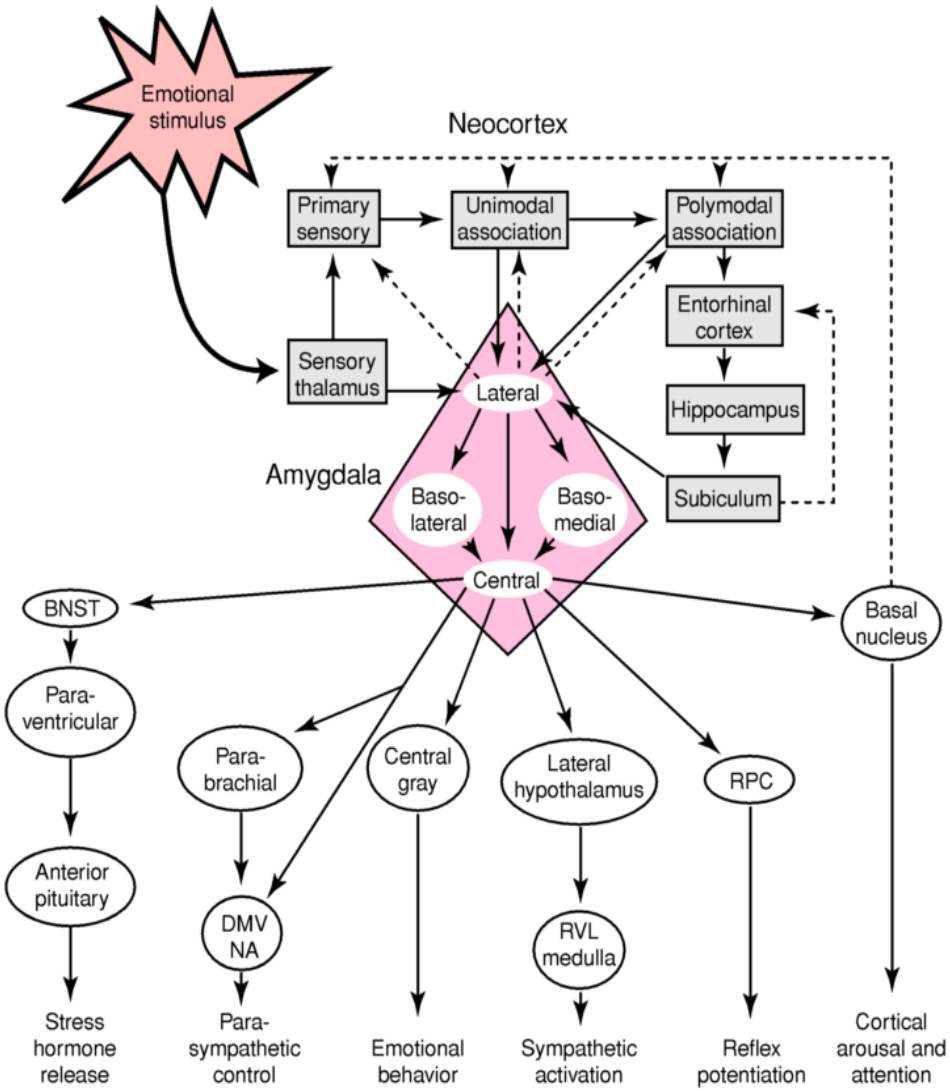
Emotional and cognitive stimulus processing:

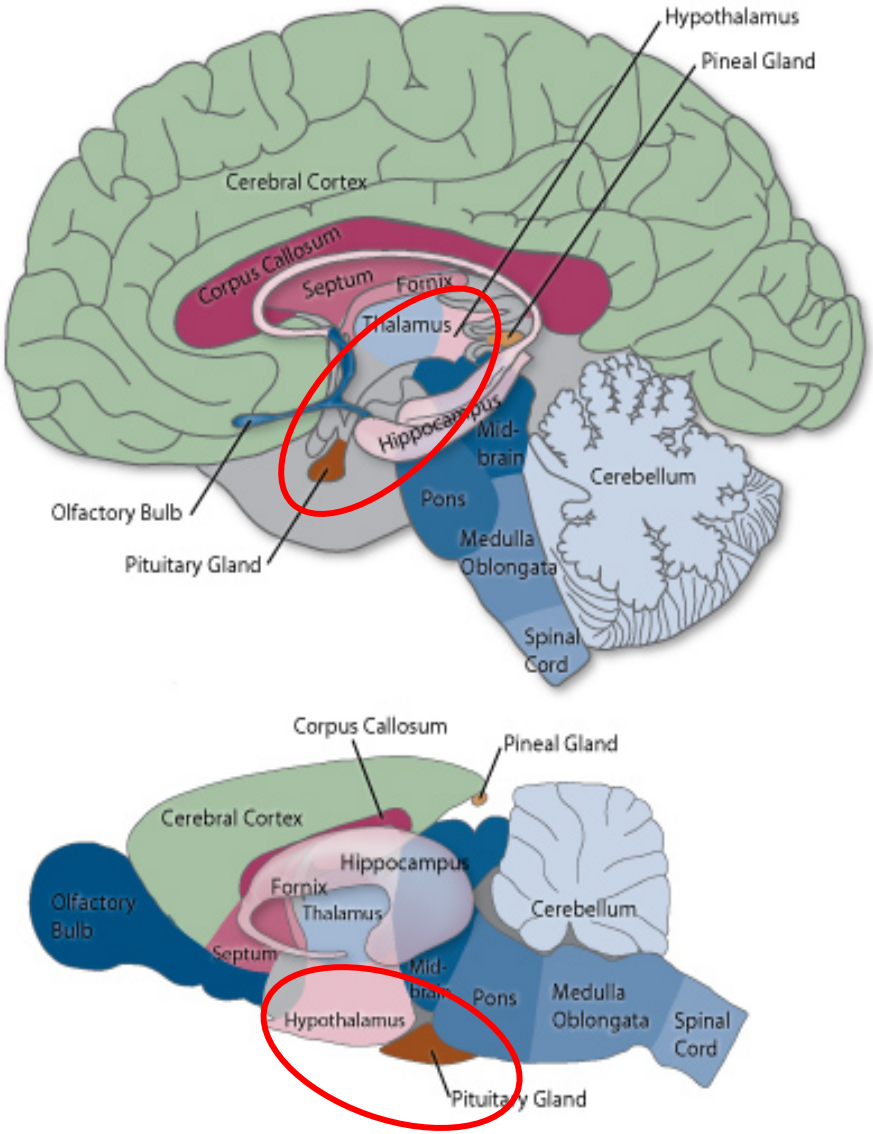
Stress, Learning and Memory

- Amygdala-Hypothalamic-Pituitary-Adrenal axis
- Neuroendocrine pathway
- CRF-ACTH-Corticosteroid
- Corticosteroid receptors
- Effects of corticosteroids on emotional behaviour, learning and memory
- Mechanisms of corticosteroid effects

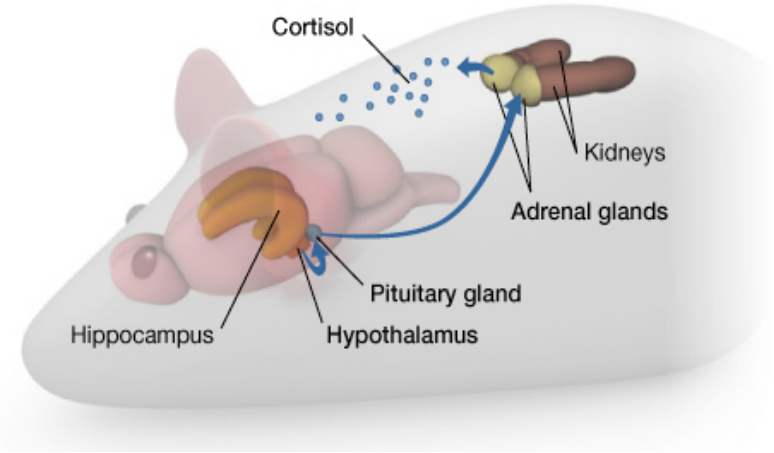
The HPA axis is a major Stress response system



