and hormones acting via receptors proteins in the membrane to modulate cAMP and hence channel phosphorylation. The number of Ca channels in the heart ventricle is increased by epinephrine, the action potential is more positive and prolonged and more Ca enters the cell. Increased Ca results in a more forceful contraction. The number of systems and the subtlety of their action are expanding too rapidly to make listing them all useful.

OVERVIEW: SYNAPSES, RECEPTORS AND TRANSMITTERS

Communication between neurons is dependent on synapses. Synapses may be electrical or chemical. Electrical synapses have a cytoplasmic continuity between the pre and postsynaptic neuron. Ions flow through specialized ion channels termed gap junctions. Transmission may be bidirectional. This type of synapse may be found in glial cells.

Almost all neuronal synapses in mammals are chemical in nature. Conduction across such synapses is slower but is unidirectional. Duration is usually 15 to 20 milliseconds which is considerably longer than the axon potential (which usually has a duration of 1-2 msec). Potentials less than the threshold potential for triggering the action potential are summed at the postsynaptic receptor and neuron. At a chemical synapse, pre and postsynaptic membranes are separated by a cleft composed of the extracellular space. This cleft is wider for type I synapses which are usually excitatory, utilize glutamate and involve the spiny processes on the dendrites (axodendritic). Type II synapses are usually inhibitory, utilize gamma amino butyric acid and involve the cell body (axosomatic). In general the axon terminals of the cerebral cortical pyramidal neurons are excitatory. Communication across this cleft is achieved on the release of chemical transmitters. When the action potential reaches the presynaptic terminals, calcium channels are activated and calcium ions enter the presynaptic terminal from the extracellular space. Phosphorylation of proteins (synapsin) occurs and these proteins then link the synaptic vesicles containing the transmitter to the cytoskeleton of the presynaptic terminal. The vesicles then fuse with the membrane of the terminal and in the process release their contents of transmitter. The transmitter then crosses...
the synaptic cleft and then binds to the postsynaptic receptor. This process results in a delay in transmission time of 0.5-1 millisecond.

The receptors (which have multiple subunits) gate ion channels and are of 2 types:

1. **Ionotropic (directly linked, fast):** these receptors directly gate ion channels. They are also referred to as ligand (or transmitter) gated channels. After binding the transmitter, a conformational change occurs with opening of the ion channel. These receptors are associated with relatively fast synaptic action lasting only a few milliseconds. Examples include the glutamate (non NMDA and NMDA,) and GABA/A and the nicotinic acetylcholine receptors.

2. **Metabotropic (second messenger mediated, slow):** These receptors gate ion channels indirectly. Two phases occur: recognition of the transmitter and activation of the effector. In the major type of this group, the receptor molecule is coupled by a guanosine nucleotide binding protein (G-protein) to the effector molecule. Examples include norepinephrine, dopamine, serotonin, GABA/B, muscarinic acetylcholine and certain types of glutamate receptors. The receptors are large protein molecules distinct from the ion channel. These receptors alter intracellular metabolic reactions with the production of a second messenger. These 2nd messengers activate protein kinases-enzymes involved in the phosphorylation of substrate proteins. Much work has centered on cyclic adenosine monophosphate (cAMP). In addition to this second messenger, gaseous second messengers such as nitric oxide and carbon monoxide have been recognized. The action of these receptors is slower with onset of action taking several hundred milliseconds to seconds and with the effect on channels lasting seconds to minutes or longer. The excitability of neurons and the strength of synaptic connections are modulated. This action is therefore sometimes referred to as modulatory.

Overall the action of transmitters on the receptor and neuron is not all or none. The postsynaptic potentials may be summated. The specific action of a transmitter may be excitatory or inhibitory. The specific action depends upon the receptor and not on the transmitter per se.

The relationship of receptors and ion channels is presented in table 5-4

### STRUCTURE OF THE IONOTROPIC RECEPTORS

The synaptic receptors for GABA, glycine, acetylcholine and glutamate are transmembrane proteins.

The GABA/A, glycine and nicotinic acetylcholine receptors all have a similar pentameric structure, coded by related families of genes. The 5 subunits surround a central channel pore (Fig. 5-23). For GABA/A and glycine, the channel selects for chloride anions. For nicotinic acetylcholine, the channel selects for cations such as sodium. Each subunit has four transmembrane helical domains labeled M1-M4.

**In contrast, the glutamate receptors** have a different proposed structure, tetramers composed of two different types of subunits. Each subunit is composed of three helical transmembrane domains and an additional helical region that dips into the membrane and lines the central pore.

The major transmitters and receptors in the central nervous system are as follows:

### EXCITATORY TRANSMITTERS AND RECEPTORS:

- **Glutamate:** This is the major excitatory transmitter in the central nervous system. Its action is mediated by channels that conduct sodium and potassium ions.

