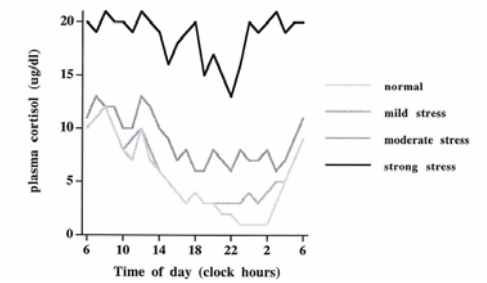
Stress hormone receptors in the primate brain

- Corticosteroid receptors – translating stress hormones into action
- Corticosteroid receptors - cellular and molecular biology
- Corticosteroid receptors in primates compared with other mammals
- Corticosteroid receptors in homeostasis, acute stress, chronic stress

1

Different psychological states are associated with different levels/patterns of cortisol

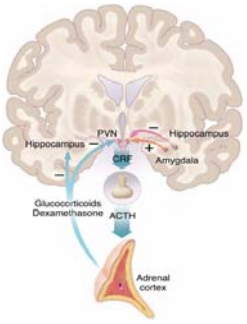


Different levels and patterns of cortisol regulate physiology, brain and behaviour via cortisol receptors, including levels and patterns of cortisol

Translating stress hormones into action

2

Hypothalamic – Pituitary – Adrenal axis, Corticosteroids, and the Brain



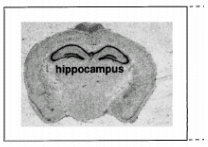
Translating stress hormones into action

3

The mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR)

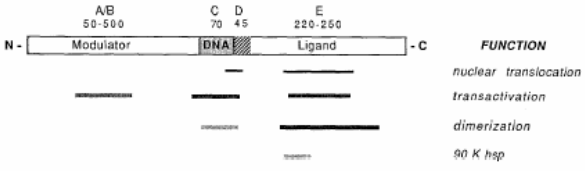
TABLE 2. Milestones in brain corticosteroid receptor research

Year	Milestone
1968	First report on selective retention of [^{3}H]corticosterone in hippocampus (18)
1972	Corticosterone receptors in pyramidal neurons of hippocampus (432)
1975	Low retention [^{3}H]dexamethasone in hippocampus; high in pituitary corticotropes (19)
1980	Selective GR agonists discriminate between MR and GR (57)
1982	*In vitro* hippocampus and kidney cytosol contain MR and GR (7, 8)
1985	MR and not GR retains [^{3}H]corticosterone in neuronal nuclei of hippocampus (9)
1985	Cloning of GR and splice variants (95)
1985	First brain map of immunoreactive GR neurons (60)
1987	Cloning of MR (103)
1988	MR and GR mRNA are expressed in hippocampal neurons (66)
1988	11-HSD confers aldosterone selectivity to MR (79, 80)
1991	First brain map of immunoreactive MR neurons (64)
1993	Identification of MR mRNA splice variants (104)
1994	*In vitro* demonstration of MR/GR heterodimerization (117)
1995	mdr1A Pgp in blood-brain barrier prevents brain penetration of dexamethasone (90–92)
1996	Colocalized immunoreactive MR/GR clusters in hippocampal neuronal nuclei (70)
1996	11-HSD regenerates *in vitro* bioactive corticosterone in hippocampus (87)



de Kloet et al. Endocrine Rev 19 (1998)

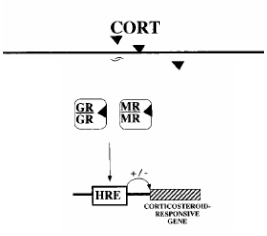
General structural and functional organization of steroid receptors

