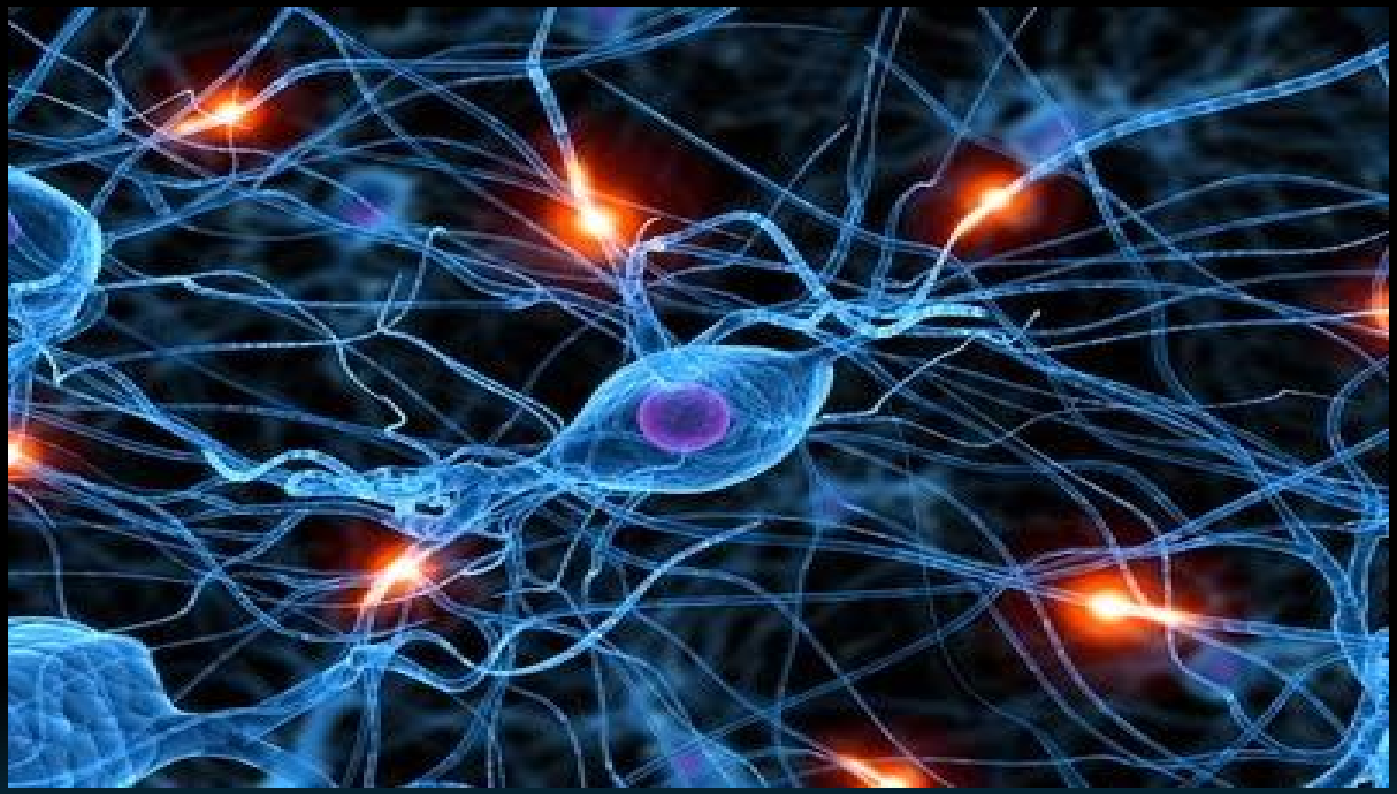
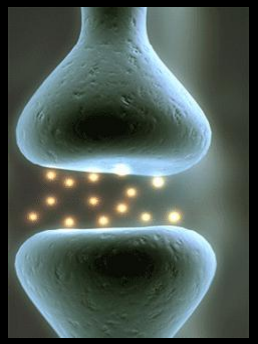
NEUROBIOLOGY OF DEPRESSION



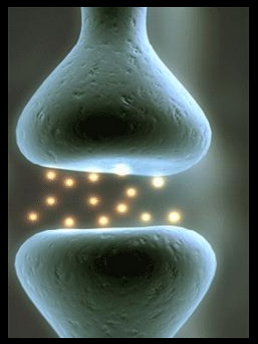
INTRODUCTION



- Many studies have reported biological abnormalities in patients with mood disorders.

