The brain is a complex assembly of interacting neurons that regulate their own and each other’s activities in a dynamic fashion. Drugs that act in the central nervous system (CNS) are invaluable therapeutically, they can, for e.g., relieve pain, reduce fever, suppress disordered movements, induce sleep or arousal, reduce appetite etc. Selectively acting drugs can be used to treat anxiety, depression, mania, or schizophrenia and do so without altering consciousness.

Although the basic processes of synaptic transmission in the central nervous system are essentially similar to those operating in the periphery but understanding how drugs affect brain function is made difficult by many factors:

1-The complexity of neuronal interconnections in the brain: bellow diagram illustrates in a schematic way the kind of interconnections that typically exist, for e.g, an adrenergic neuron in the locus coeruleus shown as neuron 1 in the diagram, releasing transmitter “a” at its terminals. Release of “a” affects neuron 2 (which releases transmitter b), and also affects neuron 1 by direct feedback and, indirectly, by affecting presynaptic inputs impinging on neuron 1. The firing pattern of neuron 2 also affects the system, partly through interneuronal connections (neuron 3, releasing transmitter “c”).

2- The effects of psychotropic drugs often take weeks to develop, so it is likely that they reflect the adaptive responses rather than the immediate pharmacodynamic effects of the drug. This is well documented for antidepressant drugs.
3-Existence of the blood-brain barrier: penetration of which requires molecules to traverse the vascular endothelial cells rather than going between them, only small non-polar molecules can diffuse passively across cell membranes. Most neuroactive drugs penetrate the blood-brain barrier in this way, but many do so via transporters, examples for this include L-dopa, valproate.

**Chemical mediators in CNS:**

The terms neurotransmitter, neuromodulator and neurotrophic factor refer to chemical mediators that operate over different timescales, more than 40 types are recognized so far, and it’s of three types:

a-Neurotransmitters are released by presynaptic terminals and produce rapid excitatory or inhibitory responses in postsynaptic neurons.

b-Neuro-modulators are released by neurons and by astrocytes, and produce slower pre- or postsynaptic responses. A precise definition of a neuromodulator is difficult to produce, since the same substance may act as a neurotransmitter in one synapse, and a neuroregulator at another synapse. For instance, ATP or adenosine itself, may function as a neurotransmitter or as a neuromodulator. Purines, eicosanoids, and nitric oxide (NO) are regarded as modulators and/or neurotransmitters.

c-Neurotrophic factors are released mainly by non-neuronal cells and act on tyrosine kinase-linked receptors that regulate gene expression and control neuronal growth e.g neuropoietic factor, fibroblast growth factor and insulin like growth factor.

It’s worth mentioning that fast neurotransmitters (e.g. glutamate, GABA) operate through ligand-gated ion channels where as slow neurotransmitters and neuromodulators (e.g. dopamine, neuropeptides, prostanoids) operate mainly through G-protein-coupled receptors.

Criteria for a mediator to be considered as a neurotransmitter are:
1. Transmitter synthesis
2. Transmitter storage
3. Transmitter release by exocytosis
4. Transmitter recognition; receptors exist on postsynaptic cells, which recognize the transmitter. Binding of a neurotransmitter to its receptor initiates a signal transduction event.
5. Termination of action. A variety of mechanisms terminate the action of the released transmitter, including hydrolysis (for acetylcholine and peptides) and reuptake into neurons by specific transporters such as NET, SERT.
**Targets for drug action in CNS**

The main target proteins of Neuroactive drugs:

a- Ion channels  
b- Receptors  
c- Enzymes  
d- Transport proteins

Among the four main receptor families; ionotropic receptors, G-protein-coupled receptors, kinase-linked receptors and nuclear receptors, neuroactive drugs target mainly the first two.

The main processes involved in synthesis, storage and release of amine and amino acid transmitters are:

1. Uptake of precursors  
2. Synthesis of transmitter  
3. Uptake/transport of transmitter into vesicles  
4. Degradation of transmitter  
5. Depolarisation by action potential  
6. Influx of Ca2+  
7. Release of transmitter by exocytosis  
8. Diffusion to postsynaptic membrane  
9. Interaction with postsynaptic receptors  
10. Inactivation of transmitter  
11. Reuptake of transmitter or degradation  
12. Uptake of transmitter by non-neuronal cells  
13. Interaction with presynaptic receptors.