Localisation of the hypothalamus and pituitary in human and rat



Neuroendocrine system: Hypothalamic-Pituitary-Adrenal Axis



Paraventricular Nucleus
Corticotropin Releasing Factor/Hormone

Neurohormone

↓

Pituitary Gland
Adrenocorticotropic Hormone

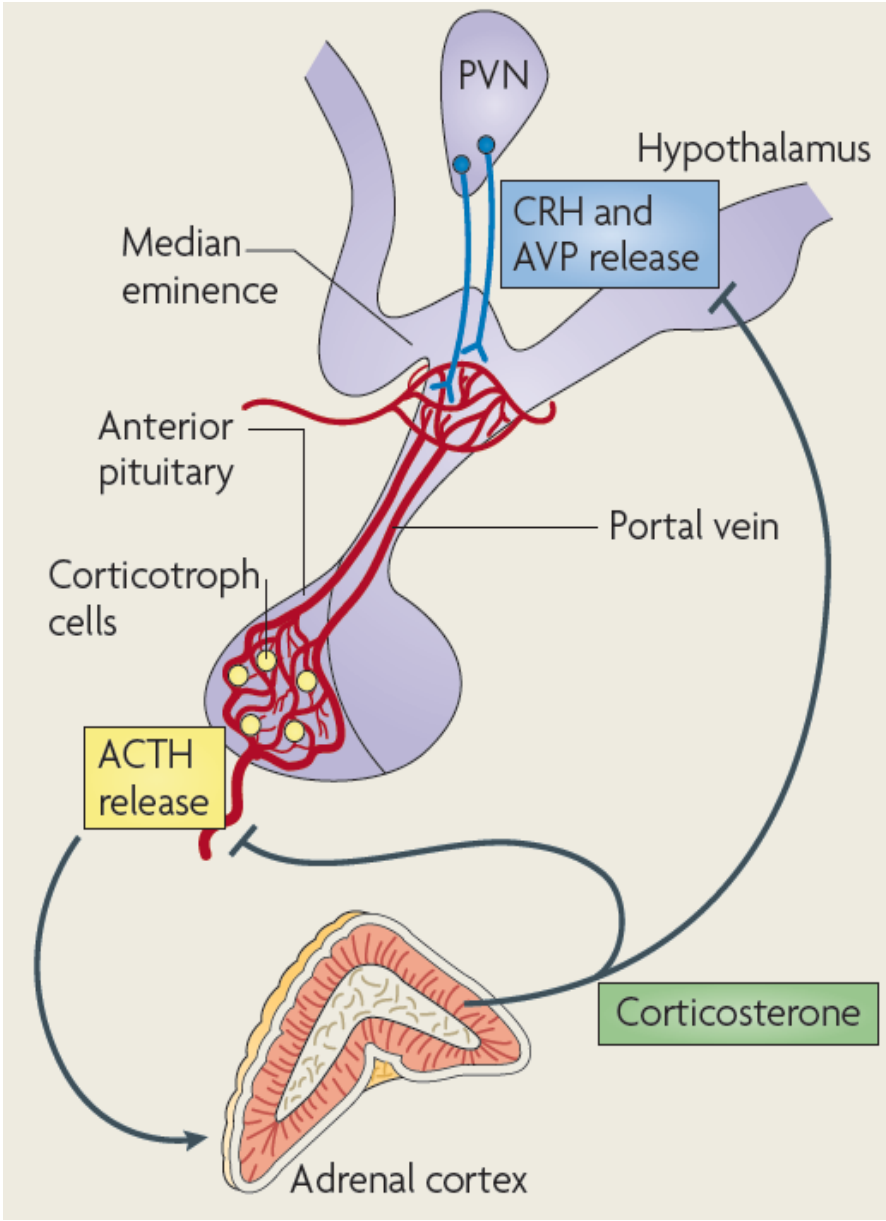
Hormone

↓

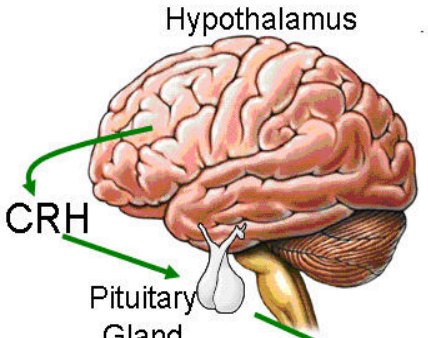
Adrenal Gland
Corticosterone/Cortisol

Hormone

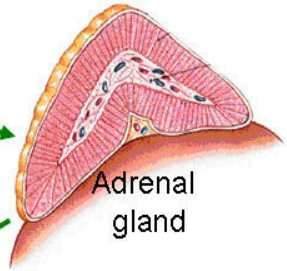
↓



Corticosteroid hormone release under control of ACTH



POMC/ACTH



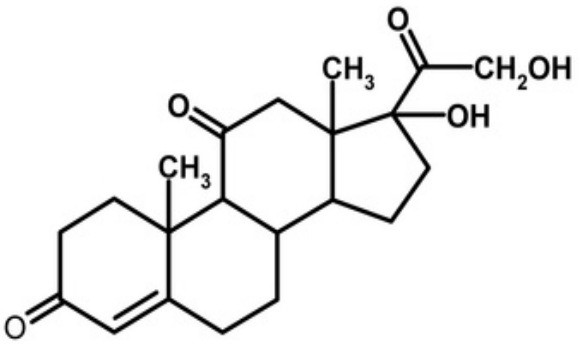
Cortisol

Metabolic Effects

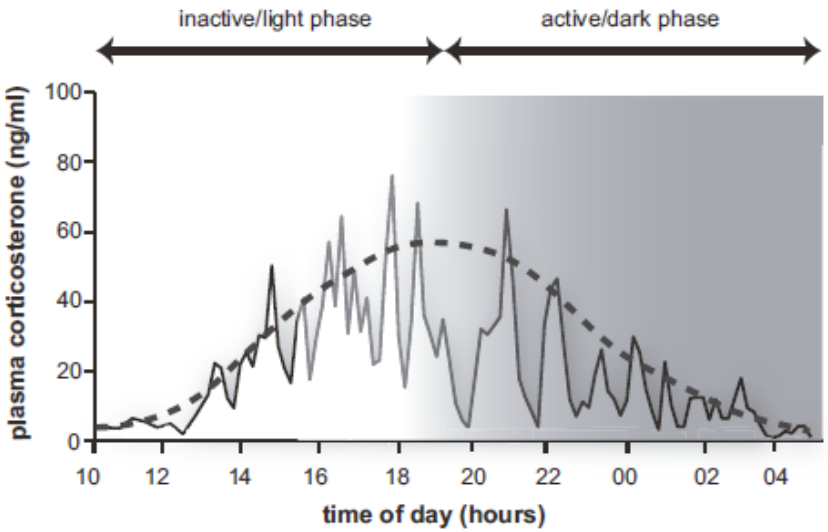
- ↑ Glucose - Liver
- ↑ FFA - adipose
- ↑ Amino acids - muscle

Other effects inc.

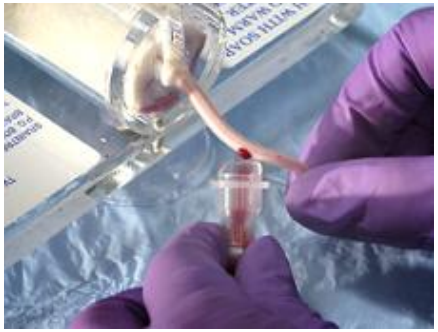
- Anti-inflammatory
- Immunosuppressive
- Inhibits bone formation

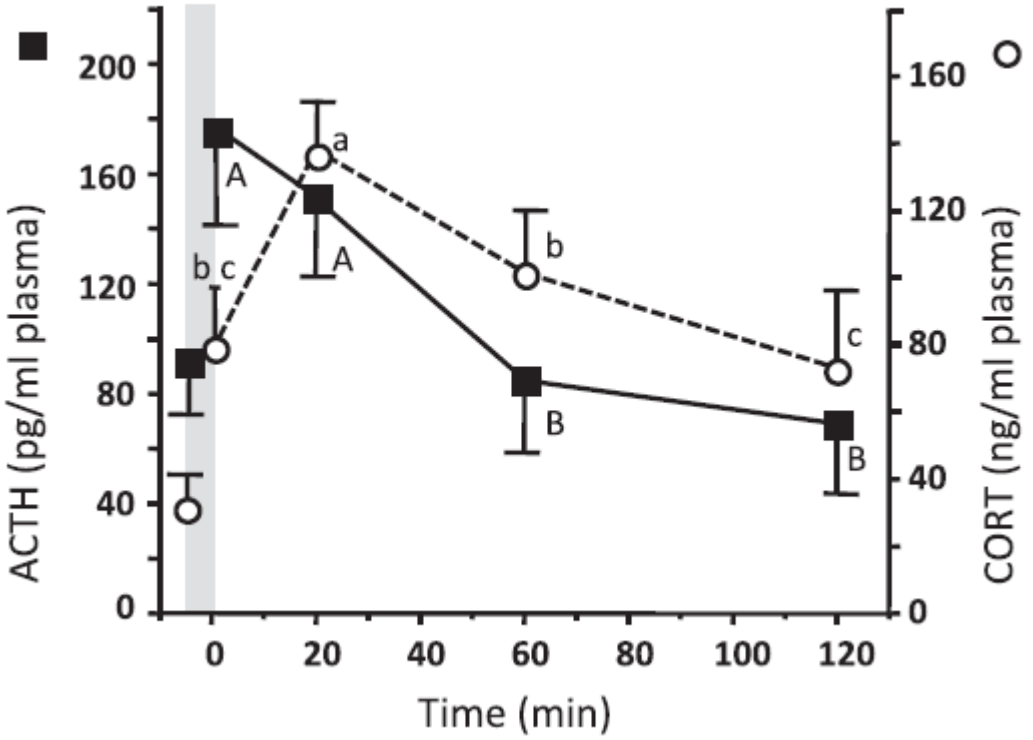


Cortisol



ACTH and Corticosterone response to stressor (blood sampling) in mouse

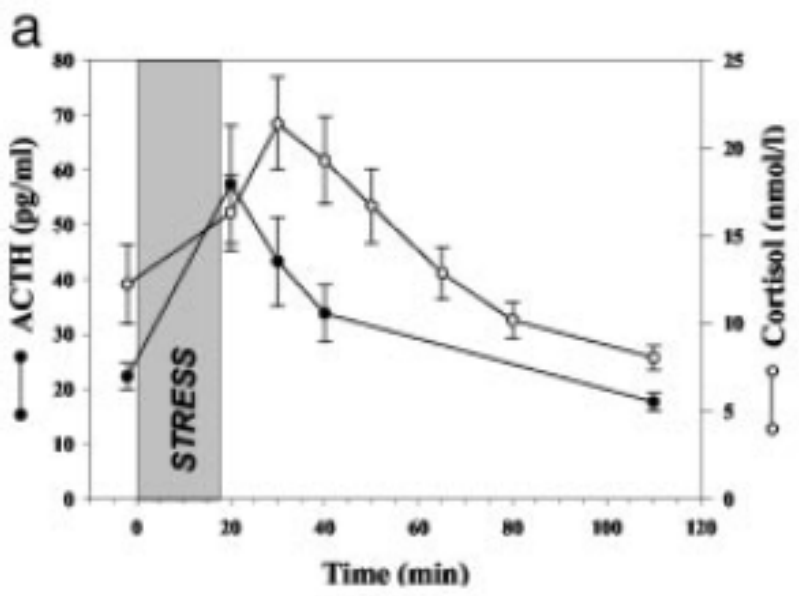




Psychosocial stress leads to increased blood levels of ACTH and Cortisol in Human

