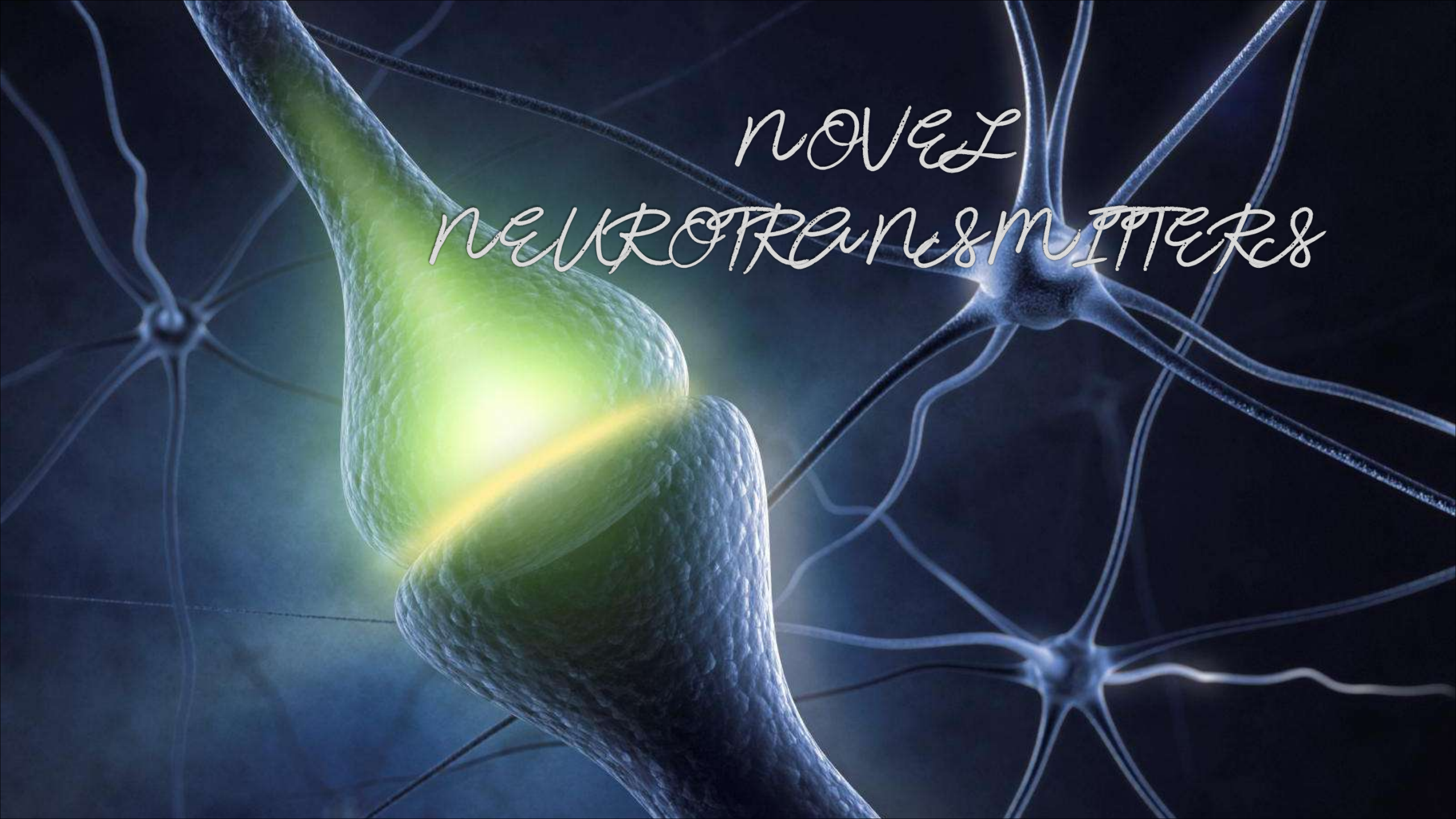

NOVEL
NEUROTRANSMITTERS

Overview

- Introduction
- Types
- Structural and Functional Considerations
- Novel Neurotransmitters
- Summary
- References

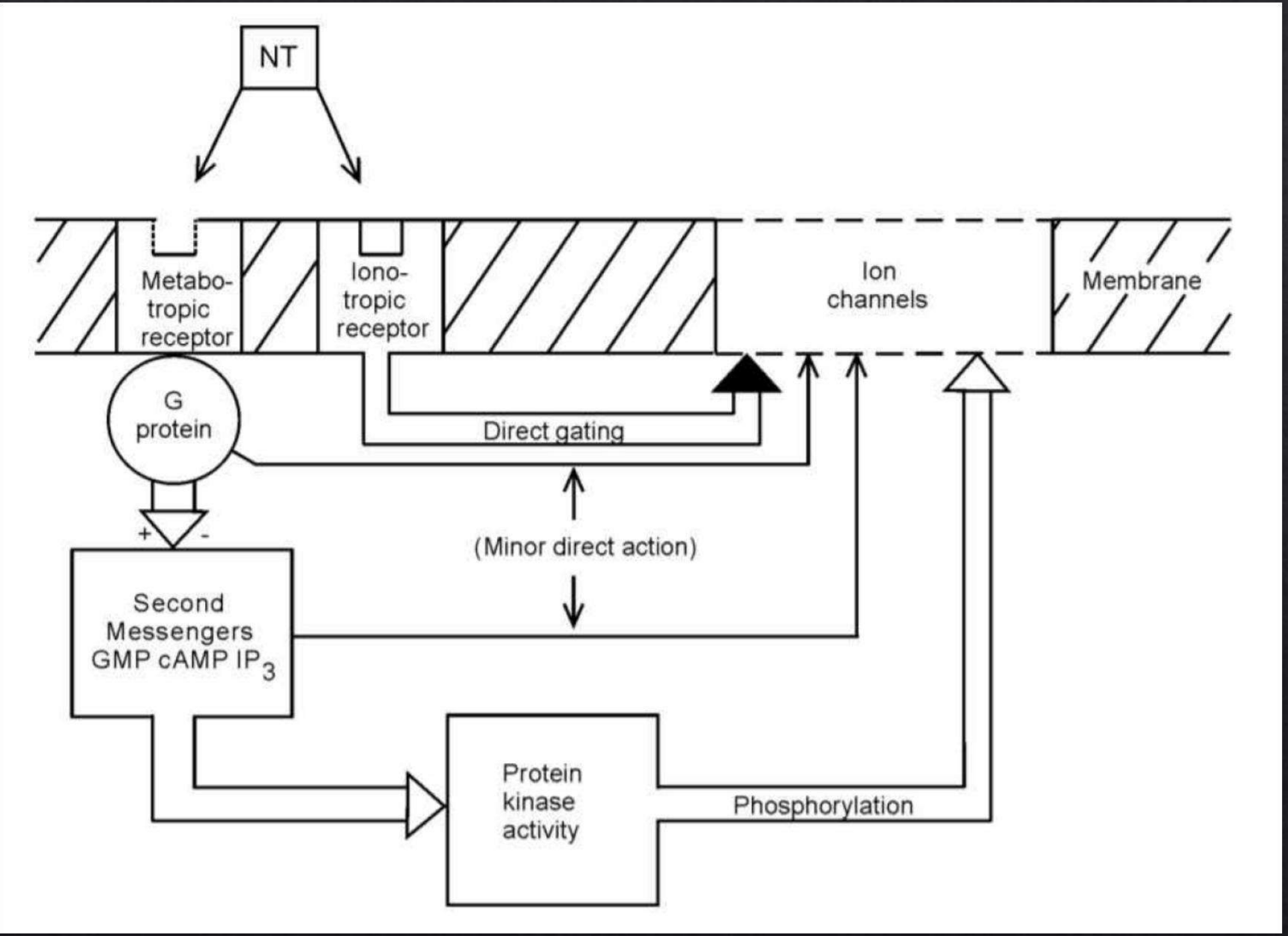
- A neurotransmitter is typically released from a presynaptic neuron and travels across a small space the synaptic cleft or synapse to act upon the postsynaptic neuron