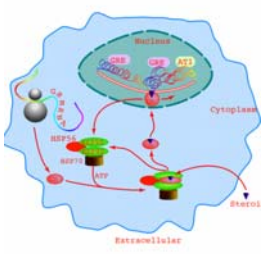


DNA = DNA Binding Region
Ligand = Cortisol Binding Region

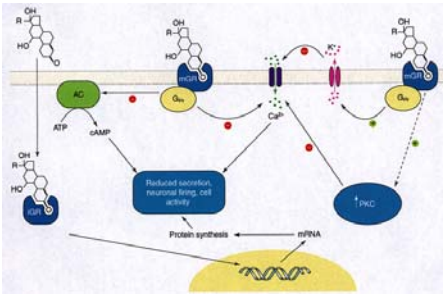
Beato, Cell 56 (1989)

The Corticosteroid Receptors, MR and GR, are transcription factors





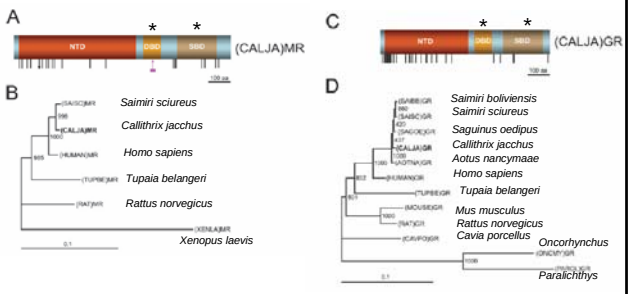
The Corticosteroid Receptors, MR and GR, are also cell membrane receptors



Comparison of the MR (type-1) and GR (type-2) Receptors

Mineralocorticoid Receptor	Glucocorticoid Receptor
• High affinity for corticosteroid	• Low affinity for corticosteroid
• Expression in hippocampus and amygdala	• Expression in hippocampus, amygdala, hypothalamus, brain stem, cortex, pituitary
• Occupied when CORT is low and when CORT is high	• Occupied when CORT is high
• Agonist: Aldosterone	• Agonist: Dexamethasone
• Antagonist: RU26752	• Antagonist: RU38486
• Mediates Permissive effects	• Mediates Suppressive effects

Conservation of MR and GR amino acid sequences within mammals/primates



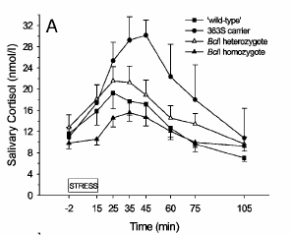
Pryce et al, Eur J Neurosci 21 (2005)

Human polymorphisms of the GR and cortisol phenotype

TABLE 2. Frequencies of the *Bcl*I, the N363S, and the ER22/23EK polymorphism in the glucocorticoid receptor gene

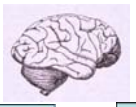
Polymorphism	Genotype	*Bcl*I CC	*Bcl*I CG	*Bcl*I GG	
N363S	AA	36[a]	38[b]	18[c]	92
	AG	9[d]	6[e]		14
	GG	3[f]			2
ER22/23EK	GAGAGG/GAAAAG	4[g]	2[e]		4
		48	46	18	2[h]

[a] Wild type.
[b] *Bcl*I G heterozygote.
[c] *Bcl*I G homozygote.
[d] 363S carrier.
[e] Excluded from further analyzes due to sample size.

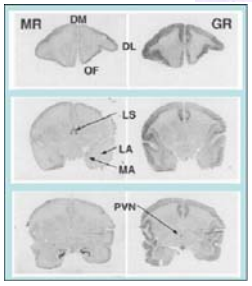


Wuest et al, JCEM 89 (2004)

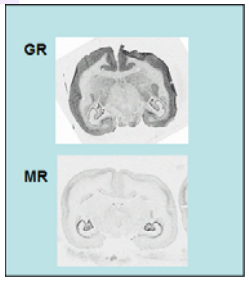
Region-specific distribution of MR and GR in the primate brain



Squirrel monkey



Common marmoset



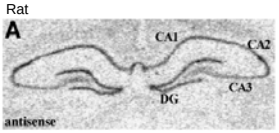
Patel et al, J Psychiatr Res 34 (2000)

Table 2 – Mineralocorticoid receptor: intra-specific relative densities of MR mRNA expression in the forebrain of adult mammals