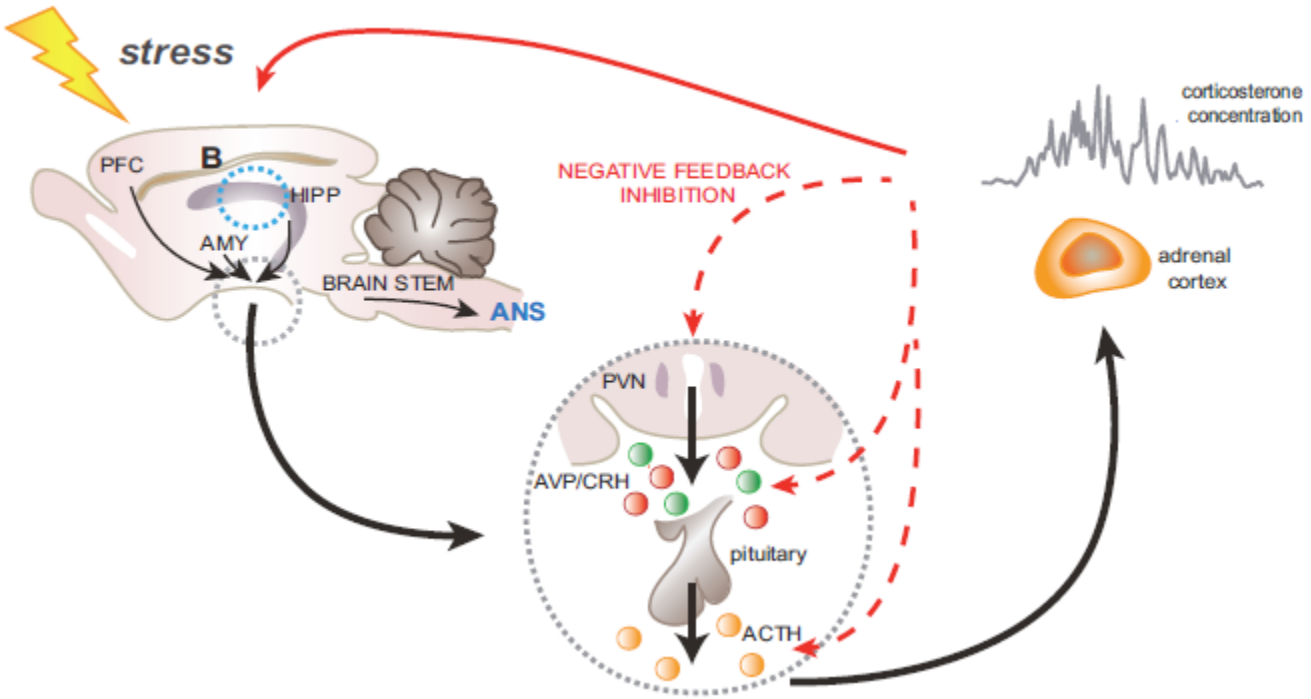
Trier Social Stress Test

Public speaking
Mental arithmetic



Bierhaus et al. (2003) PNAS 100: 1920

The Amygdala/Hippocampus-Hypothalamic-Pituitary-Adrenal Stress response

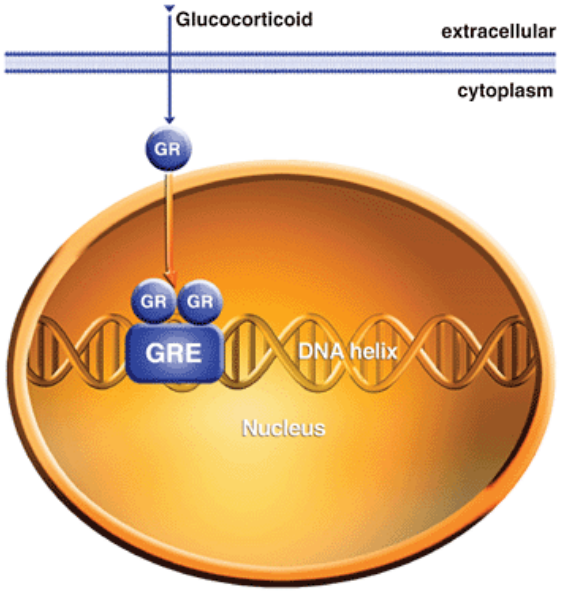


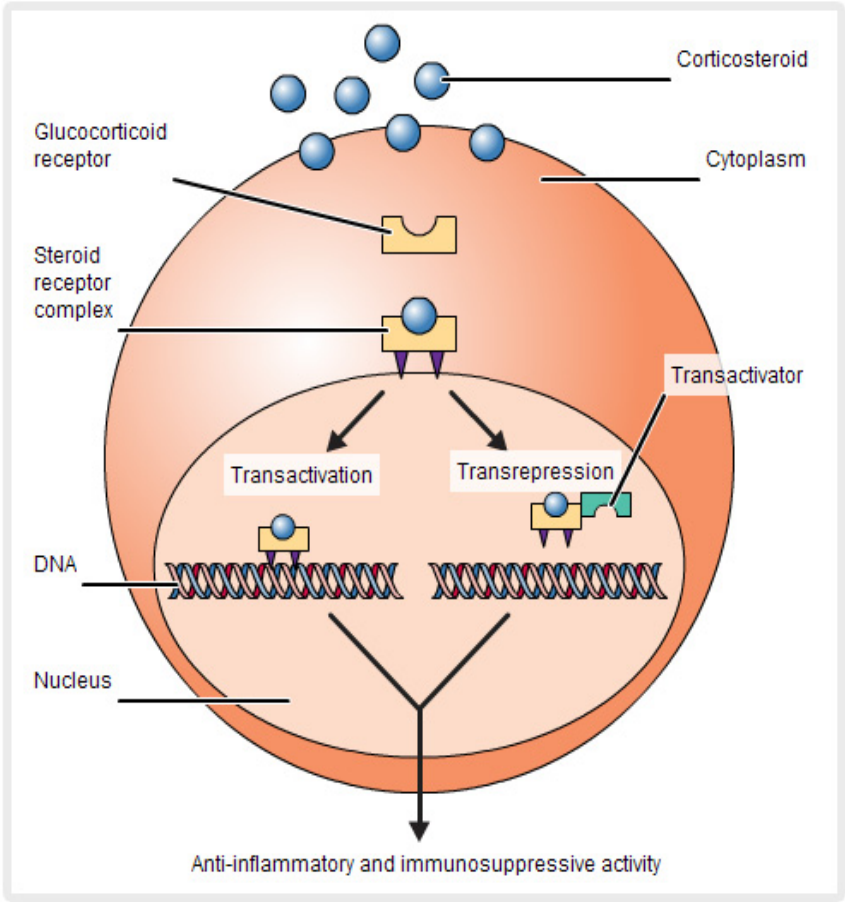
Joels et al (2012) Pharmacol Rev 64: 901

Corticosteroid hormones have two transcription factor receptors: Mineralocorticoid Receptor and Glucocorticoid Receptor

TABLE 1. Two intracellular corticosteroid receptor types in the brain

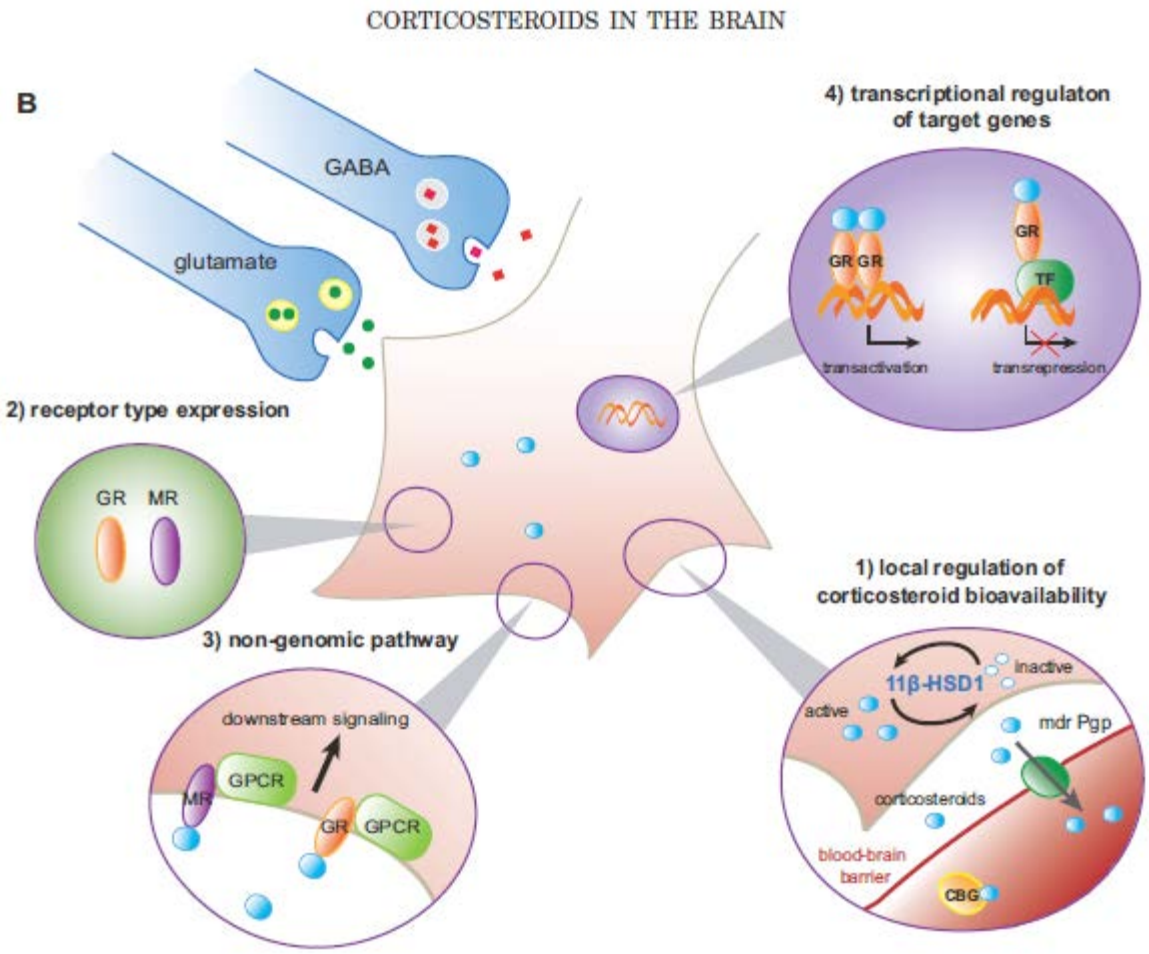
1. Mineralocorticoid receptor (MR)
   High affinity for corticosterone ($K_D \approx 0.5$ nM)
   In limbic brain structures
   Agonist: aldosterone
   Antagonist RU 26752, spironolactone
2. Glucocorticoid receptor (GR)
   Lower affinity for corticosterone ($K_D \approx 5.0$ nM)
   Ubiquitous
   Agonist: dexamethasone, RU 28362
   Antagonist: RU 38486