All the steps shown in this figure can be influenced by drugs.
Classification of psychotropic drugs:

1- Anaesthetic agents: drugs used to produce surgical anaesthesia e.g halothane, propofol

2-Anxiolytics and sedatives: Also called hypnotics, minor tranquillisers, e.g Diazepam

3-Antipsychotic drugs: neuroleptic drugs, antischizophrenic drugs, major tranquillisers e.g Chlorpromazine

4-Antidepressant drugs: Examples tricyclic antidepressants like imipramine selective serotonin reuptake inhibitors like Flouxetine

5- Analgesic drugs: e.g opiates like Morphine

6-Psychomotor stimulants like cocaine and caffeine and Psychotomimetic drugs (hallucinogens) like LSAD

7-Cognition enhancers also called nootropic drugs: Examples acetylcholinesterase inhibitors (e.g. donepezil, galantamine), and also Piracetam which is an AMPA modulator.

Some drugs are not included classification, for example lithium, which is used in the treatment of manic-depressive psychosis, and ketamine which is classed as a dissociative anaesthetic but produces psychotropic effects

1- Excitatory amino acids: Glutamate is the most abundant excitatory neurotransmitter in the vertebrate nervous system. widely distributed in the CNS, glutamate receptors, such as the NMDA receptor, bind glutamate and are activated. Because of its role in synaptic plasticity, glutamate is involved in cognitive functions like learning and memory in the brain (LTP)

Metabolism and release of amino acids:

Glutamate in the CNS comes mainly from either glucose, via the Krebs cycle, or glutamine, which is synthesised by glial cells and taken up by the neurons. The interconnection between the pathways for the synthesis of excitatory aminoacids (Glutamate) and inhibitory amino acids (GABA and Glycine), makes it difficult to study the functional role of individual amino acids, because disturbance of any step will affect both excitatory and inhibitory mediators.
In common with other transmitters, glutamate is stored in synaptic vesicles and released by Ca2+-dependent exocytosis, the action of glutamate is terminated mainly by carrier-mediated reuptake into the nerve terminals and neighbouring astrocytes. This transport can, under some circumstances, operate in reverse and constitute a source of glutamate release, this process that may occur under pathological conditions such as brain ischaemia.

Glutamate receptors: four main subtypes of receptors are known so far, namely NMDA (Memantine=antagonists, Ketamine=Channel blocker), AMPA (Piracetam/Modulator), kainate and metabotropic receptors. The first three are ionotropic receptors, they are named after their specific agonists, the most important one is the NMDA that can also be fully activated by Aspartate (another excitatory NT). The metabotropic receptors are G-protein-coupled receptors linked to intracellular second messenger systems. NMDA receptor has a Glycine modulatory site, although Glycine is recognized as an inhibitory NT in CNS, but it’s been revealed by many studies that the receptor requires glycine as well as NMDA in order to be activated, so blocking of the glycine site is an alternative way to produce antagonism. (7-Kynurenic acid act in this way)
Functional role of glutamate receptors:

1-Synaptic plasticity and long-term potentiation: Synaptic plasticity is a general term to describe long-term changes in synaptic connectivity and efficacy, either following physiological alterations in neuronal activity (LTP as in learning and memory), or resulting from pathological disturbances (as in epilepsy).

Long-term potentiation is a long-lasting (days or weeks) enhancement of synaptic transmission at various CNS synapses following a short burst of presynaptic stimulation mainly in hippocampus, which plays a central role in learning and memory.

Two special properties of the NMDA receptor underlie its involvement in LTP, namely voltage-dependent channel block by Mg2+ and its high Ca2+ permeability. At normal membrane potentials, the NMDA channel is blocked by Mg2+, a sustained postsynaptic depolarisation produced by glutamate acting repeatedly on AMPA receptors, removes the Mg2+ block, and NMDA receptor activation then allows Ca2+ to enter the cell.

'Learning' can occur if synaptic strength is enhanced following activity in both pre- and postsynaptic neurons, this usually results from enhanced activation of AMPA receptors. It does not occur if presynaptic activity fails to excite the postsynaptic neuron.

2-Excitotoxicity: Excitotoxicity due to excessive glutamate release and impaired uptake occurs as part of the ischemic cascade and is associated with stroke, and some forms of intellectual disability (like Autism), and diseases like Alzheimer's disease, this process is mainly mediated through continuous increase in Ca2+ level in the neuron.