- Neurotransmitter receptors are themselves ion channels may elicit depolarization via the neurons they conduct typically depolarization via sodium or calcium and hyperpolarization via chloride

- In metabotropic receptors that produce second messengers that may have complex effects upon target cells such as altering gene expression

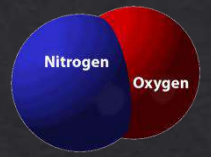
- The action potential opens voltage sensitive calcium channels in the membrane allowing for an increase in cellular calcium that results in vesicles releasing their contents into the synaptic cleft and acting upon receptors on the postsynaptic neuron membrane

CLASSICAL NEUROTRANSMISSION



TYPES

1. Gases
    1. Nitric Oxide
    2. Carbon Monoxide
    3. Hydrogen Sulphide
2. Endocannabinoids
3. Eicosanoids
4. Neurosteroids



Nitric Oxide

- In the early 1990s nitric oxide was the first gas to be a neurotransmitter function and proved to be an atypical neurotransmitter for several reasons

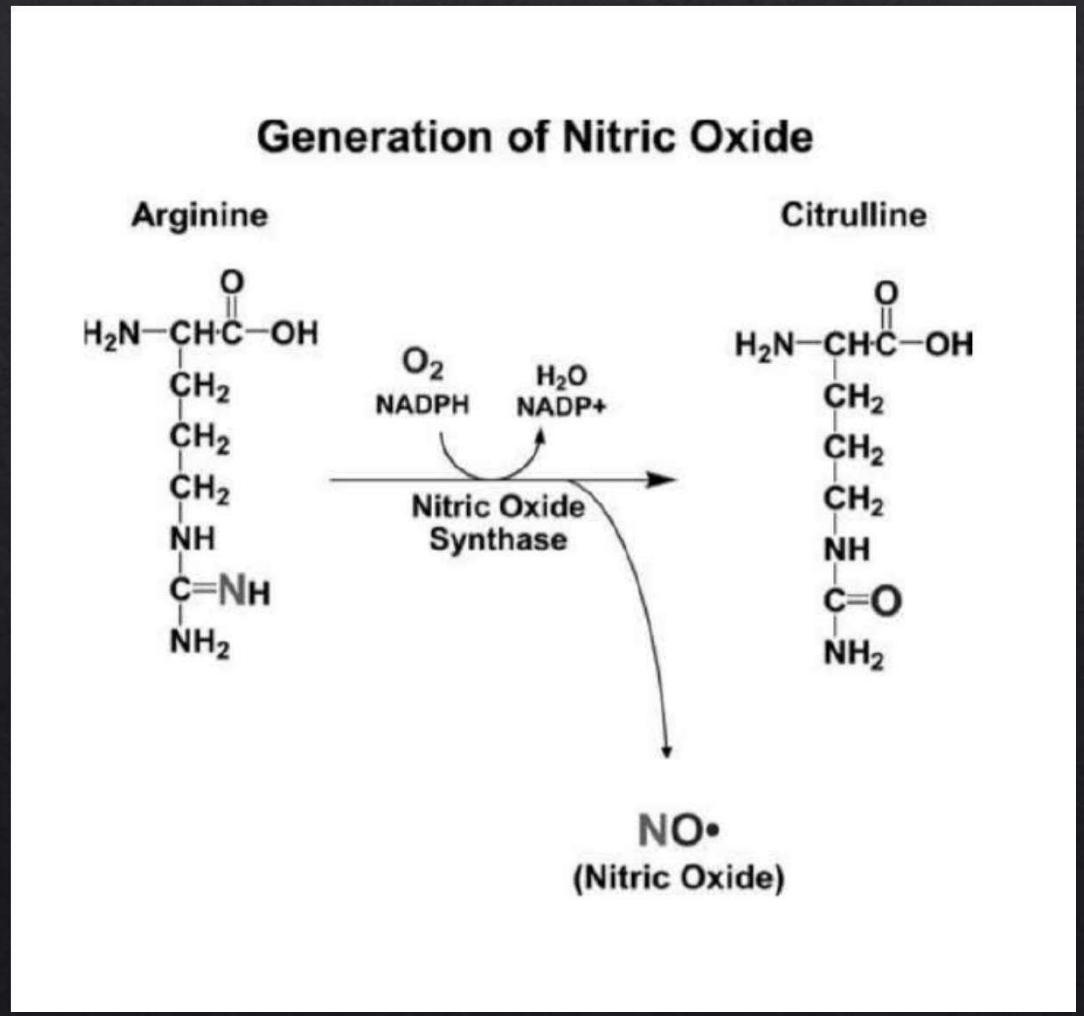
- Not stored in or released from vesicles Diffuses into target neuron