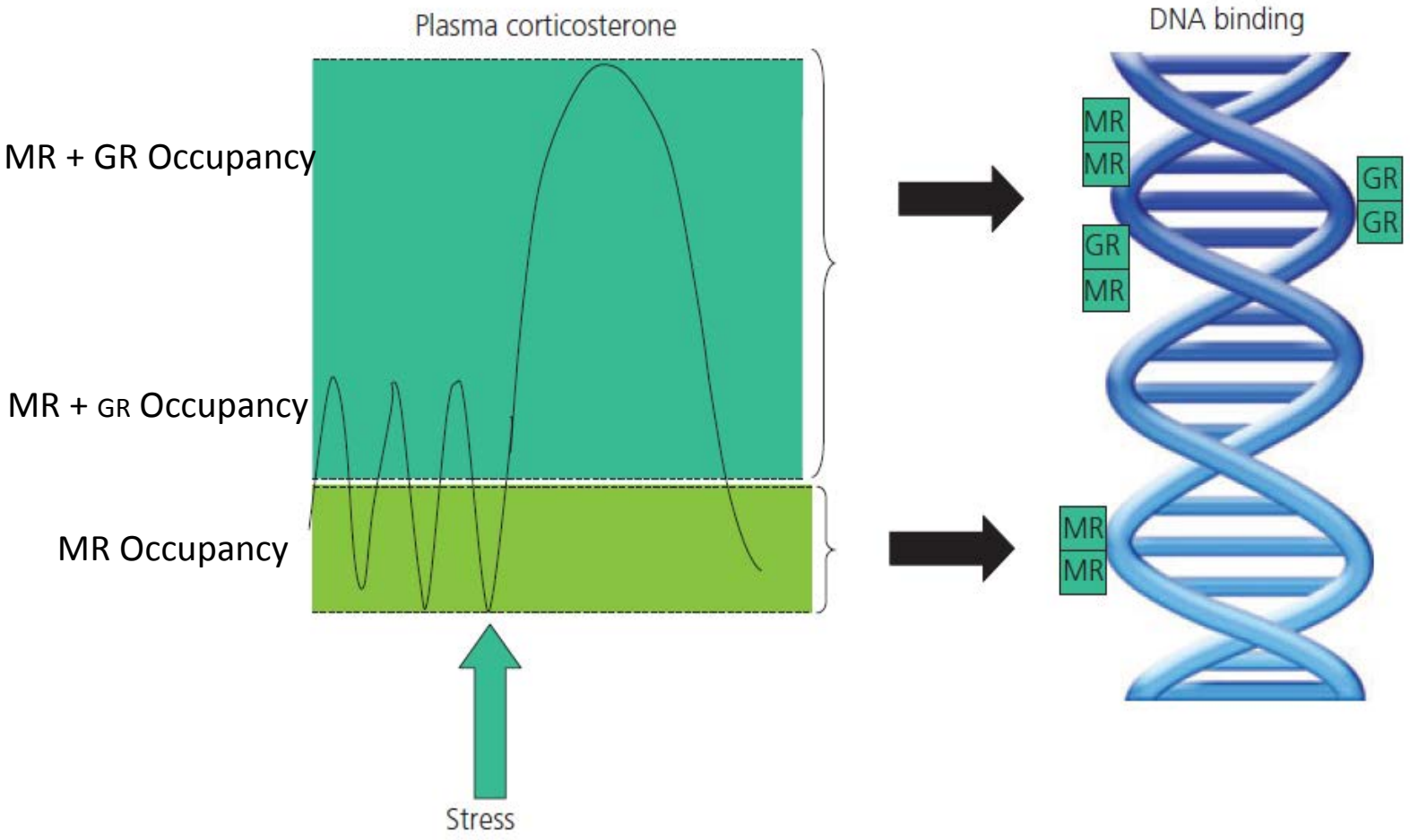
GRE = Glucocorticoid responsive element

MR and GR:
Transcription factors and also membrane-bound receptors

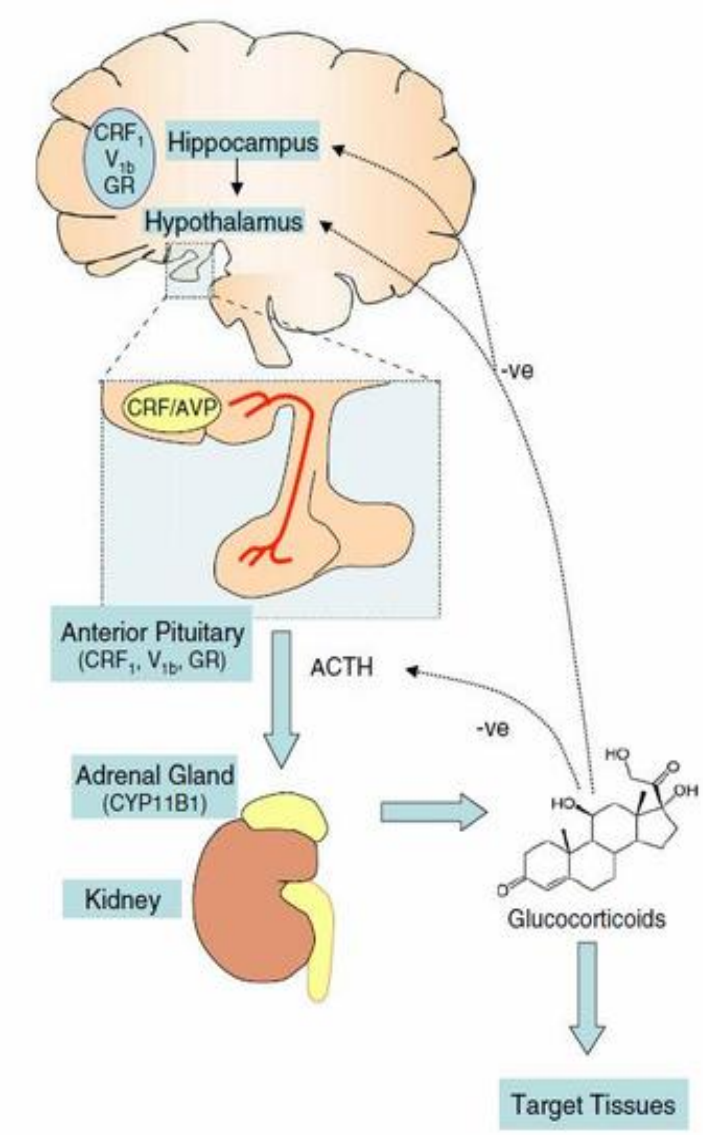


Joels et al (2012) Pharmacol Rev 64: 901

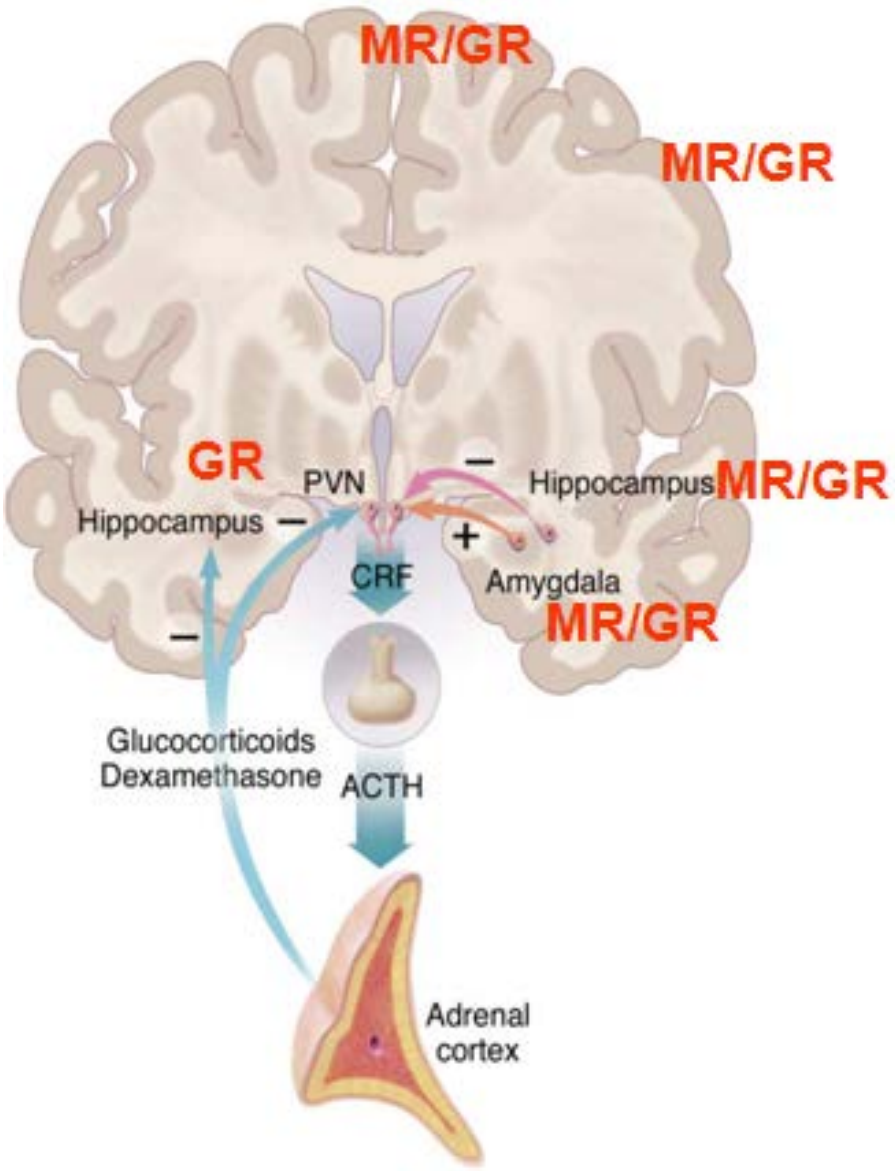
MR and GR affinities determine their state-dependent occupancy and transcription factor functioning



Glucocorticoid Receptor expressed in PVN neurosecretory cells and pituitary corticotrophs and mediates HPA axis negative feedback



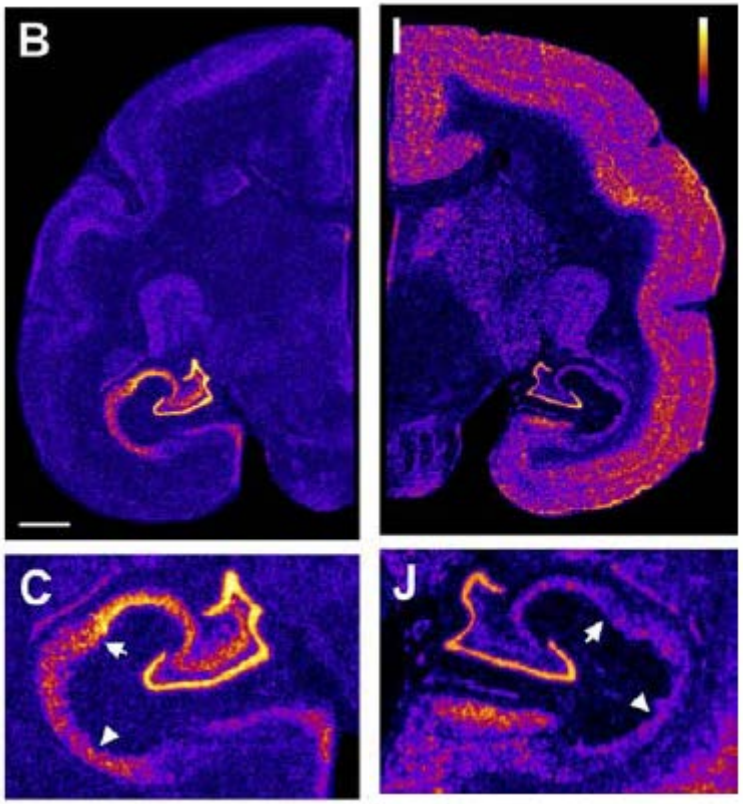
Brain regions expressing Mineralocorticoid receptor and/or Glucocorticoid receptor

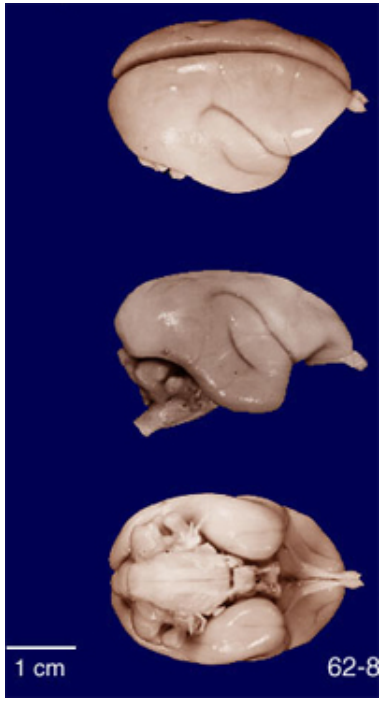


Expression of MR and GR in Temporal Cortex and Hippocampus of Marmoset monkey

Mineralocorticoid Receptor (MR)

Glucocorticoid Receptor (GR)

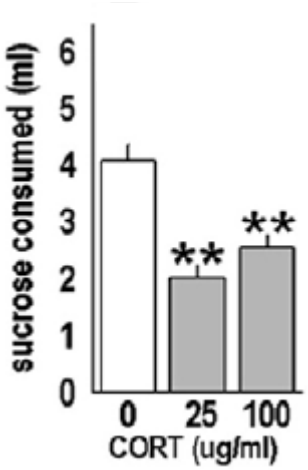




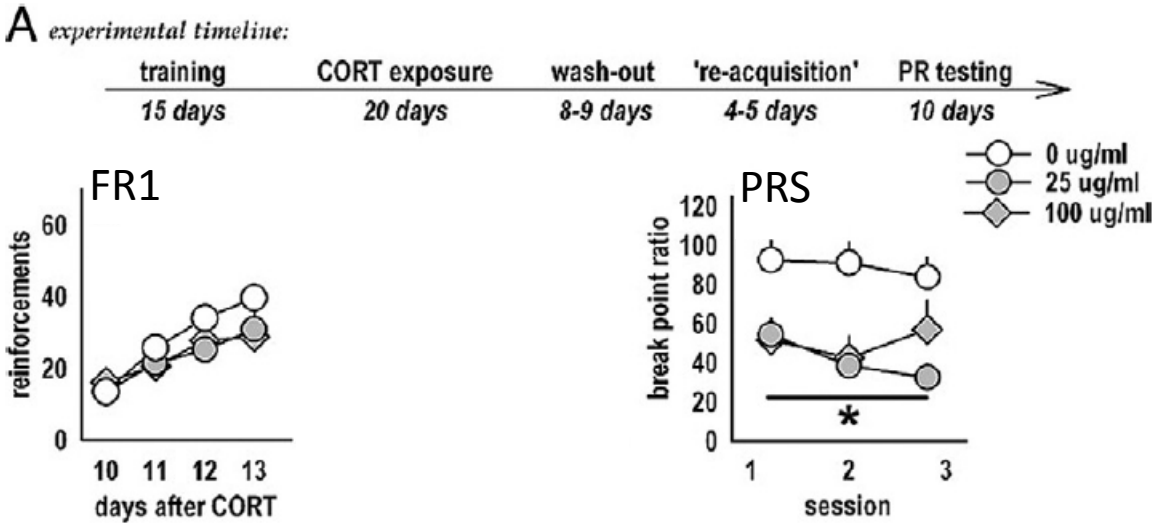
Effects of high corticosterone on reward motivation (wanting) in rat