- Until recently, the monoamine neurotransmitters- norepinephrine, dopamine, serotonin, and histamine were the main focus of theories and research

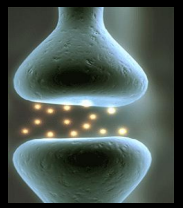
INTRODUCTION



- Methods to study these processes have been available since the 1960s.

- Of the biogenic amines, norepinephrine and serotonin are the two neurotransmitters most implicated ones.

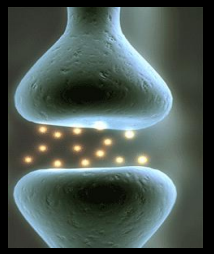
GENETIC INFLUENCES



It is now well established that bipolar affective disorder is more heritable than other mood disorders

First-degree relatives, in turn, have greater shared risk than half-siblings, grandparents, or cousins.

GENETIC INFLUENCES



It is clear that a number of alleles are associated with an increased risk of depression.

Among the several implicated alleles is the gene that codes for the promoter region of the serotonin transporter (5-HTT), which has been found to moderate the association between stressful life events and the risk of depression.

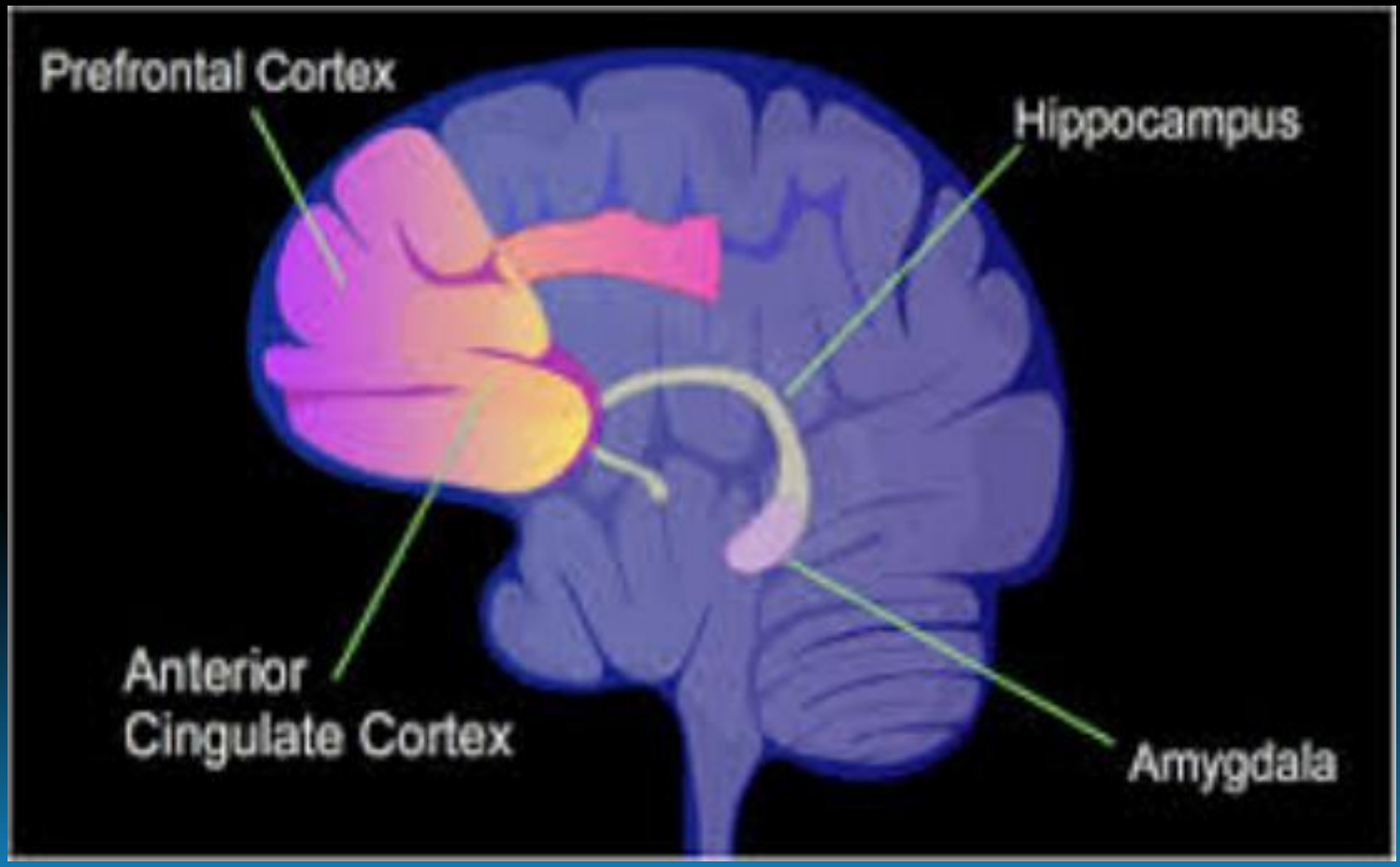
EMOTIONAL PROCESSING AND THE BRAIN

EMOTIONAL PROCESSING AND THE BRAIN

- Modern affective neuroscience focuses on the importance of four brain regions in the regulation of normal emotions:

1. The PFC
2. The anterior cingulate cortex (ACC)
3. The hippocampus
4. The amygdala

EMOTIONAL PROCESSING AND THE BRAIN



EMOTIONAL PROCESSING AND THE BRAIN

1. PFC- The structure holds representations of goals and appropriate responses to obtain these goals.

2. ACC-serve as the point of integration of attentional and emotional inputs. Its activation facilitates effortful control of emotional arousal.

EMOTIONAL PROCESSING AND THE BRAIN