In a finding in the 1970s that glutamate given orally produces neurodegeneration in vivo caused considerable alarm because of the widespread use of glutamate as a 'taste-enhancing' food additive. The 'Chinese restaurant syndrome'-an acute attack of neck stiffness and chest pain is well known.

3-Epilepsy: Glutamic acid has been implicated in epileptic seizures. Microinjection of glutamic acid into neurons produces spontaneous depolarisations around one second apart, and this firing pattern is similar to what is known as depolarizing shift in epileptic attacks.

None of the anti epileptic drugs work only on glutamate receptors, but some (such as topiramate) have this effect as well as working on other targets as well.
2-Inhibitory Amino acids: GABA (γ-aminobutyric acid) is the main inhibitory transmitter in the brain. In the spinal cord and brain stem, Glycine is also important.

Synthesis: GABA is formed from glutamate by the action of glutamic acid decarboxylase. GABA is destroyed by a transamination reaction in which the amino group is transferred to α-oxoglutaric acid to yield glutamate. This reaction is catalysed by GABA transaminase, which is inhibited by vigabatrine, a compound used to treat epilepsy.

GABAergic neurons and astrocytes take up GABA via specific transporters, and it is this, rather than GABA transaminase, which removes the GABA after it has been released. GABA transport is inhibited by guvacine and nipecotic acid.

GABA receptors:

GABA acts on two distinct types of receptor, one (the GABA\(_A\) receptor) being a ligand-gated channel, the other (GABA\(_B\)) is a G-protein-coupled receptor.

GABA\(_A\) receptors (Gabazine=Antagonist, Muscimol=Agonist, Picrotoxin=Channel blocker) located post-synaptically mediate fast postsynaptic inhibition, the channel being selectively permeable to Cl\(^-\). GABA\(_B\) receptors located presynaptically are responsible for slow inhibitory effects produced by GABA diffusing further from its site of release. Thus GABA produces inhibition by acting both as a transmitter and as a neuromodulator.

GABA\(_B\) receptors (Baclofen=Agonist, Saclofen=Antagonist,) are located pre- and postsynaptically, and they are typical G-protein-coupled receptors, GABA\(_B\) receptors exert
their effects by inhibiting voltage-gated calcium channels (thus reducing transmitter release) and by opening potassium channels (thus reducing postsynaptic excitability.

Drugs acting on GABA receptors:

GABA<sub>A</sub> receptors are the target for several important centrally acting drugs like benzodiazepines, barbiturates and neurosteroids, General anaesthetics also act on GABA<sub>A</sub> receptors, as well as on other targets, Muscimol, derived from a hallucinogenic mushroom, resembles GABA chemically and is a powerful GABA<sub>A</sub> receptor agonist.

Bicuculline, a naturally occurring convulsant compound and Gabazine, a synthetic GABA analogue are specific antagonists that blocks the fast inhibitory synaptic potential in most CNS synapses, these have no therapeutic uses.

Picrotoxin is a convulsant that acts by blocking the chloride channel associated with the GABA<sub>A</sub> receptor, thus blocking the postsynaptic inhibitory effect of GABA. It has no therapeutic uses.

Benzodiazepines, have sedative and anxiolytic effects, selectively potentiate the effects of GABA on GABA<sub>A</sub> receptors. They bind with high affinity to an accessory site (the 'benzodiazepine receptor') on the GABA<sub>A</sub> receptor, in such a way that the binding of GABA is facilitated and its agonist effect is enhanced. Studies showed that mutations in BDZ region on GABA affect the level of constitutive activity at this site, and its sensitivity to benzodiazepines, convulsant analogues, such as flumazenil are considered to be inverse agonists.

Modulators that also enhance the action of GABA, but whose site of action is less well defined than that of benzodiazepines, include other CNS depressants such as barbiturates, anaesthetic agents and neurosteroids. Neurosteroids are compounds that are related to steroid hormones but that act to enhance activation of GABA<sub>A</sub> receptors, Synthetic neurosteroids include alphaxalone, developed as an anaesthetic agent because GABA itself fails to penetrate the blood-brain barrier, more lipophilic GABA analogues were used, one of which, Baclofen, which is the GABA<sub>B</sub> agonist, is used to treat spasticity and related motor disorders

Glycine is an inhibitory transmitter mainly in the spinal cord, acting on its own receptor, structurally and functionally similar to the GABA<sub>A</sub> receptor. The convulsant drug strychnine is a competitive glycine receptor antagonist while Tetanus toxin acts mainly by interfering with glycine release.
**3-Noradrenaline:** mainly distributed in locus coeruleus (LC). Other noradrenergic neurons lie close to the LC in the pons and medulla, and project to the hypothalamus, hippocampus, there is a small cluster of adrenergic neurons, which release adrenaline rather than noradrenaline.