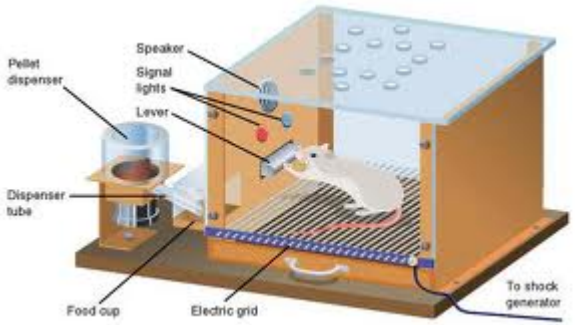
Corticosterone administered via drinking water for 14 days

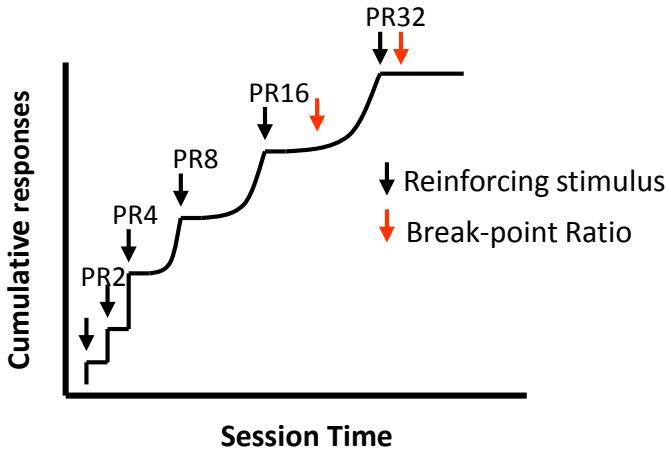
Drinking



Operant behaviour for sucrose



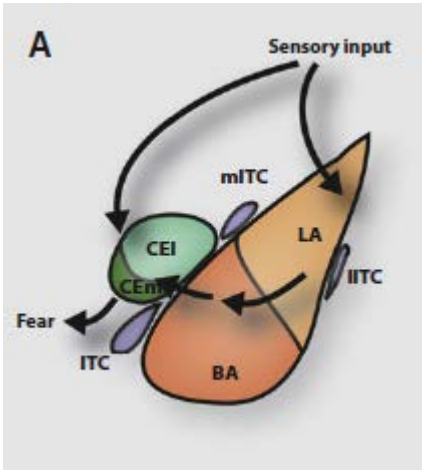




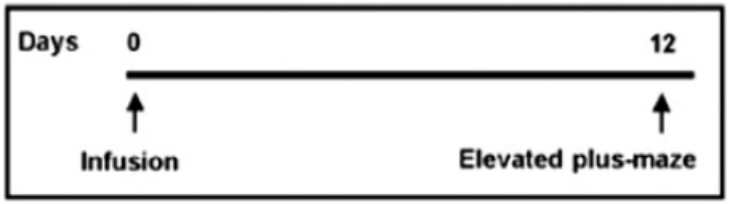
Gourley et al (2008) Biol Psychiatry 64: 884

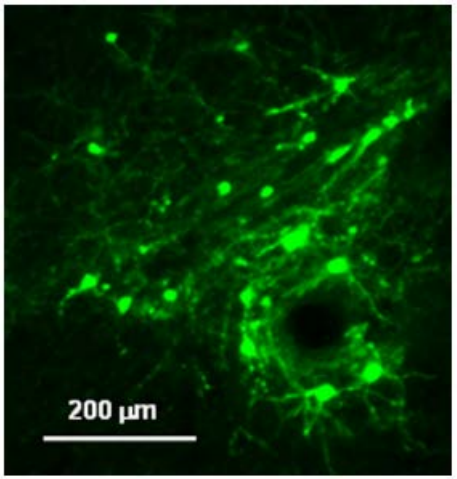
Effects of MR over-expression in basolateral amygdala on emotional reactivity

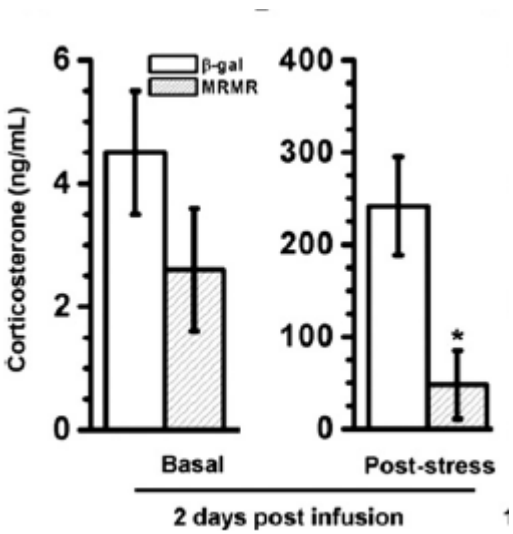
Evidence that MR sets the level of emotional responses