4.Hippocampus- Involved in learning and memory and inhibitory regulation of HPA Axis.

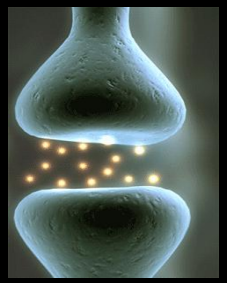
5. Amygdala- appears to be a crucial way station for processing novel stimuli of emotional significance and coordinating cortical responses.

EMOTIONAL PROCESSING AND THE BRAIN

- So, the neurocognitive changes point to dysfunction involving the hippocampus, prefrontal cortex (PFC), and other limbic structures.

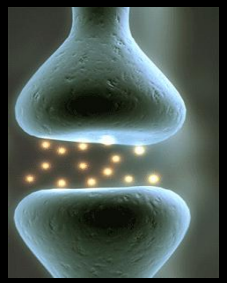
- And anhedonia, decreased psychomotor activities, and disturbed circadian rhythm occurs in depression related to dysfunction of these brain structures.

EARLY ADVERSE LIFE EVENTS



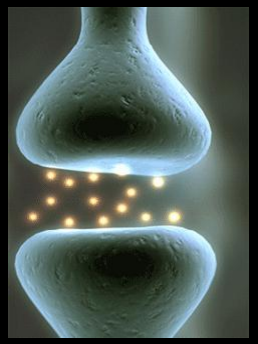
Physical, verbal, and sexual abuse and parental neglect have an indelible effect on one's life.

EARLY ADVERSE LIFE EVENTS



It has been recently shown that such a history results in a two- to threefold increase in risk of depression and is associated with important biological differences in depressive states.

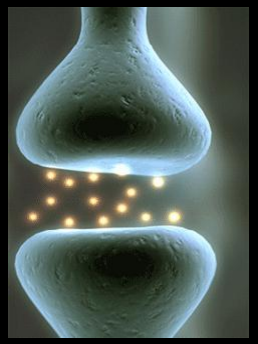
MONOAMINES SYSTEM



- In the early 1960s, Nobel prize-winning research had just elucidated the importance of monoamines in neurotransmission.

- Moreover, it was possible to measure the metabolites of the catecholamine NE in various body fluids and 5-HIAA, the principal metabolite of 5-HT, in cerebrospinal fluid (CSF).

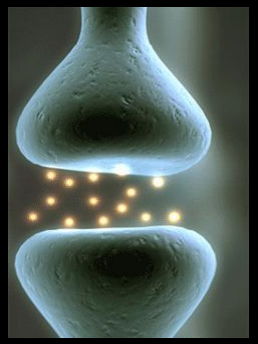
MONOAMINES SYSTEM



- The early monoamine hypotheses formulated by Joseph J. Schildkraut, Alexander H. Glassman, Arthur J. Prange, Jr., John Davis, Herman van Praag, Jonathan Cole, and others have undergone much revision.