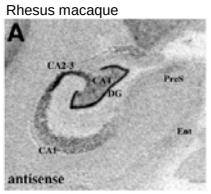
Species	Order	Hypothalamus	Amygdala	Hippocampus			Neocortex
		PVN	LA/CE/ME	DG	CA1, 2	CA3, 4	Pre/Frontal
Mouse	Rodentia	–	+	+++	+++, +++	++, +	+
Rat	Rodentia	–	+/++	+++	+++, +++	+++, +++	++
Tree shrew	Scandentia	–	+	+++	+++, +++	++, ++	–
Marmoset	Primates, NW	–	+	+++	++, ++	++, +	+/++
Squirrel monkey	Primates, NW	–	+	+++	++, ++	++, +	+/++
Macaque	Primates, OW	–	?	+++	+, ++	++, +	?
Human	Primates, OW	–	?	+++	+, ++	++, +	?

Data sources: mouse, Allen Brain Atlas (http://www.brain-map.org); rat (Bohn et al., 1994; Van Eekelen et al., 1991); tree shrew (Meyer et al., 1998); common marmoset (Pryce et al., 2005a); squirrel monkey (Patel et al., 2000); rhesus macaque (Sanchez et al., 2000); human (Perlman et al., 2007; Seckl et al., 1991).
For clarification of abbreviations and symbols, see Table 1.

Rat



Rhesus macaque



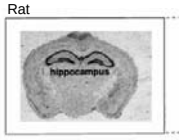
Sanchez et al J Neurosci 20 (2000)
Pryce, Brain Res Rev 57 (2008)

Table 1 – Glucocorticoid receptor: intra-specific relative densities of GR mRNA expression in the forebrain of adult mammals

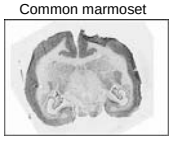
Species	Order	Hypothalamus	Amygdala	Hippocampus			Neocortex
		PVN	LA/CE/ME	DG	CA1, 2	CA3, 4	Pre/Frontal
Mouse	Rodentia	++	+	+++	+++, +++	+, +	+
Rat	Rodentia	+++	+++	+++	+++, +++	+, +	++
Tree shrew	Scandentia	++	+	+++	+, ++	++, +	+
Marmoset	Primates, NW	++	++	++	+, ++	+, +	+++
Squirrel monkey	Primates, NW	+++	++	+++	++, ++	+, +	+++
Macaque	Primates, OW	+++	?	+	+, +	+, +	++/+++
Human	Primates, OW	?	?	+++	++, ++	++, +	+++

Data sources: mouse, Allen Brain Atlas (http://www.brain-map.org); rat (Bohn et al., 1994; Van Eekelen et al., 1991); tree shrew (Meyer et al., 1998); common marmoset (Pryce et al., 2005a); squirrel monkey (Patel et al., 2000); rhesus macaque (Sanchez et al., 2000); human (Perlman et al., 2007; Seckl et al., 1991).
OW, Old World; NW, New World; PVN, paraventricular nucleus; LA, lateral nucleus of amygdala; CE, central nucleus of amygdala; ME, medial nucleus of amygdala; DG, dentate gyrus; CA1–4, Cornu ammonis subregions 1–4.
Relative within-species GR mRNA optical density levels: –=absent, +=low, ++=moderate, +++=high, ?=data not available.

Rat



Common marmoset

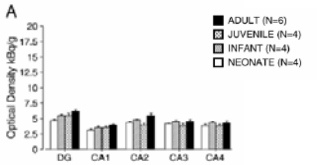


Pryce, Brain Res Rev 57 (2008)

Table 3 – Intra-specific relative densities of GR mRNA expression in the hippocampus during postnatal development

Region	Stage	Mouse	Rat	Marmoset	Human
Dentate gyrus	Neonate	–	–	++	?
	Infant	–/++	+/++	++	+++
	Adolescent	+++	+++	++	+++
	Adult	+++	+++	++	+++
CA3	Neonate	–	–	++	?
	Infant	–/+	+	++	++
	Adolescent	+	+	++	++
	Adult	+	+	++	++
CA1	Neonate	+	–	++	?
	Infant	++	+/++	++	++
	Adolescent	+++	+++	++	++
	Adult	+++	+++	++	++