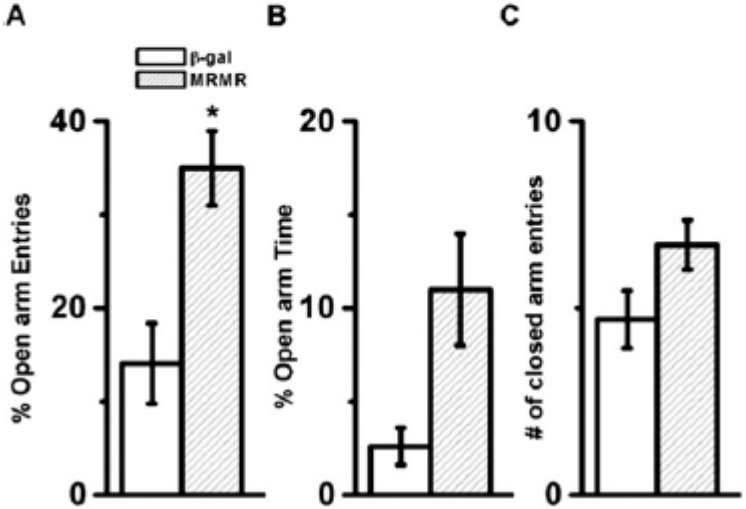


Viral vector over-expression

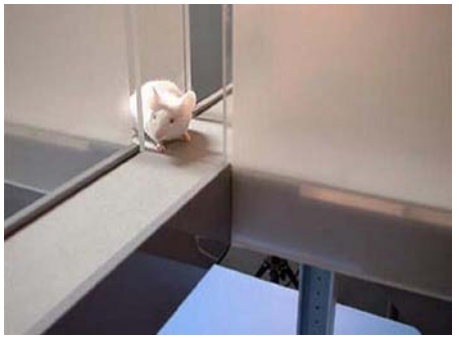








Elevated Plus Maze

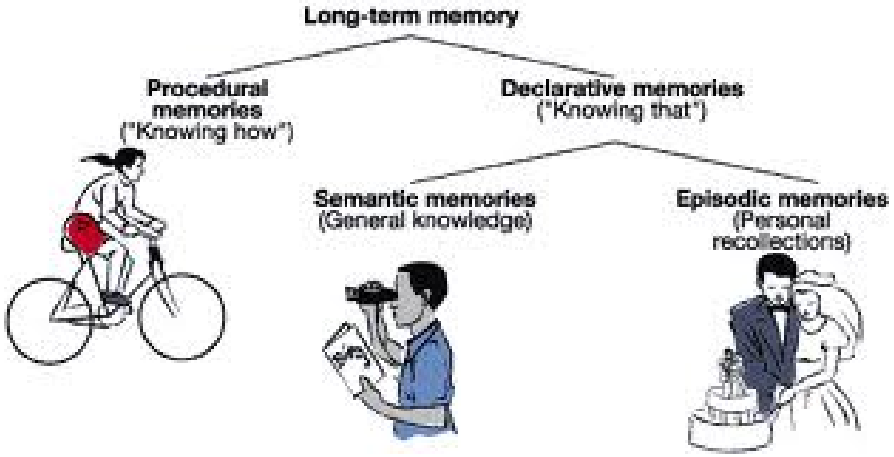


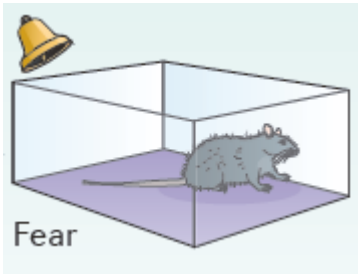
30-min after 2-hr immobilization

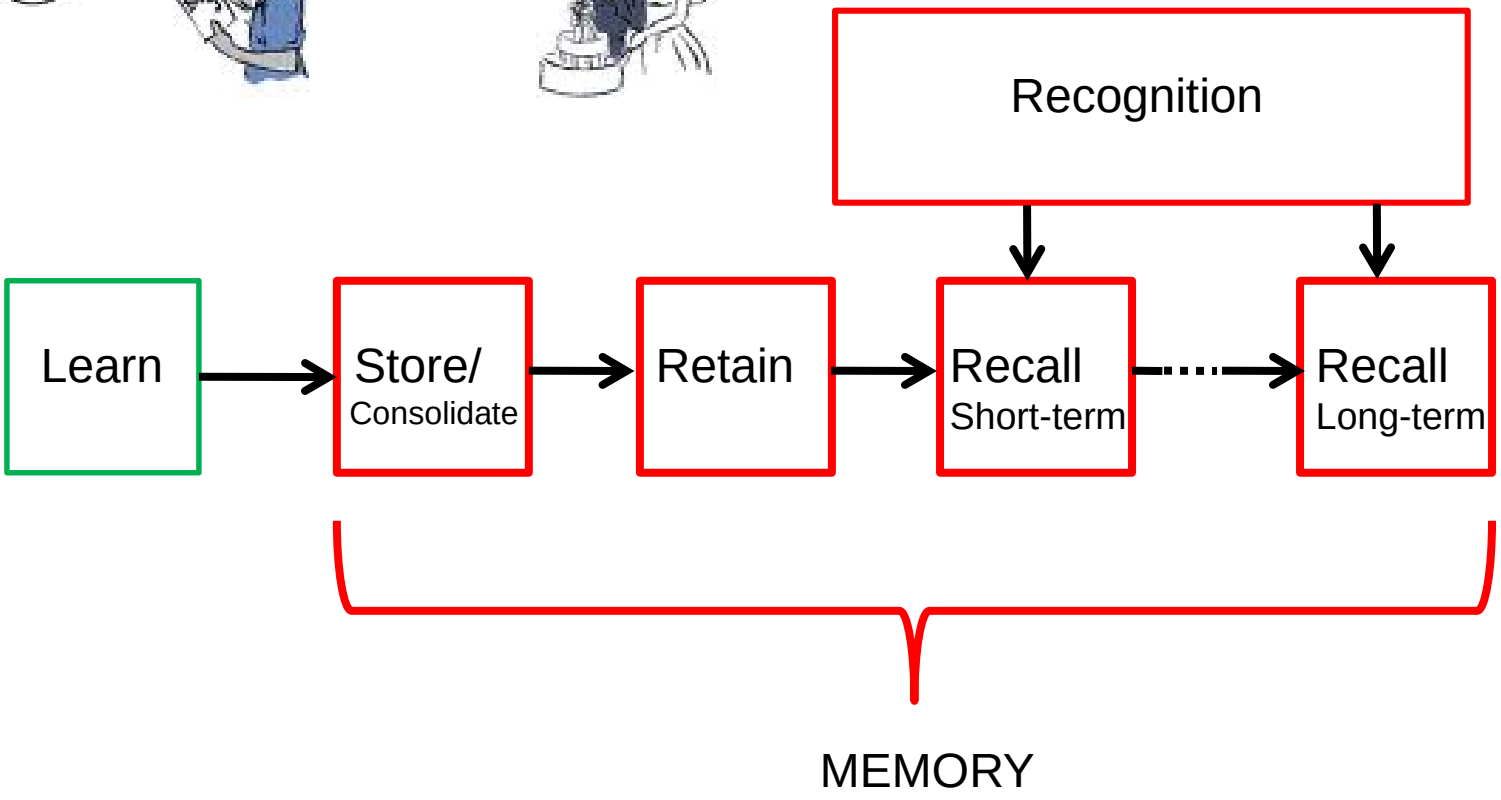
Elevated plus maze

Mitra et al (2009) Biol Psychiatry 66: 686

Sequence of processes that together make up (most) memory types





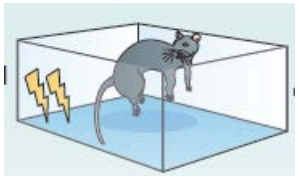


Effects of MR antagonism on contextual fear conditioning

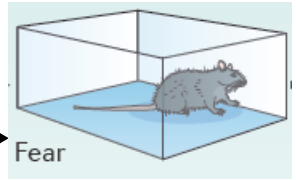
CORT-MR is essential for learning but not for consolidation

MR-Antagonist
Before Learning

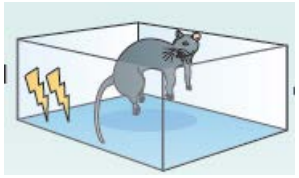
0.5 h



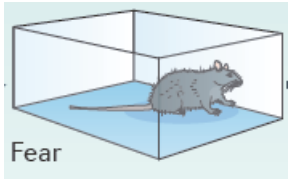
3 h or
24 h

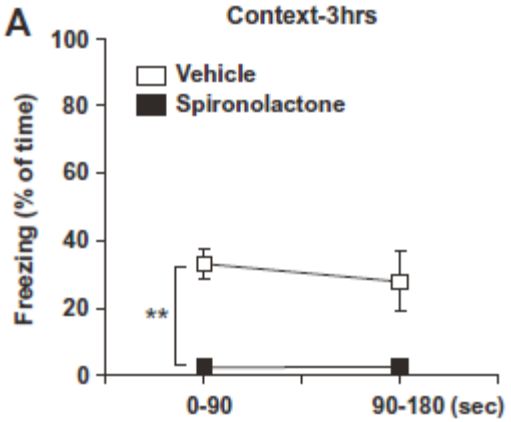


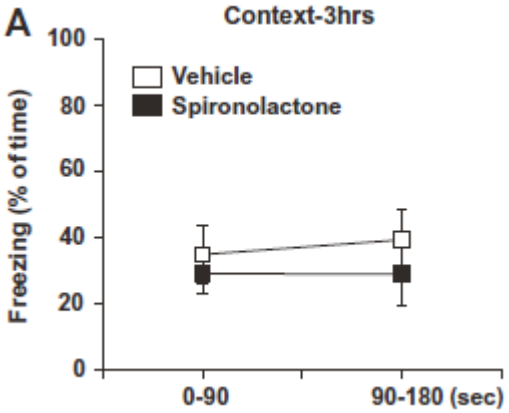
MR-Antagonist
After Learning

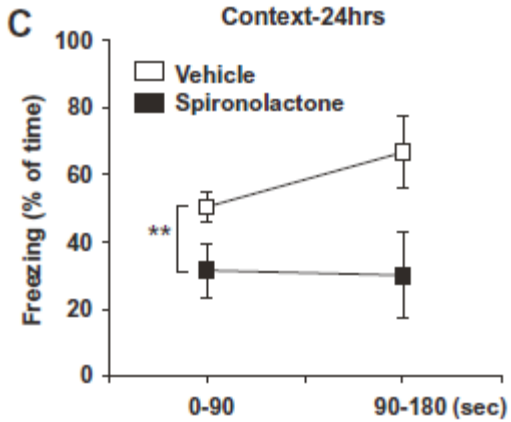


3 h







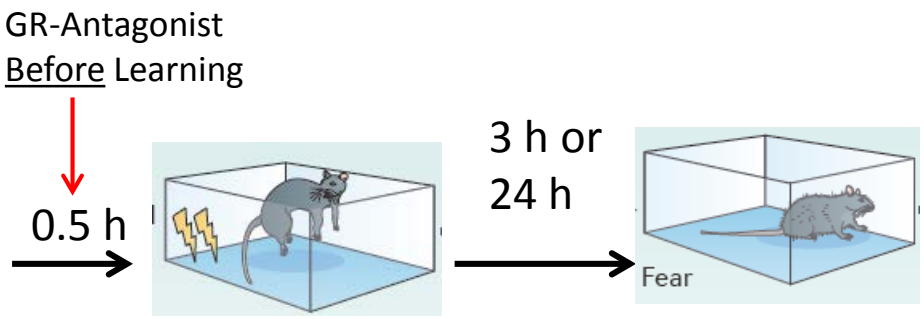


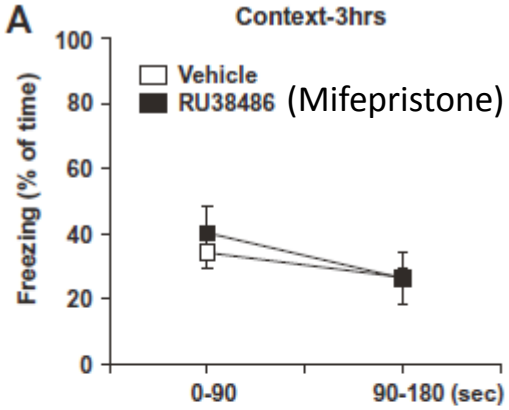
Zhou et al (2010) Neurobiol Learn Memory 94: 530

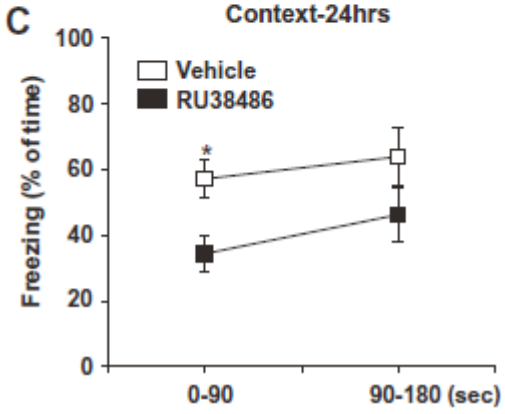
Effects of GR antagonism on contextual fear conditioning