- Target is not a receptor on surface Intracellular protein

- No reuptake mechanism

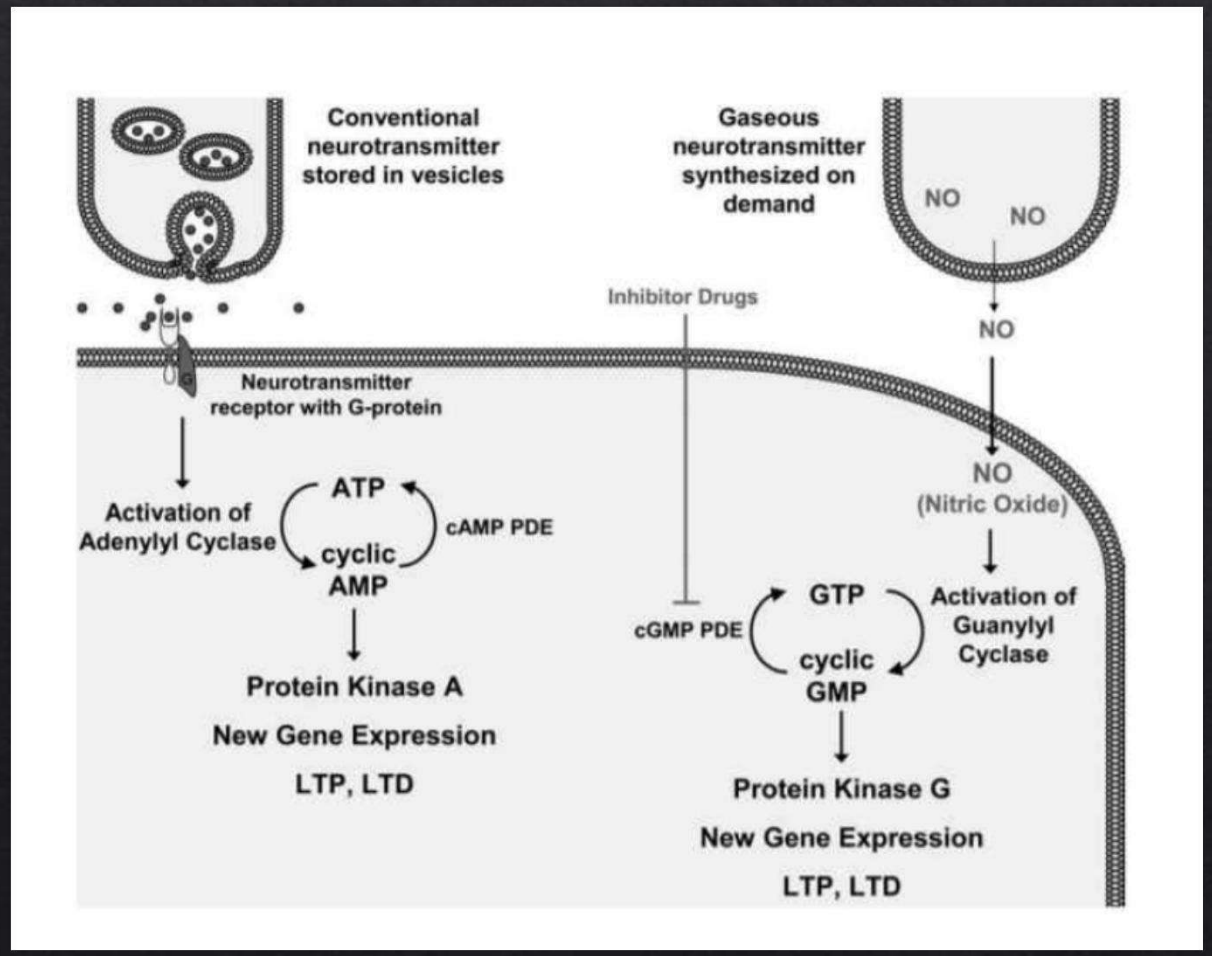
- short half life enzymatic degradation

SYNTHESIS OF NO



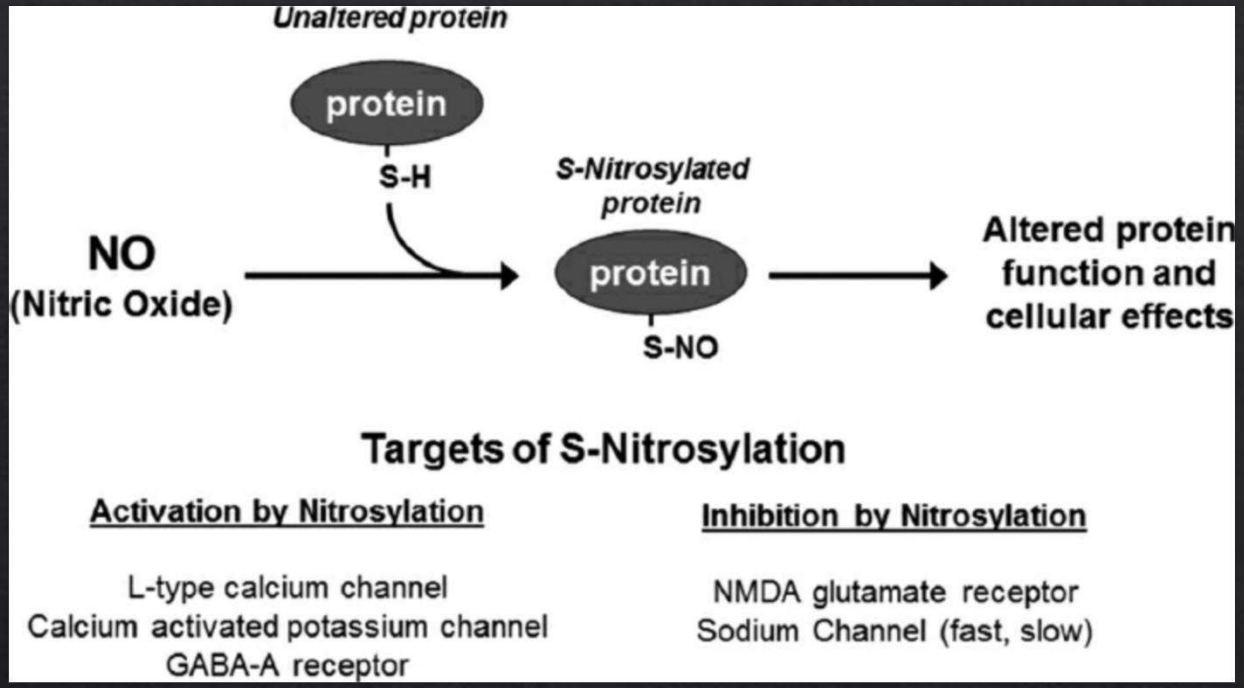
- Specific enzyme exists to generate nitric oxide within cells nitric oxide synthase NOS
- Three distinct enzymatic forms of NOS exist
  - Neuronal nitric oxide synthase nNOS
  - Endothelial NOS eNOS
  - inducible NOS iNOS