Synthesis and storage:

The precursor for noradrenaline is L-tyrosine, taken up by adrenergic neurons. The cytosolic enzyme Tyrosine hydroxylase catalyses the conversion of tyrosine to (dopa), conversion of dopa to dopamine is catalysed by dopa decarboxylase, The tyrosine analogue α-methyltyrosine strongly inhibits tyrosine hydroxylase and may be used experimentally to block noradrenaline synthesis.

Dopamine-β-hydroxylase converts dopamine to noradrenaline, Many drugs inhibit this enzyme, including and Disulfiram (a drug used mainly for its effect on ethanol metabolism).

Phenylethanolamine N-methyl transferase catalyses conversion of noradrenaline to adrenaline. The main location of this enzyme is in the adrenal medulla. Vesicular monoamine transporter, which is similar to the amine transporter responsible for noradrenaline uptake into the nerve terminal, Certain drugs such as Reserpine block this transport and cause nerve terminals to become depleted of their noradrenaline stores.

Functional aspects:

Noradrenaline applied to individual neurons usually causes inhibition, and in most cases this is produced by activation of β-adrenoceptors linked to cAMP accumulation. In some situations, however, noradrenaline has an excitatory effect, which is mediated by either α- or β-adrenoceptors.

1-Arousal and mood: LC neurons, which is the source of most of the noradrenaline released in the brain, are silent during sleep, and their activity increases with behavioural
arousal. Amphetamine-like drugs, which release catecholamines in the brain, increase wakefulness, alertness and exploratory activity.

There is a close relationship between mood and state of arousal; depressed individuals are usually lethargic and unresponsive to external stimuli. The catecholamine hypothesis of depression suggested that depression results from a functional deficiency of noradrenaline in certain parts of the brain, while mania results from an excess while subsequent findings suggest that 5-HT may be more important than noradrenaline in relation to mood.

2-Blood pressure regulation: The role of central, as well as peripheral, noradrenergic synapses in blood pressure control is shown by the action of hypotensive drugs such as Clonidine and Methyl Dopa, which decrease the discharge of sympathetic nerves emerging from the CNS. They cause hypotension when injected locally into the medulla in much smaller amounts than are required when the drugs are given systemically.

Some catecholamine-containing cells in the brain stem contain phenylethanolamine N-methyl transferase which is the enzyme that converts noradrenaline to adrenaline and inhibition of this enzyme interferes with the baroreceptor reflex.

4-Dopamine

Dopamine is particularly important in relation to neuropharmacology, because it is involved in several common disorders of brain function, notably Parkinson's disease, schizophrenia and attention deficit disorder, as well as in drug dependence.

Dopamine receptors:

There are five dopamine receptor subtypesD1 D2 D3 D4 and D5, D1 and D5 receptors are linked to stimulation of adenylyl cyclase. D2, D3 and D4 receptors are linked to inhibition of adenylyl cyclase. Most known functions of dopamine appear to be mediated mainly by receptors of the D2 family, dopamine receptors also mediate various effects in the periphery (mediated by D1 receptors), notably renal vasodilatation.

Dopaminergic pathways in the CNS: There are three main dopaminergic pathways:

1-Nigrostriatal pathway, important in motor control

2-Mesolimbic/mesocortical pathways, running from groups of cells in the midbrain to parts of the limbic system, especially the nucleus accumbens, and to the cortex; they are involved in emotion and drug-induced reward systems

3-Tuberohypophyseal neurons running from the hypothalamus to the pituitary gland, whose secretions they regulate.
Functional aspects:

1-Dopamine and motor systems: studies showed that bilateral destruction of the substantia nigra in rats, which destroys the nigrostriatal neurons, causes profound catalepsy, the animals becoming so inactive that they die of starvation. Unilateral lesions produced by 6-hydroxydopamine injection (a substance selectively destroys dopaminergic nerve terminals) caused the animal to turn in circles towards the lesioned side, because of an imbalance of dopamine action in the corpus striatum between the two sides of the brain.

Conversely, unilateral injection of apomorphine (a dopamine receptor agonist) into the striatum causes circling away from the injected side.