CORT-GR is not essential for learning or short-term consolidation

CORT-GR is essential for long-term consolidation

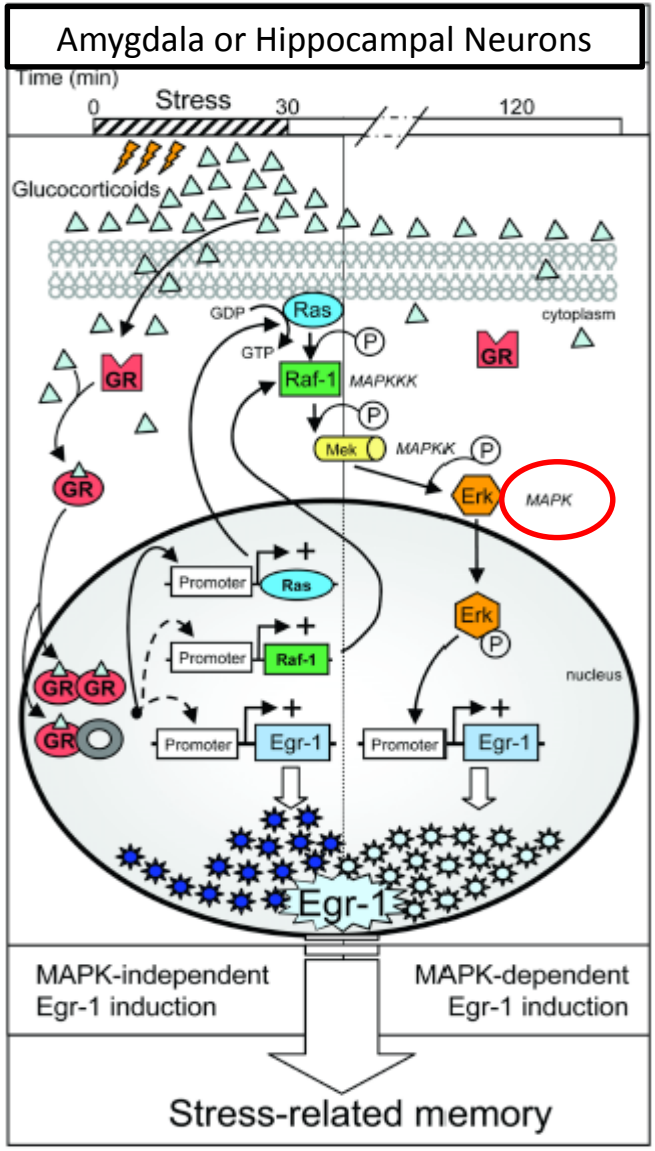


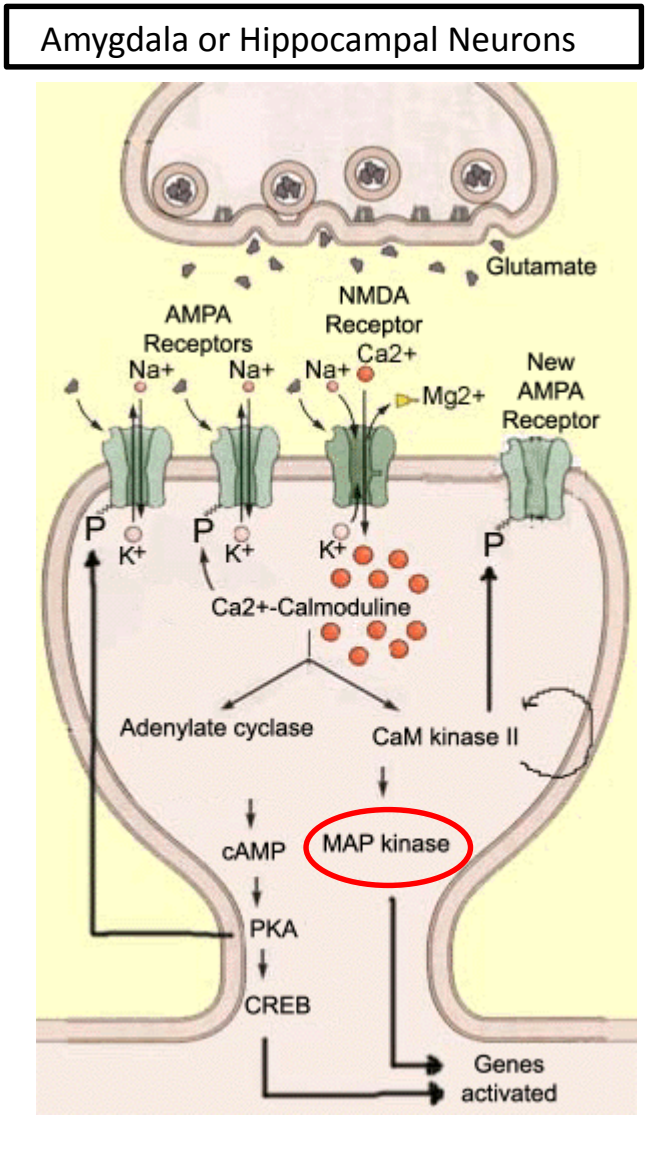




Zhou et al (2010) Neurobiol Learn Memory 94: 530

GR regulation of signalling pathways of LTP in amygdala and hippocampus



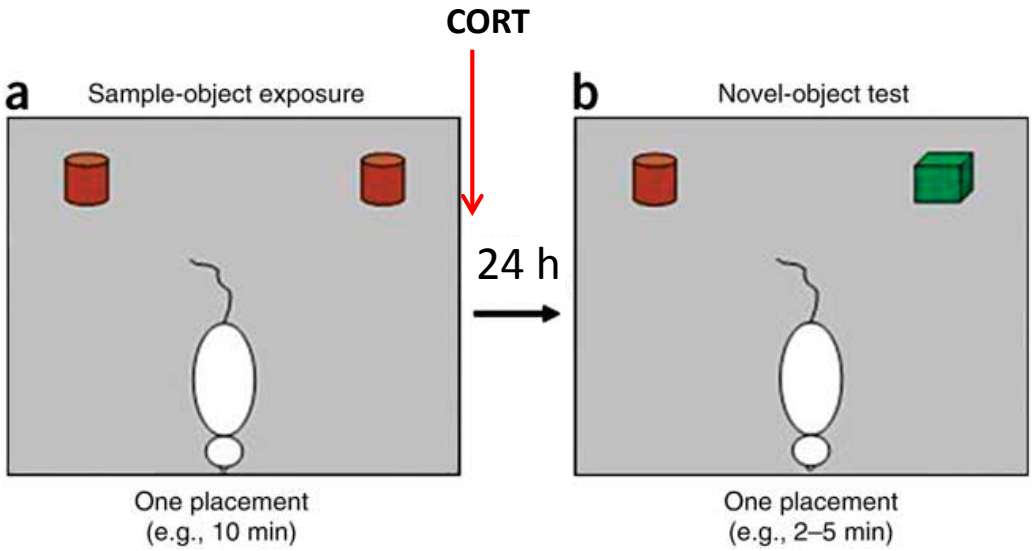


MAPK = Mitogen-activated protein kinase (synaptic plasticity, memory)
ERK = Extracellular-signal regulated kinase (synaptic plasticity, memory)
Egr1 = early growth response gene 1 (IEG, synaptic plasticity, memory)

Revest et al. (2005)
Nature Neuroscience 8: 664

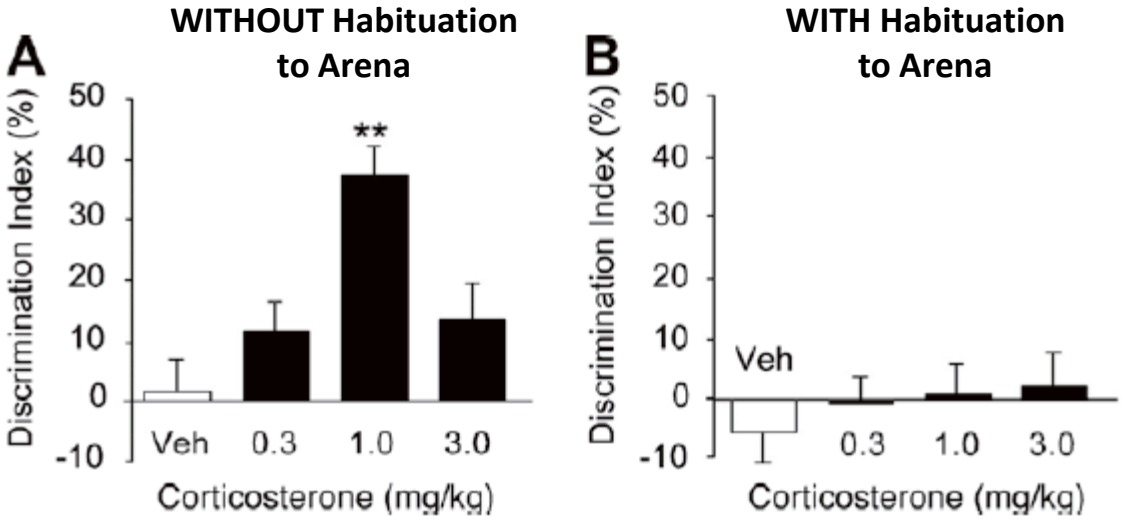
Enhancing effects of corticosterone on memory depend on emotional arousal

Corticosterone administered after Sample-object exposure



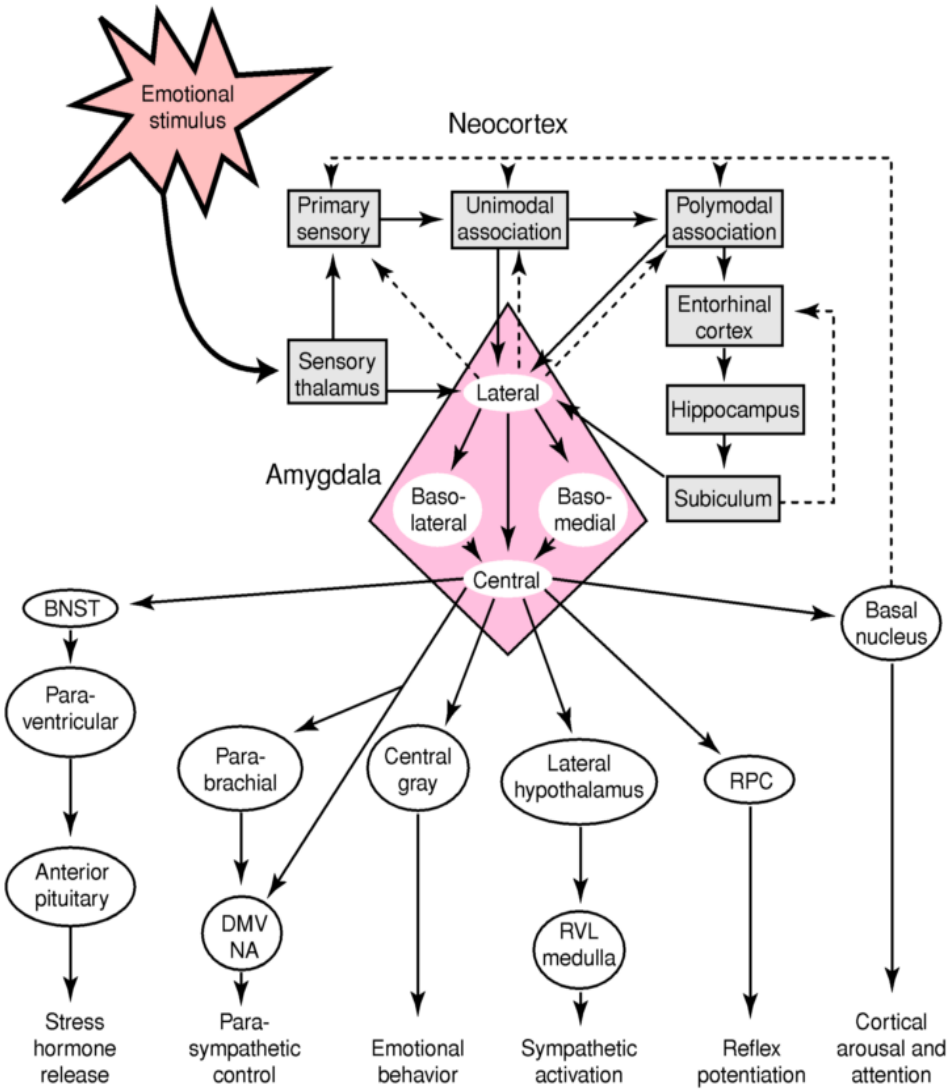
Exploration time:

$$\frac{\text{Novel object} - \text{Familiar object}}{\text{Both objects}}$$



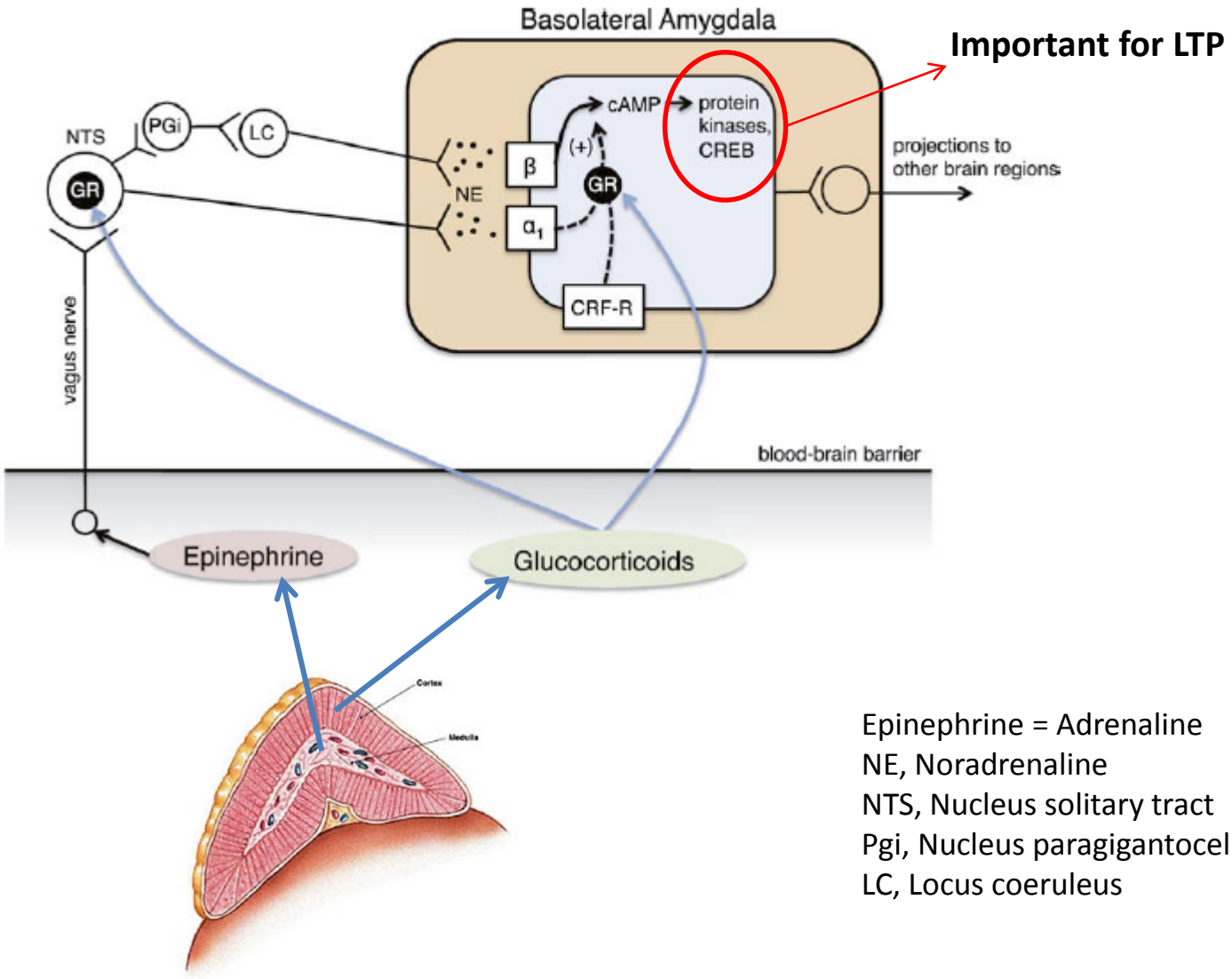
de Quervain et al (2009) Front Neuroendocrinology 30: 358