Mechanism of Action of Nitric Oxide



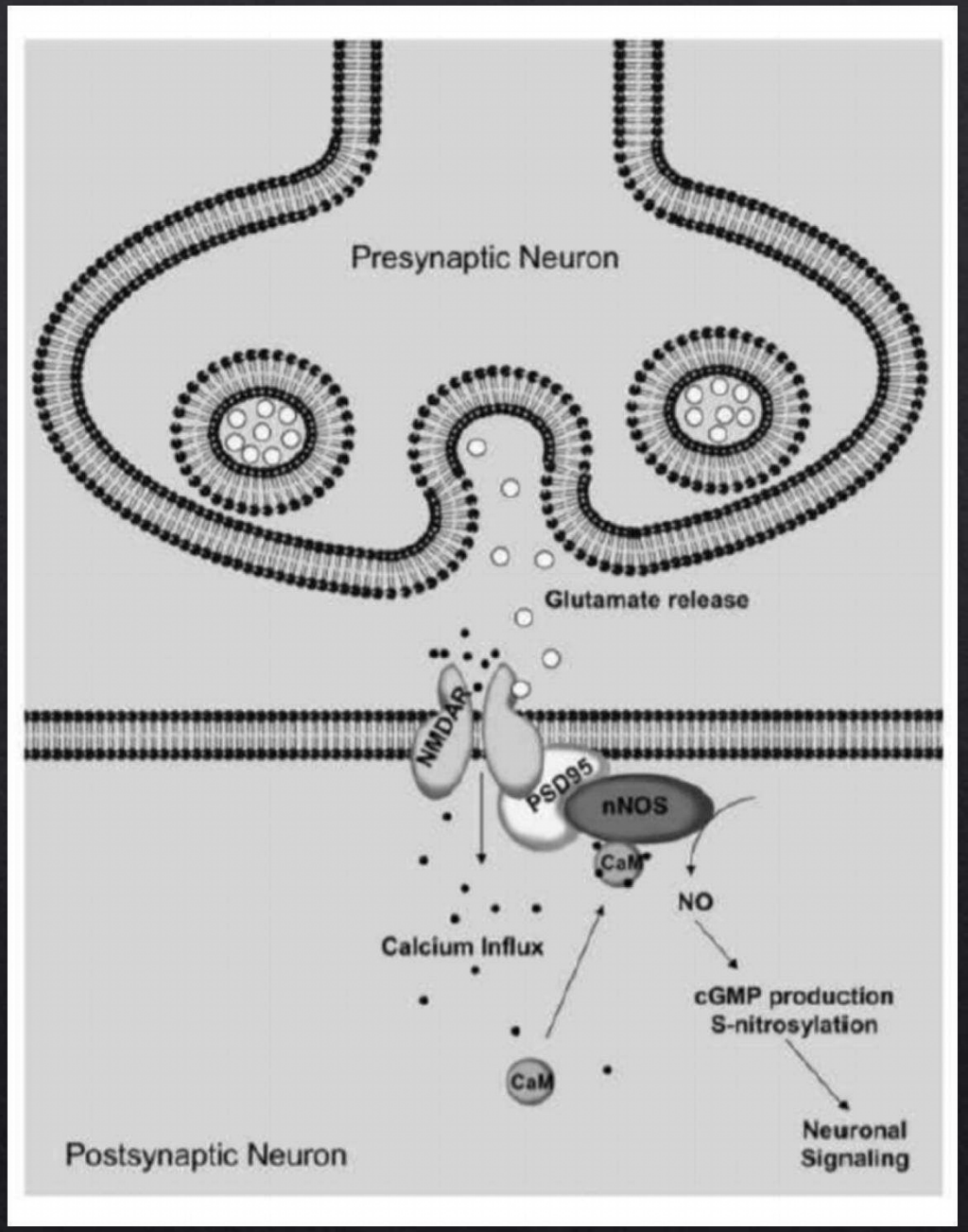
- Cyclic GMP Pathway

- Cyclic guanosine monophosphate cGMP is a prototypic intracellular messenger whose synthesis by guanylyl cyclase
- nitric oxide directly activates soluble guanylyl cyclase
- guanylyl cyclase contains a heme group cofactor whose iron atom is bound by nitric oxide



S Nitrosylation Pathway

- nitric oxide directly modifies the sulpfur atom of a protein cysteine residue forming S nitrosothiol group
- modification requires no enzyme
- Proteins that have been nitrosylated vary in their response
- S nitrosylation as a means of signal transduction is analogous to protein phosphorylation


Presynaptic Neuron
Glutamate release
NMDAR
PSD95
nNOS
CaM
NO
Calcium Influx
cGMP production
S-nitrosylation
CaM
Neuronal
Signaling
Postsynaptic Neuron

Nitric Oxide and Behaviour

- nNOS deficient male mice aggressive tendencies increased sexual activity In female mice the contrary is true

- Sleep wake cycle
  - nNOS expressing neurons occur in several areas that initiate REM sleep
  - NO releasing subs decrease wakefulness increase slow wave sleep
  - NOS inhibitors decrease slow and deep wave sleep

Nitric Oxide and mood disorder

- NOS expressing neurons Areas implicated in depression DRN PFC
- SSRI Inhibit NOS activity Antidepressant Response
- Soluble guanylyl cyclase inhibitors can achieve antidepressant like effects
- Plasma NO in Bipolar Control
- Depression low plasma NO high nitrite by product of NO
- Serotonin promotes neurogenesis in hippocampus nitric oxide inhibits neurogenesis
- Smaller hippocampal volume may be a risk factor for mood and anxiety disorders

Nitric Oxide and Schizophrenia

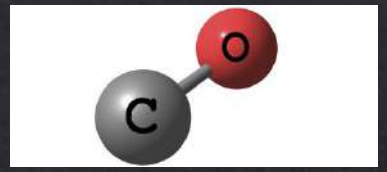
- Two genetic studies have identified schizophrenia associated single nucleotide polymorphisms SNPs in CAPON a protein that associates with nNOS

- Autopsy studies NOS changes
  - Found to have abnormally localized NOS expressing neurons in the prefrontal cortex hippocampus and lateral temporal lobe

- Elevated NOS activity in platelet

Neuropathological role of Nitric Oxide

- Combines with superoxide to cause toxic damage to cells *protein nitration*
- Involved in cell loss resulting from ischemic stroke
  - overstimulation of the glutamate NMDA receptor a process termed *excitotoxicity*
- Overabundance of NO signalling predispose to the dysfunction and cell death of dopaminergic neurons in Parkinson disease
- Alzheimer and Parkinson disease brains PDI protective cellular protein appears *S nitrosylated*