Parkinson's disease is a disorder of motor control, associated with a deficiency of dopamine in the nigrostriatal pathway, many antipsychotic drugs are D2 receptor antagonists, whose major side effect is to cause movement disorders, probably associated with block of D2 receptors in the nigrostriatal pathway.

2-Behavioural effects: There is some evidence that schizophrenia in humans is associated with dopaminergic hyperactivity. Chronic administration of amphetamine (which releases both dopamine and noradrenaline) to a few rats in a large colony produces various types of abnormal social interaction, including withdrawal and aggressive behavior.

Amphetamine, cocaine (which acts by inhibiting the dopamine transporter) and also other addictive drugs activate mesocortical dopaminergic 'reward' pathways, which play a key role in drug dependence. The main receptor involved appears to be D1.

3-Neuroendocrine function: The tuberohypophyseal dopaminergic pathway is involved in the control of prolactin secretion. Many antipsychotic drugs, acts by blocking D2 receptors, increase prolactin secretion and can cause breast development and lactation. Bromocriptine, a dopamine receptor agonist derived from ergot, is used to suppress prolactin secretion by tumours of the pituitary gland.

4-Vomiting: Pharmacological evidence strongly suggests that dopaminergic neurons have a role in the production of nausea and vomiting. Nearly all dopamine receptor agonists (e.g. Bromocriptine) and other drugs that increase dopamine release in the brain (e.g. LevoDopa) cause nausea and vomiting as side effects, while many dopamine antagonists (e.g. Phenothiazines, Metoclopramide) have antiemetic activity. D2 receptors occur in the area of the medulla (chemoreceptor trigger zone) associated with the initiation of vomiting, and are assumed to mediate this effect.
5-Serotonin (5-hydroxytryptamine): the distribution, storage and release of 5-HT resembles nor adrenaline, found mainly in Raphe nuclei. Its precursor is tryptophan, an amino acid derived from dietary protein.

5-HT receptors: 14 subtypes are identified so far, they are all G-protein-coupled receptors except for 5-HT3, which is a ligand-gated cation channel.

5-HT1 receptors are predominantly inhibitory in their effects, 5-HT1B and 5-HT1D receptors are found mainly as presynaptic inhibitory receptors in the basal ganglia. Agonists acting on peripheral 5-HT1D receptors are used to treat migraine such as Sumatriptan, 5-HT2 receptors exert an excitatory postsynaptic effect, 5-HT2 receptor antagonists such as Methysergide used in treating migraine, 5-HT3 is excitatory ionotropic receptor, and specific antagonists (e.g. Ondansetron) are used to treat nausea and vomiting.

Functional aspects

1-Sleep, wakefulness and mood: Lesions of the Raphe nuclei, or depletion of 5-HT by PCPA (a substance inhibit synthesis of 5-HT) administration, abolish sleep in experimental animals, whereas microinjection of 5-HT at specific points in the brain induces sleep.

There is evidence that 5-HT, as well as noradrenaline, may be involved in the control of mood, antipsychotic drugs (e.g. Clozapine), which owe their efficacy partly to an action on 5-HT receptors.

2-Feeding and appetite: In experimental animals, 5-HT1 agonists cause hyperphagia, leading to obesity. Antagonists acting on 5-HT2 receptors, including several antipsychotic drugs used clinically, also increase appetite and cause weight gain. On the other hand, antidepressant drugs that inhibit 5-HT uptake cause loss of appetite.

3-Sensory transmission: After lesions of the raphe nuclei or administration of PCPA, animals show exaggerated responses to many forms of sensory stimulus, Thus depletion of 5-HT by selective lesions to the 5-HT-containing neurons that run to the dorsal horn, antagonise the analgesic effect of morphine, while inhibitors of 5-HT uptake have the opposite effect.
**6-Acetylcholine:** Acetylcholine is very widely distributed in the brain, occurring in all parts of the forebrain (including the cortex), midbrain and brain stem.

There are two types of acetylcholine receptors: muscarinic AChRs and nicotinic AChRs. Nicotinic ACh receptors fall into three main classes, the muscle (N2), ganglionic (N1) and CNS types and all are ionotropic receptors. Muscarinic receptors are typical G-protein-coupled receptors of five subtypes (M1-M5) are known, members of the group (M1 “pirenzepine = antagonist”, M3, M5) couple with Gq to activate the inositol phosphate pathway while (M2 “Gallamine and Black mamba = blocker” M4) act through Gi to inhibit adenyl cyclase and thus reduce intracellular cAMP, they all can be inhibited nonselectively by atropine, M1, M2 and M3 receptors occur also in specific locations in the CNS, M4 and M5 receptors are largely confined to the CNS.