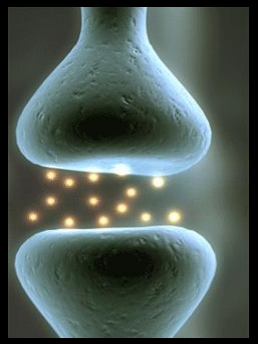
- The monoaminergic systems are thus now viewed primarily as broader, neuromodulatory systems

NORADRENERGIC SYSTEMS



- The correlation suggested by basic science studies between the decreased sensitivity of beta-adrenergic receptors and clinical antidepressant responses
- It is probably the single most compelling piece of data indicating a direct role for the noradrenergic system in depression

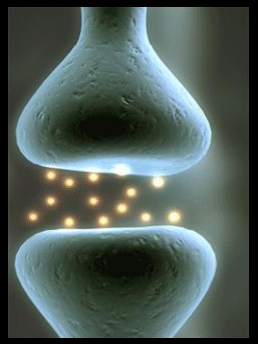
NORADRENERGIC SYSTEMS



- The cell bodies of almost all noradrenergic neurons in the brain are located in the locus ceruleus of the brainstem.

- Noradrenergic projections to the amygdala and hippocampus are implicated in emotional memory and behavioral sensitization to stress

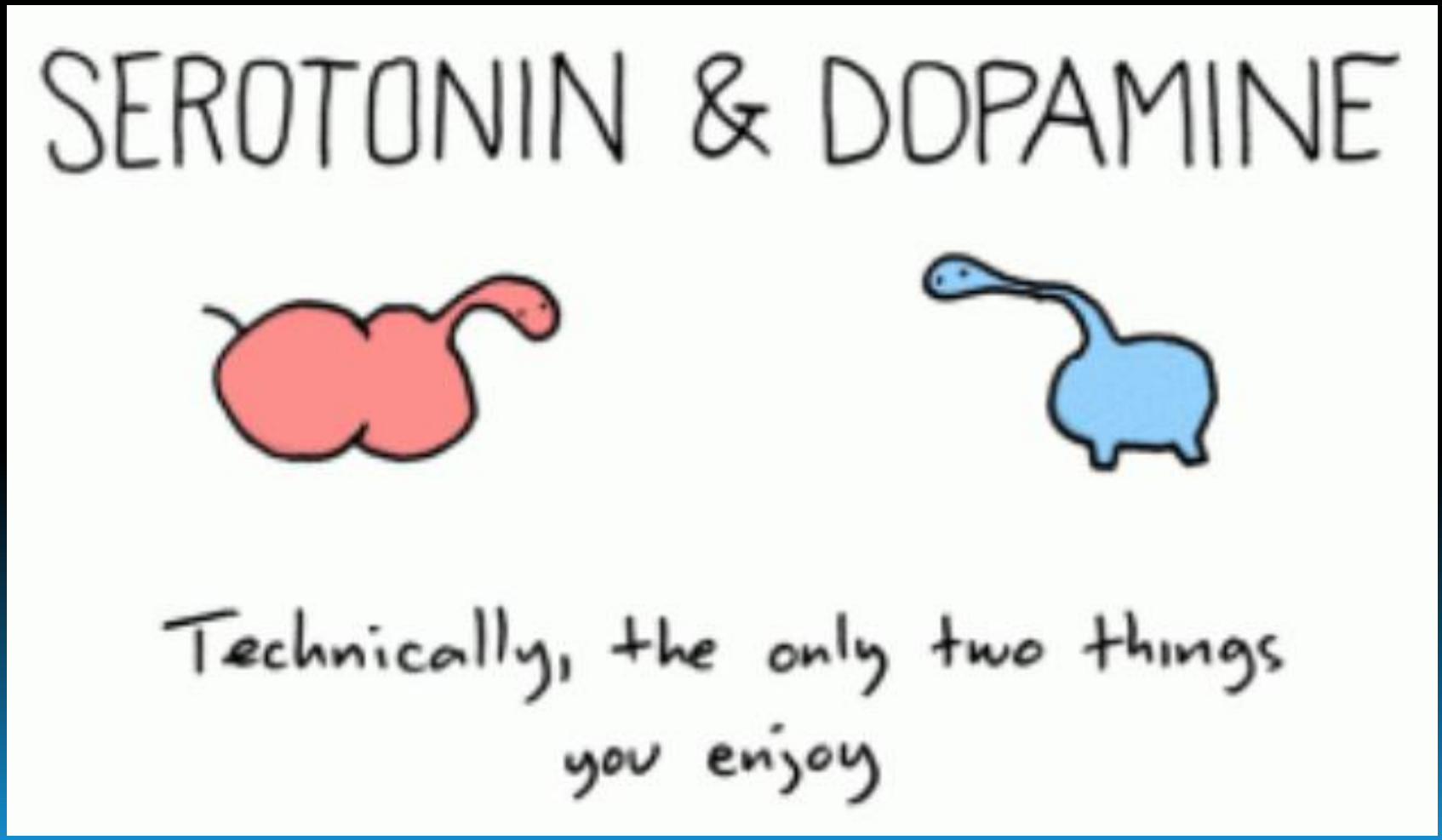
NORADRENERGIC SYSTEMS



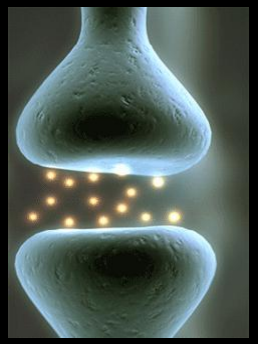
- The medial forebrain bundle (MFB) is the key ascending NE pathway to anterior cortical structures

- Sustained stress eventually results in decreased MFB neurotransmission, which may account for anergia, anhedonia, and diminished libido in depression.

SEROTONERGIC AND DOPAMINERGIC SYSTEMS



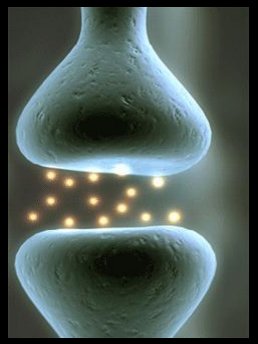
SEROTONERGIC SYSTEMS



- Serotoninergic neurons project from the brainstem dorsal raphe nuclei to the cerebral cortex, hypothalamus, thalamus, basal ganglia, septum, and hippocampus.