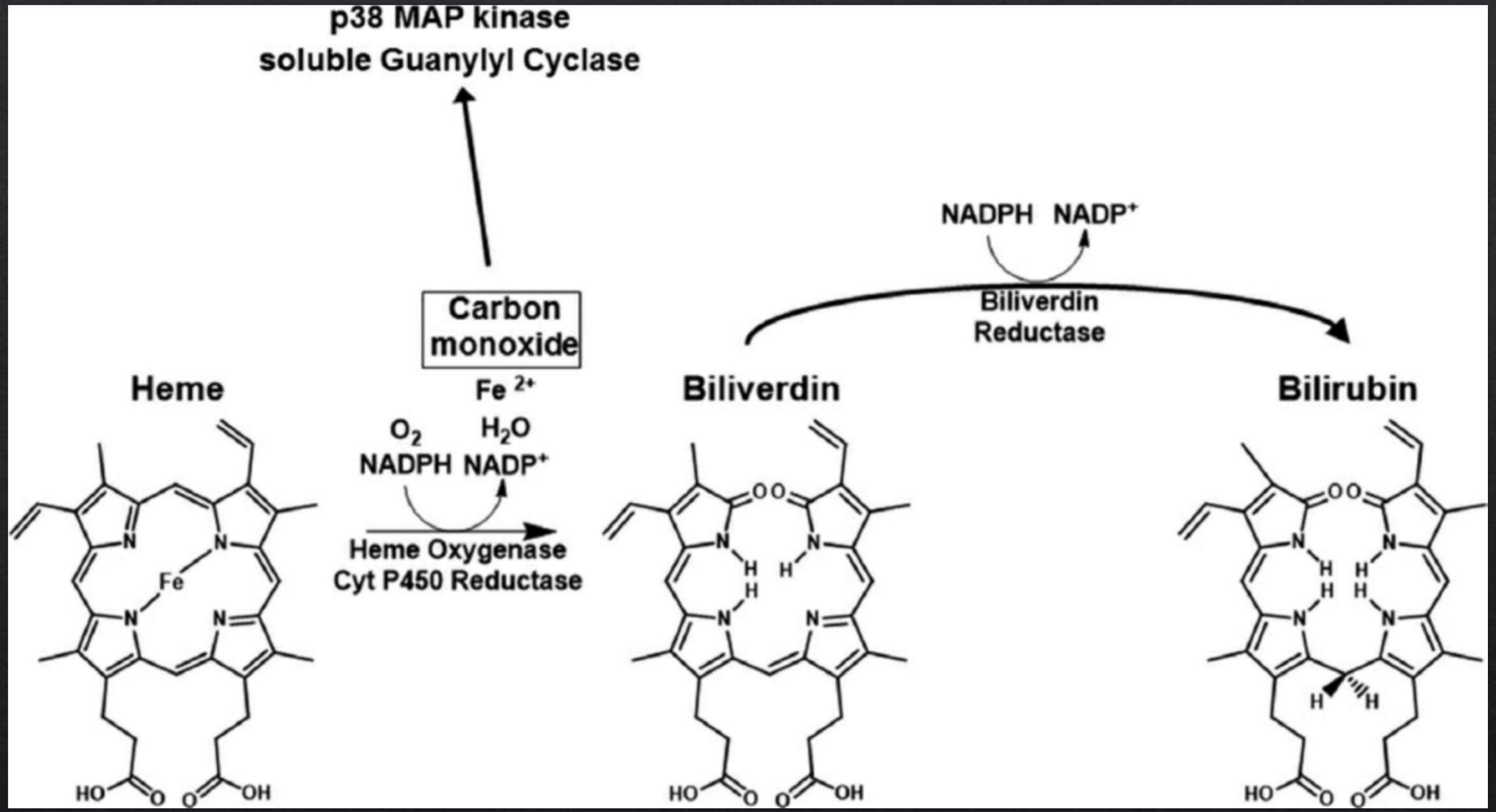
Carbon Monoxide

- Far better known for its toxic effects than its activities at physiologic concentrations
- Carbon monoxide CO is increasingly recognized to play an important role in regulating a variety of physiological processes
  - regulation of olfactory Neurotransmission
  - blood vessel relaxation
  - smooth muscle cell proliferation
  - platelet aggregation

Enzymatic Generation of Carbon Monoxide

- Carbon monoxide produced by heme oxygenase HO
- Three forms of HO exist
  1. HO1
  2. HO2
  3. HO3

- HO2 expressed in discrete neuronal populations throughout the brain including cortical and hippocampal pyramidal cells dentate gyrus granule cells the olfactory bulb thalamus hypothalamus brainstem and cerebellum


p38 MAP kinase
soluble Guanylyl Cyclase
Carbon monoxide
Fe 2+
Heme
O2
H2O
NADPH NADP+
Heme Oxygenase
Cyt P450 Reductase
NADPH NADP+
Biliverdin Reductase
Biliverdin
Bilirubin
Fe
HO
OH

Carbon Monoxide and Neurotransmission

- CO like NO activates soluble guanylyl cyclase though it is approximately 30 fold less potent
- Appears to participate in the neurotransmission of odorant perception
- Odorants lead to carbon monoxide production and subsequent cGMP synthesis that promotes long term adaptation to odor stimuli
- Potential to regulate a variety of perceptual and cognitive processes yet untested
- May also participate in adaptation to chronic pain

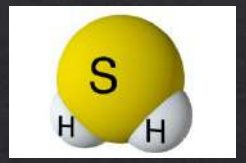
- In GI nervous system CO serves as a neurotransmitter to relax the internal anal sphincter in response to nonadrenergic noncholinergic NANC nerve stimulation and VIP

- Heme Oxygenase Pathway Neuroprotective role

- Neuroprotective function of HO inhibited in Alzheimer's

- Amyloid precursor proteins APP Inhibit HO

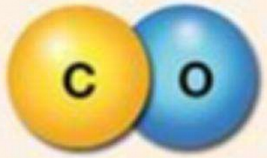
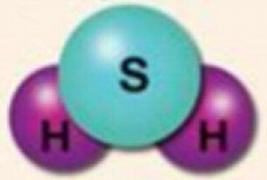
- APP mutants early onset Alzheimer's potent at blocking HO function



Hydrogen Sulphide

- The Newest Gaseous Messenger Molecule
- At least two enzymes can generate hydrogen sulphide Cystathionine β synthase CBS and cystathionine γ lyase CSE
- Role in regulating brain function exists at concentrations as high as 100 micromolar
- CBS deficient mice have altered hippocampal LTP and hydrogen sulphide potentiates NMDA receptor currents

ENDOGENOUS GASOTRANSMITTERS

	Nitric Oxide	Carbon Monoxide	Hydrogen Sulfide
			
Enzymatic Production	nNOS iNOS eNOS	HO-1	CBS CSE (CGL) 3MST
Blood Concentration	low nM	nM-μM	high nM – low μM
Half-life (*in vivo*)	seconds	minutes	seconds – minutes
Year of Discovery as a Physiological Modulator	1987	1991	1996
Second Messenger Signal	sGC-cGMP	sGC-cGMP	K_{ATP} Channel
Cardioprotective	Yes	Yes	Yes
CV Therapeutic in Patients	Yes (BiDil® PDE5 inhibitors)	No	No