**TABLE 5-4**

<table>
<thead>
<tr>
<th>TYPE OF RECEPTOR</th>
<th>ION CHANNEL AND/OR METABOLIC EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIRECT ION GATED</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Excitatory</strong></td>
<td>Increase sodium and calcium permeability</td>
</tr>
<tr>
<td><strong>Inhibitory</strong></td>
<td>Increase chloride permeability</td>
</tr>
<tr>
<td><strong>G-PROTEIN COUPLED</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Excitatory** | Stimulate cAMP  
Increase intracellular calcium  
Decrease potassium permeability |
| **Inhibitory** | Inhibit cAMP  
Decrease permeability of calcium  
Increase potassium permeability |

Increased permeability = channels open
Four receptors may be specified. Three are
ionotropic, one is metabotropic.

The ionotropic receptors are named according
to the specific action of synthetic agonists.

**Non-NMDA receptors:** these receptors gate
ion channels which are permeable to both sodium
and potassium but not calcium. Two types are rec-
ognized:

1. Kainate (Kainic acid) and 2. AMPA (a-
amino-3-hydroxy-5methylisoxazole-4propionic
acid).

As regards the kainate receptor, both kainic
acid and domoic acid are agonists that are convul-
sant agents acting on this system. The amino acid
domoic acid was implicated as a marine toxin pro-
duced by a marine organism diatom infecting
mussels off the eastern coast of the Canadian
Maritimes, anchovies, bivalves and crustaceans on
the Pacific coast of northern California, Oregon
and Washington state. This agent produces signif-
icant damage to the hippocampus resulting in
seizures and disorders of recent memory (an
amnestic syndrome). The anterior horn cells are also severely affected. All of these effects are con-
sidered to be due to glutamate excitotoxicity since
domoic acid is 30 to 100 times more potent than glutamic acid and 3 times more potent than kainic
acid.

The **AMPA receptor** is diffusely distributed
within the central nervous system and through the
opening of sodium channels produces fast excita-
tion.

**NMDA (N-methyl-D-aspartate) receptor.**
This receptor controls a cation channel that is per-
meable to calcium, sodium, and potassium ions.
Opening of the channel requires extracellular
glycine as a cofactor. Opening of the channel
depends on membrane voltage as well as chemical
transmitter. Maximum current flow occurs only
after the membrane is already depolarized and glutamate is already present. Magnesium ions
must also be expelled from the channel into the
extracellular space for action to occur. This chan-
nel opens relatively slowly in response to glutamate as opposed to the non-NMDA receptors.
However the action is still more rapid than at metatobotropic receptors. Calcium ions are impor-
tant in the passage of current. In contrast to the
AMPA receptor, prolonged bursts of depolariza-
tion occur. At certain sites AMPA and NMDA
receptors are clustered together and interact. The
following convulsant agents act at this location to
enhance excitability: NMDA, quinolinic acid, low
magnesium and estrogens. Progesterone metabo-
lites may decrease action at the site. The influx of
calcium has other implications. Calcium depend-
ent enzymes and 2nd messenger protein kinase
are activated with a long-standing modification in
synaptic activity (long term potentiation). This has
implications for both learning and more persistent
seizure effects particularly as regards the hip-
pocampus. The influx of calcium may trigger
processes that contribute to apoptotic cell death
(glutamate excitotoxicity).

The activation of **metabotropic glutamate recep-
tors** also results in increased levels of intra-
cellular calcium with the cascade actions described
above.

**Acetylcholine:** This agent may have either
excitatory or inhibitory actions depending on the
receptor and site of action. **There are 2 general
classes of receptors:** 1. **Nicotinic** and
2. **Muscarinic.**

**Nicotinic receptors** are excitatory and are
found at the postsynaptic neuromuscular junction
of skeletal muscle and in the peripheral autonomic
ganglia and other neural crest derived tissues.
The Renshaw cell of the spinal cord is activated by
nicotinic collaterals of the alpha motor neuron and
then feeds back to inhibit the alpha motor neuron.
Nicotinic receptors are also located at presynaptic
sites and when activated produce an increase in
neurotransmitter release. Nicotinic receptors are
ligand gated ion channels for sodium. The action
is excitatory. Although nicotinic receptors are pre-
sent to some degree in the brain, the major CNS
receptor category for acetylcholine is muscarinic.

**Muscarinic receptors** in contrast are G-pro-
tein linked (guanosine nucleotide binding pro-
tein) and are of multiple types. M1 receptors pro-
duce a decrease in potassium conductance and
have a predominantly excitatory effect. In con-
trast, M2 receptors increase potassium conduc-
tance and are inhibitory. When these receptors are
located at presynaptic sites, the axoaxonic recep-
tors are usually inhibitory. The postsynaptic
receptor sites may be either excitatory or inhibi-
tory. Overall most central nervous action are excita-
tory. These muscarinic neurons are found in the
nucleus basalis of the basal forebrain and project to the cerebral cortex. A loss of these neurons occurs in Alzheimer's disease and contributes to memory loss (see chapter 30). Muscarinic neurons are also found in the mesopontine tegmentum, project to the thalamus and are involved in cortical activation and arousal (see chapter 29).