- The 5-HT pathways have inhibitory and facilitatory functions in the brain

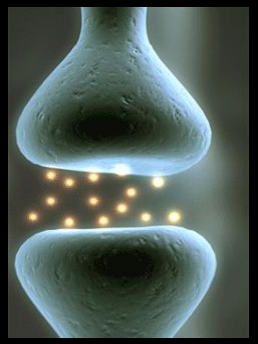
SEROTONERGIC SYSTEMS



- Much evidence suggests that 5-HT is an important regulator of sleep, appetite, body temperature, metabolism, and libido.

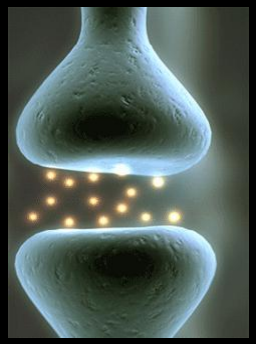
- Specifically, acute stress increases 5-HT release transiently, whereas chronic stress eventually causes decreased 5-HT activity and depletion of 5-HT stores.

SEROTONERGIC SYSTEMS



- With the huge effect that SSRIs for example, fluoxetine have made on the treatment of depression, serotonin has become the biogenic amine neurotransmitter most commonly associated with depression.

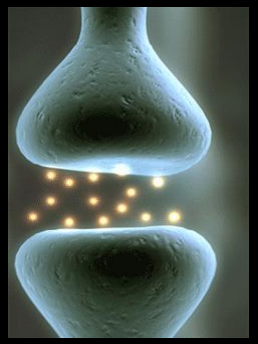
DOPAMINERGIC SYSTEMS-



- There are four relatively discrete DA pathways in the brain-

1. Tuberoinfundibular- inhibitory effect over prolactin
2. Nigrostraitial- involuntary motor activity
3. Mesolimbic- emotional expression, learning and hedonic capacity
4. Mesocortical- motivation, concentration, initiation of goal directed tasks.

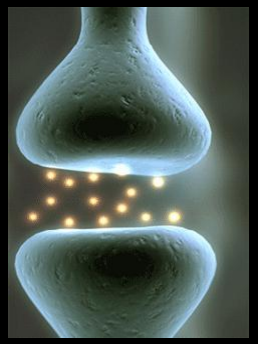
DOPAMINERGIC SYSTEMS-



- Decreased mesocortical and mesolimbic DA activity has obvious implications in the cognitive, motor, and hedonic disturbances associated with depression.