Endocannabinoids

- For years mechanisms by which the active components of marijuana cannabinoids exerted their psychoactive effects remained mystery
- Mechoulam and Gaoni in 1964 identified delta 9 tetrahydrocannabinol THC accounts for nearly all of the psychoactive effects of cannabis
- late 1980s discovery of a specific cannabinoid receptor named CB1
- Cannabinoid receptors unlikely to be evolved solely for action of plant cannabinoids
- In 1992 Mechoulam and colleagues discovered anandamide

Cannabinoid Receptors

- CB 1 receptors are possibly the most abundant G protein coupled receptors in the brain

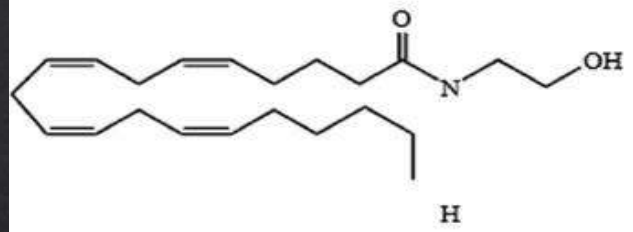
- Highest density in the basal ganglia cerebellum hippocampus hypothalamus anterior cingulate cortex and cerebral cortex particularly the frontal cortex

- Large doses of THC develop catalepsy The action of cannabinoids in the basal ganglia and cerebellum may be associated

1. CB 1 axons and nerve termini neuronal dendrites and the cell body
   - presynaptic rather than postsynaptic side of the neuronal cleft suggesting a role in regulation of neurotransmission

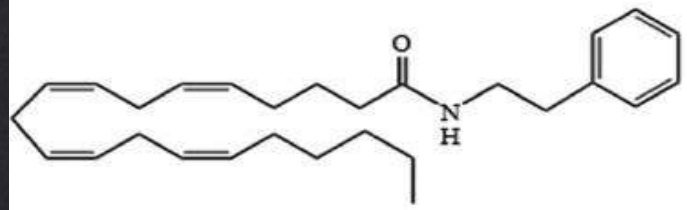
2. CB2 surface of WBC's of the immune system but small amounts appear to be present in the brainstem

Endogenous Cannabinoids



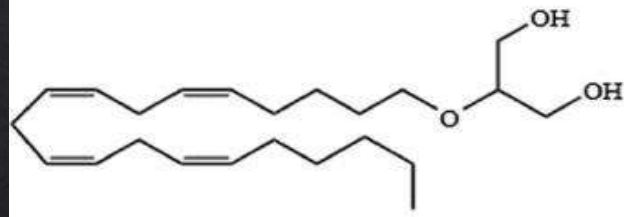
Anandamide

CB1>>CB2



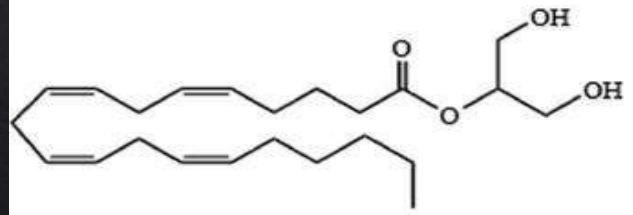
N-Arachidonoyl dopamine
(NADA)

CB1>CB2



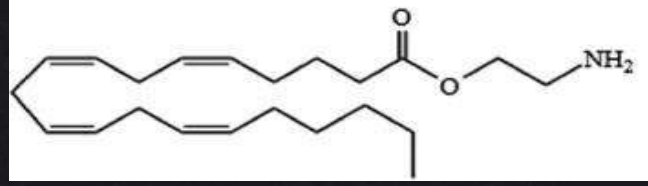
2-Arachidonoylglycerol ether
(Noladin)

CB1>CB2



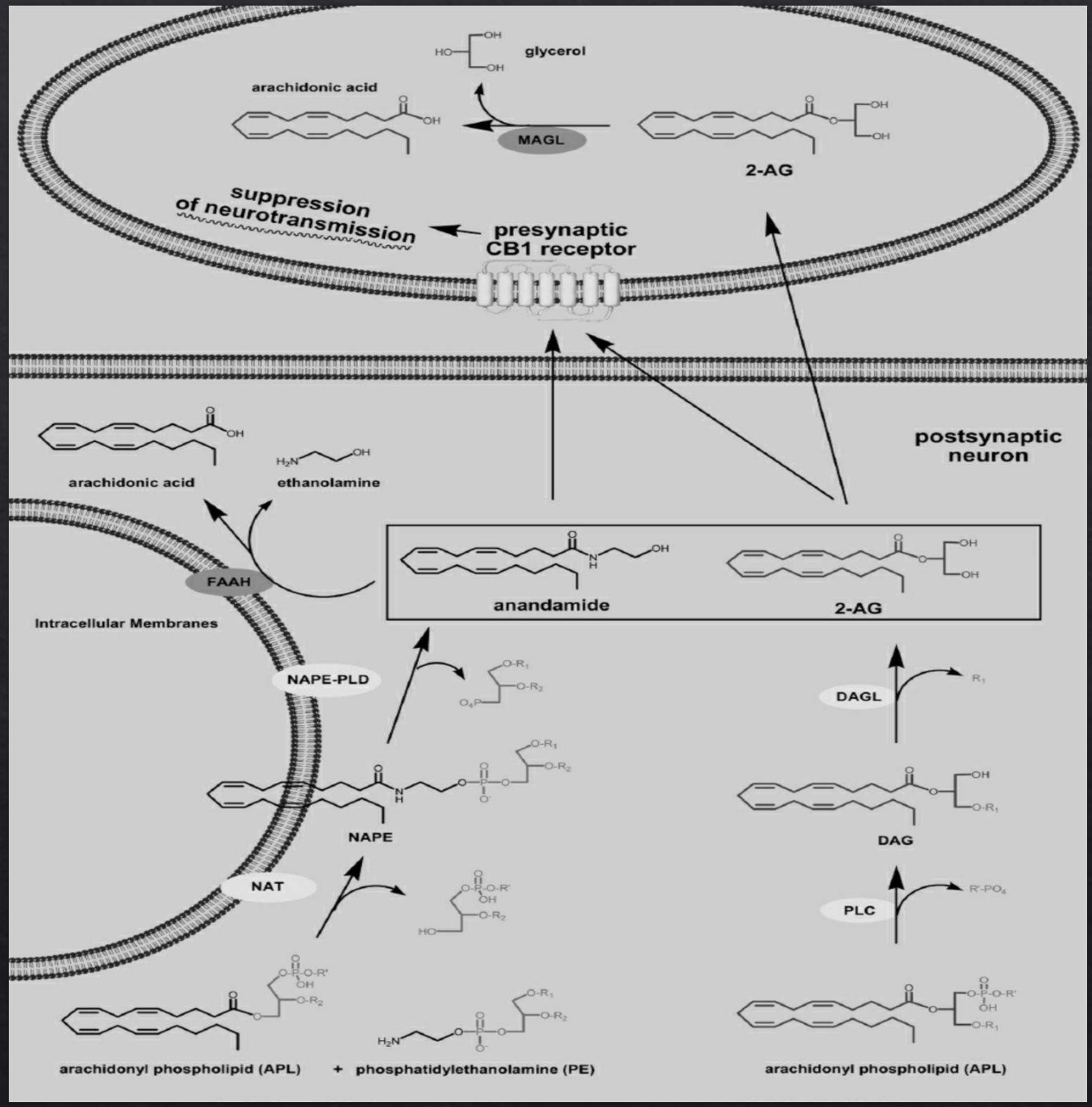
2-Arachidonoylglycerol
(2-AG)