**INHIBITORY TRANSMITTERS AND RECEPTORS:**

Gamma amino butyric acid (GABA): this is the major inhibitory agent and receptor in this category. There are 2 major receptors in this category (a 3rd has recently been described).

- GABA/A, an ionotropic receptor that gates a chloride (-) ion channels.
- GABA/B, a metabotropic receptor that activates a 2nd messenger sequence which then activates (opens) a potassium ion channel.

Either increased intracellular chloride or decreased intracellular potassium ions would result in an increased negativity of the inside of the neuron; that is additional intracellular hyperpolarization would occur. The agent baclofen acts as an agonist at the GABA/B site.

In terms of actions of convulsant agents a number of substances are antagonist at the GABA/A receptor including bicuculline, penicillin, picrotoxin, pentylenetetrazol, and estrogens. Note also that agents that inhibit GABA synthesis such as pyridoxine antagonists e.g. methoxy pyridoxine, isoniazid and l-allyl glycine may produce seizure activity particularly as regards the hippocampus. Cobalt ions may also have an acute action of this type.

The GABA/A receptor also has subunit receptor sites for benzodiazepine, barbiturates, alcohol and steroids. Benzodiazepines potentiate the GABA induced chloride conductance by increasing the frequency of chloride channel opening. Barbiturates potentiate the duration of chloride channel opening. Estrogens decrease chloride conductance, progesterone agents potentiate chloride conductance. Note that all steroids may also have more chronic actions on the neuron that do not necessarily involve the synapse.

**Glycine:** The glycine receptor is similar in structure to the GABA/A and acetylcholine nicotinic receptors. Glycine activates ionotropic GABA/A receptors. Glycine receptors are primarily located in the spinal cord and brain stem and to a lesser degree in other areas of the brain. At the spinal cord level, glycine is released by interneurons that inhibit antagonistic muscles (the Renshaw cell). Strychnine functions as a convulsant agent by antagonistic effects on the glycine receptor. When administered systemically this agent may produce convulsions primarily by action at the level of the spinal cord. However early studies of cortical function and connections in the 1930's and 40's employed direct application of strychnine to the pial surface of the monkey cerebral cortex to produce focal discharge (demonstrated later).

**MONOAMINES:**

The central monoamines include the catecholamines, serotonin and histamine. In general, these agents act at metabotropic modulatory synapses. Their action is often coupled with that of neuropeptides.
Catecholamines;
This group includes three biochemically related transmitters: dopamine, norepinephrine and epinephrine. These receptors operate through the cyclic AMP system.

**Dopamine:** several receptors (D1- D5) are recognized. The main receptors D1 and D2 both involve a 2nd messenger system which utilizes cyclic AMP. The action of dopamine at the D1 (and D5) receptors is to stimulate the formation of cyclic AMP, decreasing potassium conductance producing excitation. The action of dopamine at the D2 (and D3 and D4) receptors inhibits the formation of cyclic AMP. As a result potassium conductance is increased and inhibitory action results. D1 and D2 receptors are primarily located in the neostriatum and the nucleus accumbens and will be discussed in chapter 19. D3 and D4 receptors occur primarily in the limbic system. D4 receptors occur primarily in the frontal cortex. D5 receptors are found in the hypothalamus, thalamus and hippocampus.

**Norepinephrine and epinephrine.** In the central nervous system, neurons utilizing these transmitters are found in the locus ceruleus of the dorsal pons and the lateral tegmentum of the medulla and pons, where they have a significant role in the reticular formation and also influence areas concerned with autonomic function. Norepinephrine is also the primary neurotransmitter of the postganglionic sympathetic system. Epinephrine also functions as a circulating hormone after release from the adrenal medulla. There are a series of receptor subtypes, grouped as alpha 1, alpha 2, and beta. Alpha 1 receptors are excitatory; alpha 2 are inhibitory.

**Serotonin and histamine:** These transmitters will be discussed in the chapter on sleep (29).

Both have widespread effects. Both have multiple subtypes. Depending on the receptor the effect may be excitatory or inhibitory.

**NEUROPEPTIDES**
These agents occur in the central nervous system, endocrine and gastrointestinal system. Within the central nervous system, they are found with a high concentration in the hypothalamus, the amygdala, the autonomic nuclei, brain stem and spinal cord. In the spinal cord and brain stem, they have a role in modulation of pain. These agents also have a significant role as modulatory associated transmitters in the basal ganglia (chapter 19).

**GENETIC MUTATIONS INVOLVING CHANNELS AND RECEPTORS:** Specific defects have now been identified in several varieties of presumably monogenic seizure disorders. This topic will be discussed in chapter 29.