SECTION 2

DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM

Autonomic Nervous System: General Considerations

ORGANIZATION AND FUNCTION

The autonomic nervous system (ANS) functions largely below the level of consciousness and controls visceral functions. The major differences between the somatic and autonomic nervous systems are given in Table II.1.

Like the somatic nervous system, the ANS consists of afferents, centre and efferents.

Autonomic afferents Most visceral nerves are mixed nerves and carry nonmyelinated visceral afferent fibres as well. The cell bodies of these afferent fibres are located in the dorsal root ganglion of spinal nerves and in the sensory ganglia (e.g. nodose ganglion of vagus) of cranial nerves. They mediate visceral pain as well as cardiovascular, respiratory and other visceral reflexes.

Central autonomic connections There are no exclusively autonomic areas in the CNS; considerable intermixing and integration of somatic and autonomic innervation occurs. The highest seat regulating autonomic functions is in the hypothalamus—posterior and lateral nuclei are primarily sympathetic while anterior and medial nuclei are primarily parasympathetic. Many autonomic centres (pupillary, vagal, respiratory, etc.) are located in the mid-brain and the medulla in relation to the cranial nerves. The lateral column in the thoracic spinal cord contains cells which give rise to the sympathetic outflow.

Autonomic efferents The motor limb of the ANS is anatomically divided into sympathetic and parasympathetic. Many organs receive both

Table II.1: Differences between somatic and autonomic nervous system

	Somatic	*Autonomic*
1. Organ supplied	Skeletal muscles	All other organs
2. Distal most synapse	Within CNS	Outside CNS (in ganglia)
3. Nerve fibres	Myelinated	Pregang.—myelinated Postgang.—non-myelinated
4. Peripheral plexus formation	Absent	Present
5. Primary efferent transmitter	Acetylcholine	Acetylcholine, Noradrenaline
6. Effect of nerve section on organ supplied	Paralysis and atrophy	Activity maintained, no atrophy

sympathetic and parasympathetic innervation and the two subdivisions are functionally antagonistic in majority of these. The level of activity of innervated organ at a given moment is the algebraic sum of sympathetic and parasympathetic tone. However, refractory period of atrial fibres is decreased by sympathetic as well as parasympathetic influences. Most blood vessels, spleen, sweat glands and hair follicles receive only sympathetic, while ciliary muscle, bronchial smooth muscle, gastric and pancreatic glands receive only parasympathetic innervation. Thus, the two divisions of ANS are not merely check-and-balance physiological antagonists of each other.

Enteric nervous system

The enteric nervous system (ENS) located in the gut wall consists of a submucosal (Meissner's) and a myenteric (Auerbach's) plexus along with its afferent and efferent neurons whose fibres travel anterograde, retrograde as well as in a circular manner. It receives inputs from both sympathetic and parasympathetic divisions of ANS, but in addition functions independently to integrate bowel movements as well as regulate secretion and absorption (*see* Chap. 48.2). As such, it has also been labelled as a distinct *'enteric nervous system'*.

The general layout of ANS is depicted in Fig. II.1 and the important differences between its two subdivisions are given in Table II.2.

NEUROHUMORAL TRANSMISSION

Neurohumoral transmission implies that nerves transmit their message across synapses and neuroeffector junctions by the release of humoral (chemical) messengers.