CB1=CB2



Virodhamine

CB2>CB1


glycerol
arachidonic acid
MAGL
2-AG
suppression of neurotransmission
presynaptic CB1 receptor
postsynaptic neuron
arachidonic acid
ethanolamine
FAAH
anandamide
2-AG
Intracellular Membranes
NAPE-PLD
DAGL
NAPE
DAG
NAT
PLC
arachidonyl phospholipid (APL)
+ phosphatidylethanolamine (PE)
arachidonyl phospholipid (APL)

Effects on Neurotransmission

- CB1 receptor G protein coupled inhibit Adenylyl cyclase → decrease cAMP
- CB1 activation activate K channel inhibit N type Ca channel → block neurotransmission
- Also tend to block GABA norepinephrine and acetylcholine
- Overall inhibitory effect

Endo CBD in Anxiety and Mood

- THC tranquilising effect
- some users experience paradoxical anxiety
- CB 1 receptor deficient animal more pronounced anxiety behaviour
- Possible role in PTSD and Phobias
- In a 2007 meta analysis Christensen et al reported that those receiving rimonabant had a 25 times greater risk of stopping treatment because of depression and a threefold greater risk of stopping due to anxiety

Endo CBD in addiction

- CB1 deficient mice resistant to behavioural effects of CBD reduced opioid addiction and withdrawal reduced alcohol intake
- CBD Opioid system interaction CBD increase Dopamine release requires Mu opioid receptors
- Rats with decreased FAAH activity suggestive of greater cannabinoid signalling

Endo CBD in Psychosis

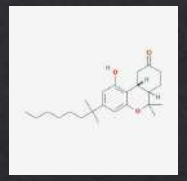
- Heavy CBD use Psychosis
- CBD use often worsens psychosis in Schizophrenia
- Elevated levels of anandamide noted in CSF of pts with schizophrenia including a follow up study of medication na ve patients
- Elevated anandamide levels also noted in blood of those with schizophrenia and such elevations normalized with clinical improvement

Endo CBD and feeding

- THC use increase appetite
- Food deprivation increased Endo CBD in hypothalamus and limbic system
- CB 1 antagonist rimonabant facilitate weight loss

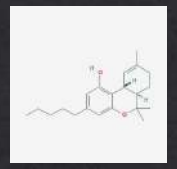
Endo CBD Brain Injury and Pain

- Mice models Traumatic Injury
  - 2-AG neuroprotective reducing brain edema infarct size and cell death improving functional outcomes
- Anandamide protected against brain injury in a model of multiple sclerosis MS
- FAAH inhibitors improved motor symptoms in a mouse model of Parkinson's disease
- THC CBD Agonist Beneficial in acute and chronic pain
- Analgesic effects lost when CB Antagonist given
- Endo CBD and opioid analgesia distinct but may share overlapping neural pathways



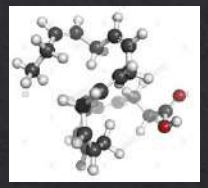
Nabilone

- sold under the brand name **Cesamet** synthetic cannabinoid
- **FDA approved** in 2006
- treat nausea and vomiting in people under chemotherapy who have failed to respond adequately to conventional antiemetic treatments
- given in 1 or 2 mg doses multiple times a day up to total 6 mg
- **antiemetic effect** caused by interaction with **CB1 receptor**
- modest effectiveness in relieving fibromyalgia
- **cytochrome P450** enzymes extensively **metabolize** various metabolites
- Adverse effects of nabilone include but are not limited to dizziness euphoria drowsiness dry mouth ataxia sleep disturbance dysphoria headache nausea disorientation depersonalization and asthenia



Dronabinol

- sold as trade names Marinol and Syndros
- oral isomer form of delta 9 tetrahydrocannabinol THC
- Dronabinol acts directly on the appetite and vomiting control centers in the brain to stimulate appetite and prevent emesis
- Phase 2/3 clinical trials for FDA approval were completed in 2017
- Indications
  1. nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments
  2. anorexia associated with weight loss in patients with acquired immunodeficiency syndrome AIDS
- Dronabinol is not recommended for use during breastfeeding because it is excreted into human milk
- mild overdose presents as drowsiness dry mouth euphoria and tachycardia severe overdose presents lethargy slurred speech decreased motor coordination and postural hypotension

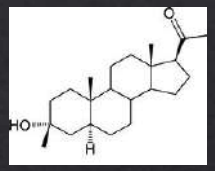


Eicosanoids

- Subfamilies of eicosanoids include prostaglandins thromboxanes leukotrienes lipoxins resolvins and eoxins
- For each subfamily at least 4 separate series of metabolites 2 of ω 6 ω 3 ω 9
- Dietary supplements of omega 3 fatty acids eicosapentaenoic acid EPA its ester ethyleicosapentaenoic E EPA and docosahexaenoic acid DHA help relieve symptoms of depression bipolar illness schizophrenia and cognitive impairment
- DHA and EPA may help reduce behavioural outbursts and improve attention in children

- Negative correlation between fish consumption and depressive symptoms
- Reduced DHA in the orbitofrontal cortex in Post mortem studies of depressive patients
- Omega 3 FA adjunct t t with Lithium Valproate in Bipolar unipolar depression Better control than drug alone
- Problem solving skills Visual acuity eye development
    - Better in infants of mother who consumed DHA rich food
- English prisoners consuming higher amount of seafoods Low assault rate

- Improvement in ve and ve symptoms of schizophrenia with omega 3 FA supplementation
- Low EPS of Haloperidol when combined with antioxidants and omega 3 FA
- EPA and DHA have been associated with decreased dementia incidence



Neurosteroids

- Synthesized from cholesterol in the brain
- Independent of peripheral formation in the adrenals and gonads
- produced by enzymatic processes
  - CYP 450 and non CYP enzymes
  - Within or outside the mitochondria
  - CNS and PNS cells

