cells *Am J Physiol* **259** (1990) F672–F678

24 Joels M and de Kloet R E Mineralocorticoid effects on electrical activity in the rat brain In *Aldosterone Fundamental Aspects* (Edited by J -P Bonvalet, N Farman, M Lombes and M -E Rafestin-Oblin) John Libbey, France (1991) pp 239–248

25 Wehling M , Christ M and Theisen K High affinity aldosterone binding to plasma membrane rich fractions from mononuclear leukocytes is there a membrane receptor for mineralocorticoids? *Biochem Biophys Res Commun* **181** (1991) 1306–1312

26 Armanini D , Strasser T and Weber P C Characterization of aldosterone binding sites in circulatory human mononuclear leukocytes *Am J Physiol* **248** (1985) E388–E390

27 Wehling M , Armanini D , Strasser T and Weber P C Effect of aldosterone on sodium and potassium concentrations in human mononuclear leukocytes *Am J Physiol* **252** (1987) E505–E508

28 Orchinik M , Murray T F and Moore F L A corticosteroid receptor in neuronal membranes *Science* **252** (1991) 1848–1851

29 Wurtman R J and Axelrod J Control of enzymatic synthesis of adrenaline in the adrenal medulla by adrenal cortical steroids *J Biol Chem* **241** (1966) 2301–2305

30 Margolis F L , Roffi J and Jost A Norepinephrine methylation in fetal rat adrenals *Science* **154** (1966) 275–276

31 Ross M E , Evinger M J , Hyman S E , Carroll J M , Mucke L, Comb M , Reis D J, Joh T H and Goodman H M Identification of a functional glucocorticoid response element in the phenylethanolamine N-methyltransferase promoter using fusion genes introduced into chromaffin cells in primary culture *J Neurosci* **10** (1990) 520–530

32 Wong D L , Lesage A , Siddall B and Funder J W Glucocorticoid regulation of phenylethanolamine *N*-methyltransferase *in vivo* *FASEB J* (1992) Submitted