The HPA axis is a major Stress response system



Interactions of Corticosteroids and Noradrenaline in emotional memory

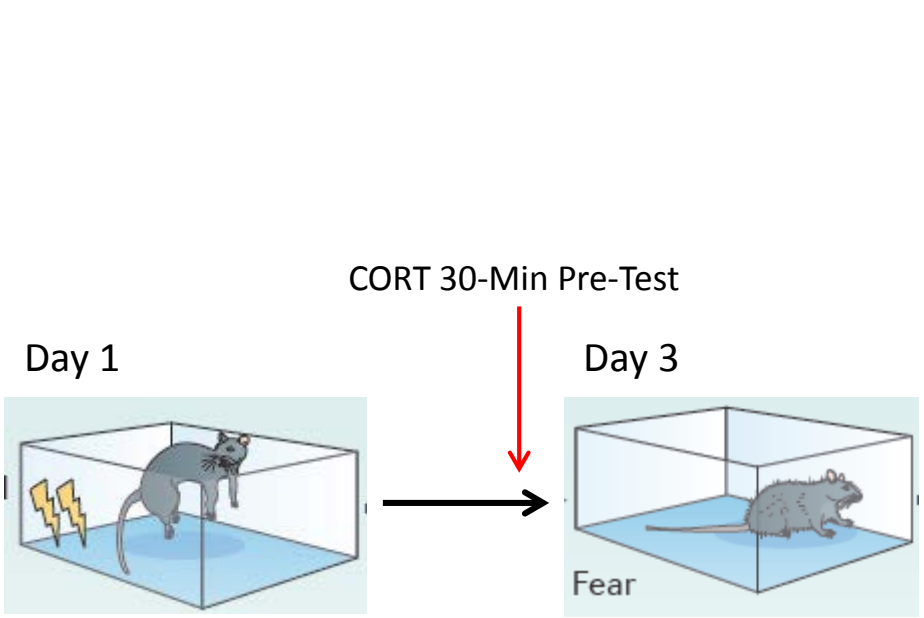
Coincident emotion-induced corticosteroid and noradrenaline signalling in basolateral amygdala

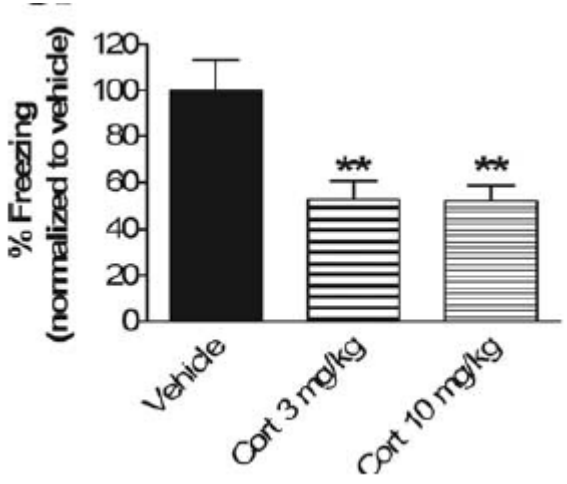


Epinephrine = Adrenaline
NE, Noradrenaline
NTS, Nucleus solitary tract
Pgi, Nucleus paragigantocellularis
LC, Locus coeruleus

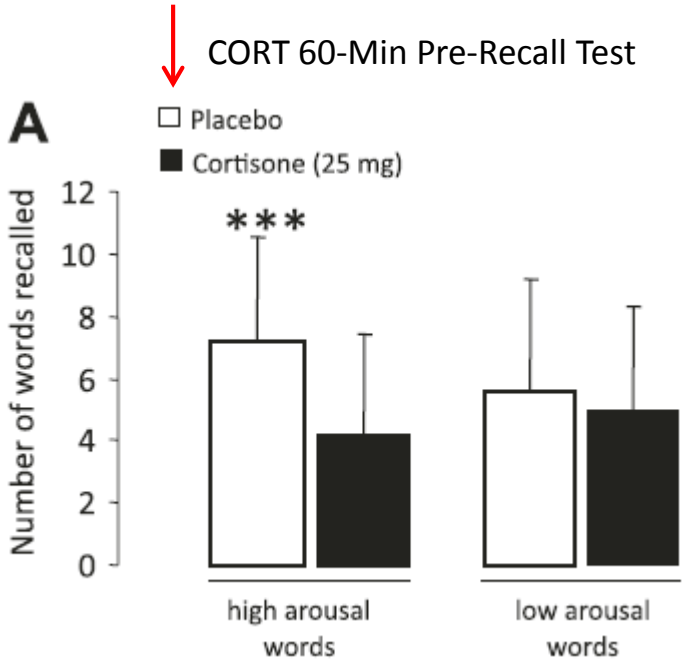
de Quervain et al (2009) Front Neuroendocrinology 30: 358

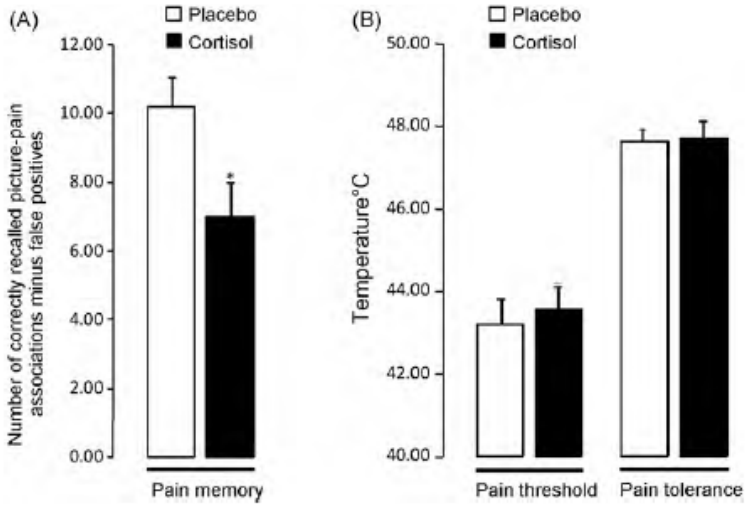
Rat and Human evidence that corticosteroids inhibit recall of emotional memory





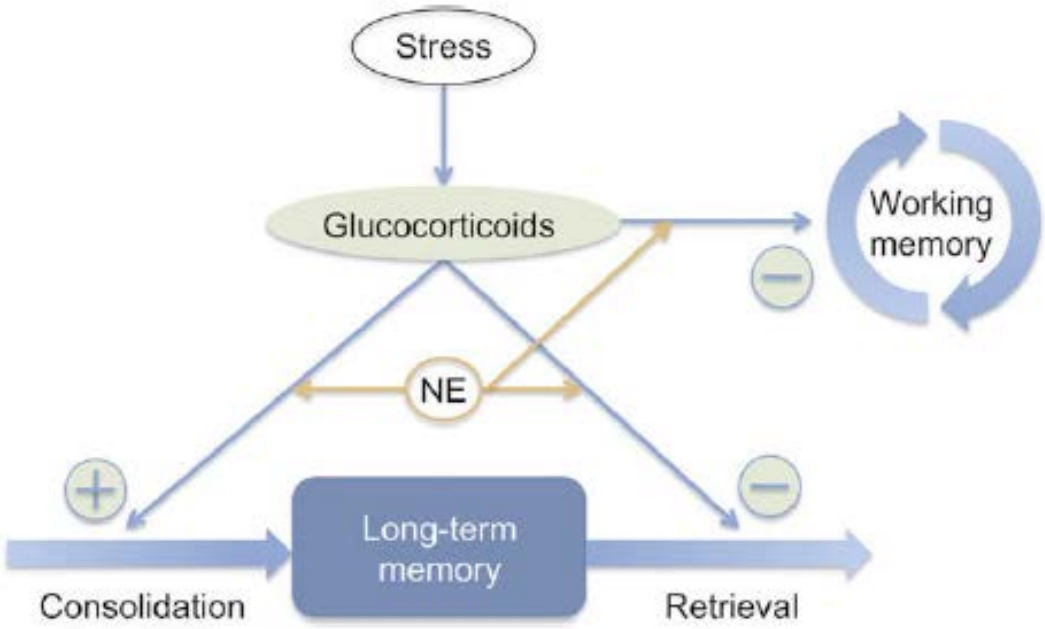
Cai et al (2006) J Neuroscience 26: 9560





de Quervain et al (2009) Front Neuroendocrinology 30: 358
Schwegler et al (2010) Psychoneuroendocrinology 35: 1270

Summary of effects of Stress/Corticosteroid on emotional memory



de Quervain et al (2009) Front Neuroendocrinology 30: 358

Stress, Learning and Memory

• One of the emotional/stress responses controlled by the amygdala is the hypothalamic-pituitary-adrenal (HPA) axis

• CRF (CRH) is a neurohormone and ACTH and cortisol/corticosterone are hormones

• Basal cortisol/corticosterone (CORT) has important metabolic functions

• Following amygdala signalling, the HPA axis is stimulated

• There are 2 types of CORT receptor, mineralocorticoid receptor (MR) and glucocorticoid receptor (GR)

• MR and GR are intracellular transcription factors ("slow effects") and membrane-bound receptors (probably G protein-coupled) ("fast effects")

• MR has higher affinity for CORT than does GR

• GR in pituitary gland and hypothalamic PVN mediate HPA axis negative feedback (return to homeostasis)

• In CNS, GR is widely distributed and MR is localized

• CORT-MR effects on emotional behaviour include: decreasing anxiety, supporting fear learning (but not consolidation)

• CORT-GR effects on emotional behaviour include: supporting long-term fear memory (but not learning or short-term memory), inhibiting memory recall

• The signalling pathways activated by GR are involved in LTP, indicating common points at which CORT-GR can regulate memory

• The CORT-GR emotional memory effect is dependent on simultaneous noradrenaline signalling in the basolateral amygdala. This applies to both increased long-term memory and decreased long-term recall