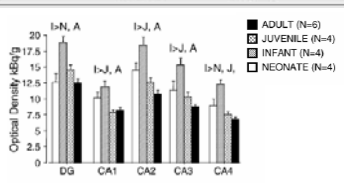
A



Pryce, Brain Res Rev 57 (2008)

Table 4 – Intra-specific relative densities of MR mRNA expression in the hippocampus during postnatal development

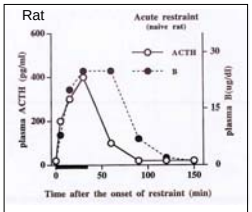
Region	Stage	Mouse	Rat	Marmoset
Dentate gyrus	Neonate	+	++	++
	Infant	++	++	++++
	Juvenile/Adolescent	+++	+++	+++
	Adult	+++	+++	+++
CA3	Neonate	+++	+++	++
	Infant	++	+++	+++
	Juvenile/Adolescent	++	+++	++
	Adult	++	+++	++
CA1	Neonate	++	+++	+++
	Infant	++	+++	+++
	Juvenile/Adolescent	++	+++	++
	Adult	++	+++	++



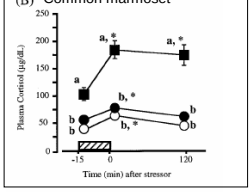
Pryce, Brain Res Rev 57 (2008)

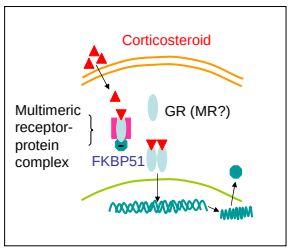
Hyper-cortisolism in some NW primates is due to high levels of an inhibitory protein

Rat



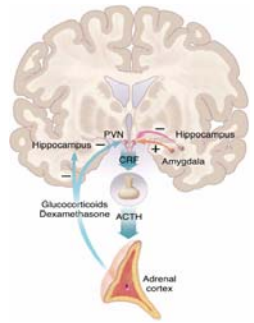
(B) Common marmoset

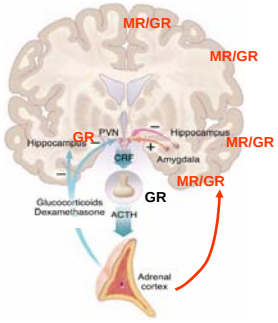




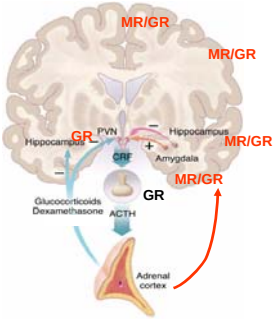
Relevant to:
- Evolutionary ecology
- Psychiatry

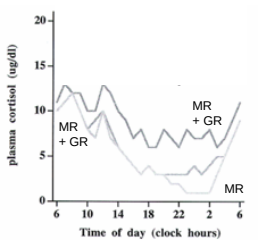
Corticostreoid receptors – translating stress hormones into action



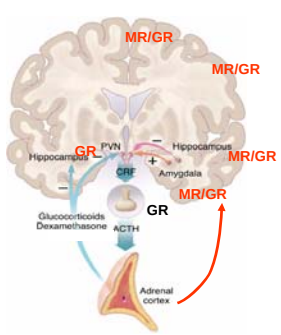


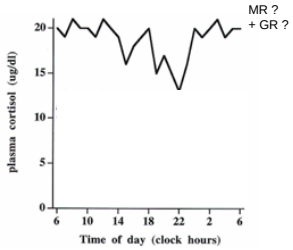
Hypothalamic – Pituitary – Adrenal axis:
an example of MR and GR translation of cortisol effects





Chronic stress and hyper-cortisolism:
Are the effects of chronic stress due to over- or under-activity of MR and GR ?





- **Increased cortisol in depression**
- **Decreased GR in depressed brain**
- **Equivocal findings for MR in depressed brain**