- The data suggest that dopamine activity may be reduced in depression and increased in mania.

DOPAMINERGIC SYSTEMS-



- Drugs that reduce dopamine concentration for example, reserpine and diseases that reduce dopamine concentrations (e.g., Parkinson's disease) are associated with depressive symptoms.

- In contrast, drugs that increase dopamine concentrations, such as tyrosine, amphetamine, and bupropion, reduce the symptoms of depression.

OTHER NEUROTRANSMITTER DISTURBANCES

- Acetylcholine (ACh) is found in neurons that are distributed diffusely throughout the cerebral cortex.
- Abnormal levels of choline, which is a precursor to ACh, have been found at autopsy in the brains of some depressed patients.

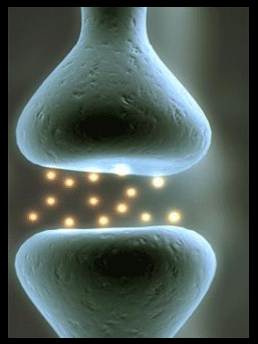
OTHER NEUROTRANSMITTER DISTURBANCES

- GABA has an inhibitory effect on ascending monoamine pathways, particularly the mesocortical and mesolimbic systems.
- Reductions of GABA have been observed in plasma, CSF, and brain GABA levels in depression.

OTHER NEUROTRANSMITTER DISTURBANCES

- The amino acids glutamate and glycine are the major excitatory and inhibitory neurotransmitters in the CNS.
- Emerging evidence suggests that drugs that antagonize NMDA receptors have antidepressant effects.

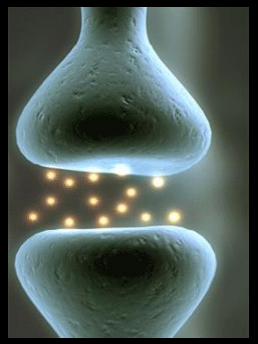
SECOND MESSENGERS AND INTRACELLULAR CASCADES



- The binding of a neurotransmitter and a postsynaptic receptor triggers a cascade of membrane-bound and intracellular processes mediated by second messenger systems.

- Receptors on cell membranes interact with the intracellular environment via guanine nucleotide-binding proteins (G proteins)