Many of the behavioural effects associated with cholinergic pathways seem to be produced by ACh acting on mAChRs, Deletion of the various CNS-specific nAChR subtypes generally has rather little effect, although some cognitive impairment can be detected.

Functional aspects:

1-Aura and Learning: Administration of physostigmine (an anticholinesterase that crosses the blood-brain barrier) produces state of arousal, whereas atropine has the opposite effect, and also many studies showed that Nicotine increases alertness and also enhances learning and memory.

2-Memory: Intracerebral injection of a muscarinic agonist, Arecoline, immediately after the training session reduces the percentage of animals that forget the correct path, when retested, whereas an injection of the muscarinic antagonist Scopolamine produces amnesia, degenerative disease like Alzheimer’s disease is obviously due to progressive degeneration of cholinergic neurons.

**7-Histamine:** Histamine acts on three types of receptor (H1, H2 and H3), all of which are G-protein-coupled receptors and occur in most brain regions. H1 receptors are mainly located postsynaptically and cause excitation; H2 and H3 receptors are inhibitory, respectively post- and presynaptic, H3 receptors being inhibitory autoreceptors on histamine-releasing neurons.

H1 receptors in the cortex contribute to arousal and wakefulness, and H1 receptor antagonists produce sedation. Antihistamines are widely used to control nausea and vomiting, for example in motion sickness and middle ear disorders, suggesting a role for histamine in these reflexes.
8- **Purines:** in 2001, it’s been proven that both adenosine and ATP act as transmitters and/or modulators in the CNS.

Adenosine produces its effects through G-protein-coupled receptors (A1, A2a, A2b and A3) and also P1, while ATP acts on P2 receptors, P2x being ligand-gated cation channels, P2y being G-protein-coupled.

The overall effect of adenosine, or of various A receptor agonists, is inhibitory, leading to effects such as drowsiness, motor incoordination, analgesia and anticonvulsant activity. Xanthines, such as caffeine, which are antagonists at A2 receptors, produce arousal and alertness.

ATP receptors may play a role in nociception, because ATP is released by tissue damage and causes pain by stimulating unmyelinated afferent nerve terminals, which express P2x receptors.

9- **Melatonin:** It is synthesised from 5-HT exclusively in the Pineal, an endocrine gland that plays a role in establishing circadian rhythms, it’s secretion is high at night and low by day, this rhythm is controlled by input from the retina, via a noradrenergic retinohypothalamic tract, a structure often termed the 'biological clock', This retinal control system serves to inhibit melatonin secretion when the light intensity is high.

Melatonin receptors are typical G-protein-coupled receptors, found mainly in the brain and retina but also in peripheral tissues, Melatonin is used clinically as a means of controlling jet lag, A single dose appears to have the effect of re-synchronising the physiological secretory cycle, although it is not clear how this occurs.

10- **Nitric oxide (NO):** The main defining criteria for transmitter substances like that neurons synthesis, storage, exocytosis, and interaction with specific receptors do not apply to NO.

Nitric oxide in the nervous system is produced mainly by the constitutive neuronal nitric oxide synthase which is calmodulin-dependent enzyme and is activated by a rise in intracellular Ca2+ concentration, which can occur by many mechanisms, including action potential conduction and neurotransmitter action.
Functional aspect: NO plays a role in long-term potentiation and depression because these phenomena are reduced or prevented by NOS inhibitors, in experiment it’s been observed that LTP is absent in transgenic mice in which the nNOS gene has been disrupted.

Nitric oxide exerts its effects in two main ways.

1-By activation of soluble guanylate cyclase, leading to the production of cGMP, leading to various phosphorylation cascades. This 'physiological' control mechanism operates at low NO concentrations.

2-By reacting with the superoxide free radical to generate peroxynitrite, a highly toxic anion that acts by oxidising various intracellular proteins, his requires higher concentrations which are achieved in brain ischaemia.

References:

1-Rang and Dale Pharmacology, Chapter 34, P473.

2-Goodman and Gillman’s Pharmacology, Section 2, Chapter 14, P362.

3-Modern Pharmacology with clinical applications, Chapter 24, P281.

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