- Operate through a nongenomic pathway to regulate neuronal excitability through their effects on neurotransmitter gated ion channels
- GABA receptor particularly GABA
- Allopregnanolone 3α 5α tetrahydro progesterone pregnanolone PREG and tetrahydrodeoxycorticosterone THDOC
- Dehydroepiandrosterone sulfate DHEA S the most prevalent neurosteroid acts as noncompetitive modulator of GABA
- DHEA inhibitory effects at the GABA receptor
- Progesterone also considered a neurosteroid regulate gene expression at progesterone receptors

NS in Neurodevelopment

Neuroprotection

- General Effects: stimulate axonal growth and promote synaptic transmission

- DHEA: Regulate brain serotonin and dopamine levels, suppress cortisol, increase hippocampal primed burst potentiation and cholinergic function, decrease amyloid-3 protein, inhibit the production of proinflammatory cytokines, and prevent free radical scavenging

- DHEA and DHEAS — glial development and neuronal growth and to promote their survival in animals
- Progesterone — repair of damaged neural myelination
- Allopregnanolone — reduction of contacts during axonal regression

Role of Neurosteroids in Mental illness

- Depression
- Anxiety disorder
- Eating disorder
- Psychotic disorder
- Childhood Mental illness
- Substance abuse
- Memory and aging

Depression

- Low plasma and CSF concentrations of allopregnanolone Inverse relation with severity
- Fluoxetine increase level of certain neurosteroids
- Debate over therapeutic properties

Anxiety disorders

- Allopregnanolone stimulates GABAergic activity with 20 times the strength of benzodiazepines and 200 times the potency of barbiturates

- Both positive and negative regulation of the GABA$_A$ receptor are correlated with anxiolytic and anxiogenic action respectively

Psychotic disorders

- DHEA decrease anxiety in patients with schizophrenia
- DHEA and DHEAS suppress GABA inhibition heighten the neuronal response at the NMDA and sigma receptors
- DHEA and DHEAS levels are typically elevated in the initial episode of a patient with schizophrenia

Childhood Mental Illnesses

- ADHD
  - Clinical symptomology inversely correlated with DHEA and pregnenolone levels

Substance Abuse

- Alcohol
  - Regulate GABA receptor induce denovo steroid synthesis in the brain
  - Sharp increase in alcohol mimic acute stress response elevate neuro steroid concentration by HPA axis

- Drug abuse
  - DHEAS increased after cocaine abstinence decreased after relapse

Eating disorders

- DHEA diminish food intake temper obesity moderate insulin resistance and lower lipids in rats with a model of youth onset hyperphagic and genetic obesity
- Low DHEA and DHEAS recorded in young women with anorexia nervosa
- Oral DHEA supplementation increased bone density and tempered the emotional problems associated with the disorder

Memory disorders and aging

- DHEA level at age 70 20 of that at late 20's
- DHEA supplementation prevent or slow the cognitive declines associated with the aging process conflicting results
- DHEA levels markedly decreased in Alzheimer's

SUMMERY

- Gases cannabinoids and eicosanoids not stored in vesicles generated released on demand
- Endocannabinoids transmit signals backward from the postsynaptic neuron to the presynaptic neuron
- Gases do not act on membrane receptor diffuse into cell and act on cellular proteins
- Nitric Oxide Arachidonic Acid CBD CO Retrograde Transmitters diffusing back to the presynaptic neuron to facilitate further neurotransmission

- Scientific research in last decades has led to discovery of novel neurotransmitters
- Novel neurotransmitters challenge the classical criteria of Neurotransmitter
- Research into and understanding of Novel neurotransmitters is important for better understanding and future directions in treatment of a large number of psychiatric illnesses

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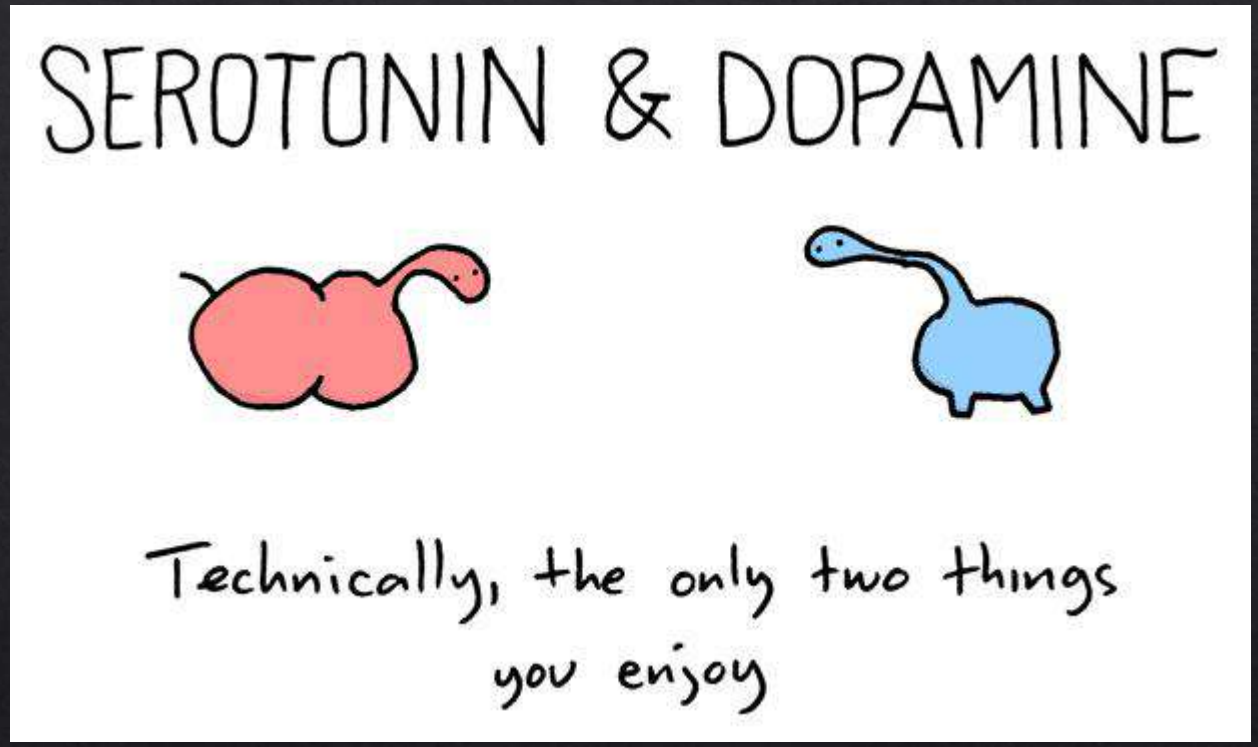
SEROTONIN & DOPAMINE
Technically, the only two things you enjoy