SECOND MESSENGERS AND INTRACELLULAR CASCADES

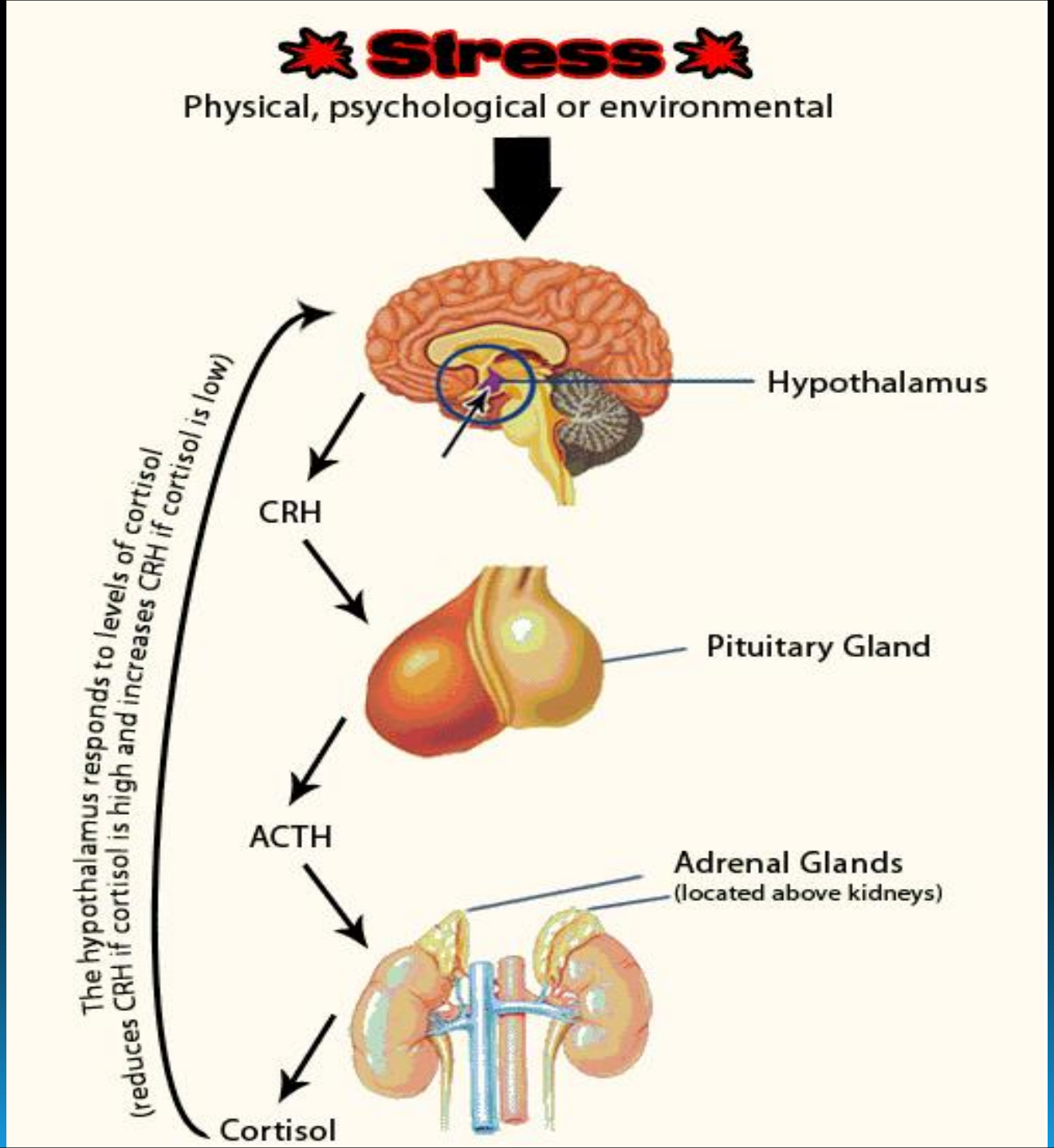


- The G proteins, in turn, connect to various intracellular enzymes that regulate utilization of energy and formation of second messengers.
- Some studies have reported abnormalities in platelet adenylate cyclase activity, phosphoinositide hydrolysis, intracellular calcium metabolism, and G-protein function in depressive disorders.
- Increasing evidence also indicates that mood-stabilizing drugs act on G proteins or other second messengers.

ALTERATIONS OF HORMONAL REGULATION

HPA ACTIVITY-

- Stress simultaneously triggers and releases CRH from neurons in the hypothalamus and cerebral cortex. Hypothalamic CRH activates synthesis and release of ACTH from the anterior pituitary, which, in turn, triggers release of cortisol and other glucocorticoids (from the adrenal cortex.


Stress
Physical, psychological or environmental
Hypothalamus
CRH
Pituitary Gland
ACTH
Adrenal Glands
(located above kidneys)
Cortisol
The hypothalamus responds to levels of cortisol
(reduces CRH if cortisol is high and increases CRH if cortisol is low)

ALTERATIONS OF HORMONAL REGULATION

- Elevated HPA activity is a hallmark of mammalian stress responses and one of the clearest links between depression and the biology of chronic stress.
- Evidence of increased HPA activity is apparent in 20 to 40 percent of depressed outpatients and 40 to 60 percent of depressed inpatients.

ALTERATIONS OF HORMONAL REGULATION

- Elevated HPA activity in depression has been documented via excretion of urinary free cortisol (UFC), 24-hour (or shorter time segments) intravenous (IV) collections of plasma cortisol levels, salivary cortisol levels.

ALTERATIONS OF HORMONAL REGULATION

- A disturbance of feedback inhibition in depressed patients is tested by administration of dexamethasone (.5 to 2.0 mg), which normally suppresses HPA axis activity for 24 hours.

- Nonsuppression of cortisol secretion is indicative of impaired feedback inhibition.

ALTERATIONS OF HORMONAL REGULATION

THYROID AXIS ACTIVITY-

- Approximately 5 to 10 percent of people evaluated for depression have previously undetected hypothyroidism.
- To date, the major therapeutic implication of a blunted TSH response is evidence of an increased risk of relapse despite preventive antidepressant therapy.

ALTERATIONS OF HORMONAL REGULATION

- It is reflected by low levels of circulating thyroid hormone, an elevated basal thyroid-stimulating hormone (TSH) level, or an increased TSH response to a 500-mg infusion of the thyroid-releasing hormone (TRH).

ALTERATIONS OF HORMONAL REGULATION

GROWTH HORMONE-

- Growth hormone (GH) is secreted from the anterior pituitary after stimulation by NE and Dopamine (DA).
- Secretion is inhibited by somatostatin and CRH. Decreased CSF somatostatin levels have been reported in depression, and increased levels have been observed in mania.

ALTERATIONS OF HORMONAL REGULATION

PROLACTIN HORMONE-

- Prolactin is released from the pituitary by serotonin stimulation and inhibited by DA.
- Most studies have not found significant abnormalities of basal prolactin secretion in depression.

ALTERATIONS OF SLEEP NEUROPHYSI

An 8-hour night of sleep thus typically includes four or five cycles consisting of non-rapid eye movement (NREM) sleep and REM sleep

Depression is associated with a premature loss of deep (slow wave) sleep and an increase in nocturnal arousal.

ALTERATIONS OF SLEEP NEUROPHYSI

It is reflected by four types of disturbance:

(1) an increase in nocturnal awakenings

(2) a reduction in total sleep time

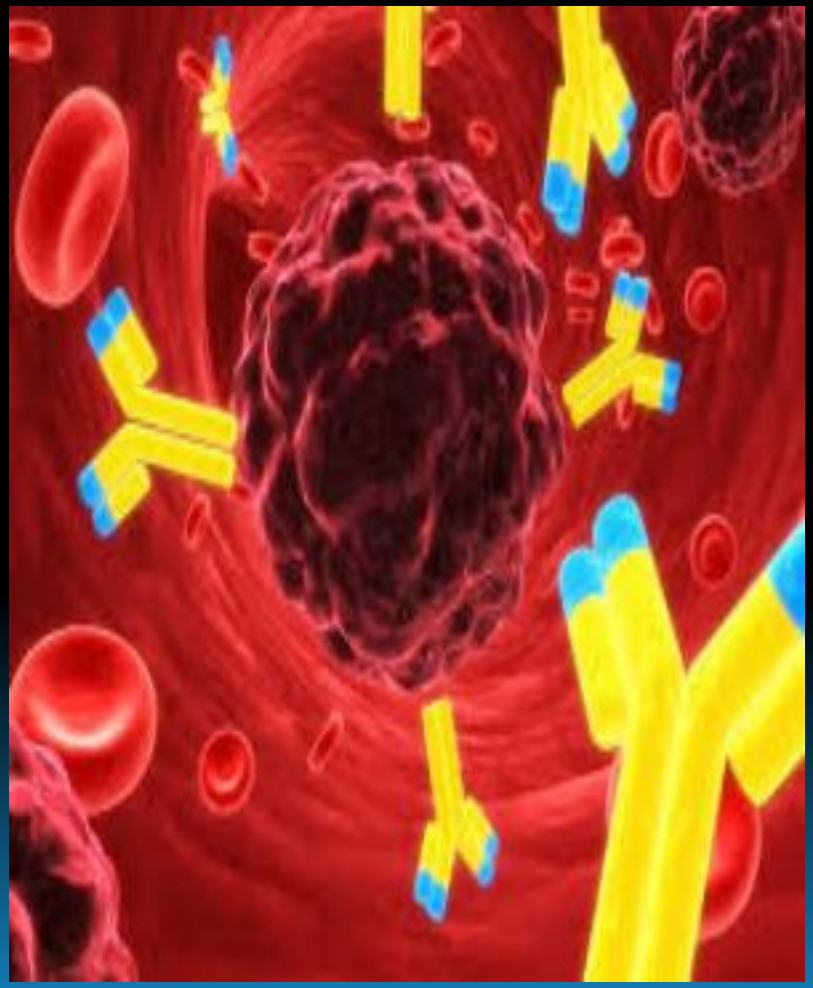
(3) increased phasic REM sleep

(4) increased core body temperature

IMMUNOLOGICAL DISTURBANCES

Depressive disorders are associated with several immunological abnormalities.

Including decreased lymphocyte proliferation in response to impaired cellular immunity. These lymphocytes produce corticotropin-releasing factor (CRF), and cytokines, peptides known as interleukins



IMMUNOLOGICAL DISTURBANCES

There appears to be an association with clinical severity, hypercortisolism, and immune dysfunction, and the cytokine interleukin-1 may induce gene activity for glucocorticoid synthesis.

THANK YOU !