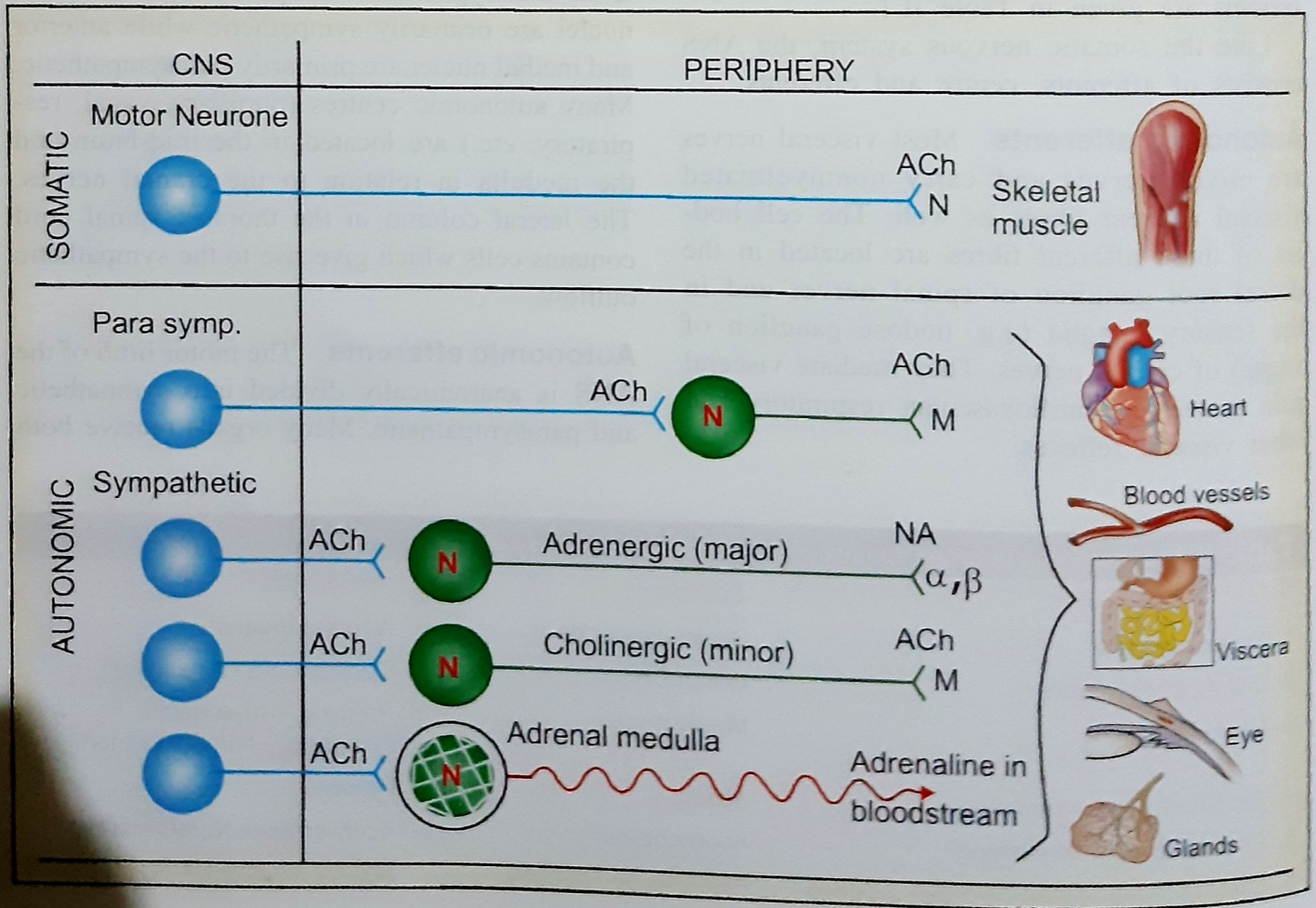

Fig. II.1: The general outlay of efferent autonomic nervous system. The transmitter released and the primary postjunctional receptor subtype is shown at each synapse/neuroeffector junction
ACh—Acetylcholine, NA—Noradrenaline, N—Nicotinic, M—Muscarinic, α—α adrenergic, β—β adrenergic

Table II.2: Differences between sympathetic and parasympathetic divisions of the autonomic nervous system

	Sympathetic	*Parasympathetic*
1. Origin	Dorso-lumbar (T_1 to L_2 or L_3)	Cranio-sacral (III, VII, IX, X; S_2–S_4)
2. Distribution	Wide	Limited to head, neck and trunk
3. Ganglia	Away from the organs supplied	On or close to the organ supplied
4. Postgang. fibre	Long	Short
5. Pre: post ganglionic fibre ratio	1: 20 to 1: 100	1: 1 to 1: 2 (except in enteric plexuses)
6. Neuroeffector transmitter	Major: NA Minor: ATP, NPY, DA, ACh	Major: ACh Minor: VIP, NO
7. Stability of transmitter	NA stable, diffuses for wider actions	ACh—rapidly destroyed locally
8. Important function	Tackling stress and emergency	Assimilation of food, conservation of energy

NA—Noradrenaline, ACh—Acetylcholine, ATP—Adenosine triphosphate, NPY—Neuropeptide Y, DA—Dopamine, VIP—Vasoactive intestinal peptide, NO—Nitric oxide

Junctional transmission was thought to be electrical (it does occur in some lower animals and probably in certain areas of mammalian brain) but observations at the turn of last century prompted Elliott (1905) to suggest that sympathetic nerves functioned by the release of an adrenaline-like substance, and Dixon (1907) to propose that vagus released a muscarine like chemical. Otto Loewi (1921) provided direct proof of humoral transmission by perfusing two frog hearts in series. Stimulation of vagus nerve of the first heart caused arrest of both. Thus, a chemical must have been released by vagal stimulation in the first heart which passed in the perfusate and arrested the second heart. This *vagusstoff* was found in 1926 to be acetylcholine, which earlier Dale (1914) had characterised as 'parasympathomimetic'. The sympathetic transmitter was eventually shown to be noradrenaline in 1946 by Von Euler. Many humoral transmitters (dopamine, 5-HT, GABA, glutamic acid, purines, peptides, etc.) are now known.

To be considered as a postjunctionally acting neurohumoral transmitter a substance must fulfill the following criteria:

(i) It should be present in the presynaptic neurone (usually along with enzymes synthesizing it).

(ii) It should be released in the medium following nerve stimulation.

(iii) Its application should produce responses identical to those produced by nerve stimulation.

(iv) Its effects should be antagonized or potentiated by other substances which similarly alter effects of nerve stimulation.

Steps in neurohumoral transmission

I. Impulse conduction The resting transmembrane potential (70 mV negative inside) is established by high K^+ permeability of axonal membrane and high axoplasmic concentration of this ion coupled with low Na^+ permeability and its active extrusion from the neurone. Stimulation or arrival of an electrical impulse causes a sudden increase in Na^+ conductance → depolarization and overshoot (reverse polarization: inside becoming 20 mV positive); K^+ ions then move out in the direction of their concentration gradient and repolarization is achieved. The ionic distribution is normalized during the refractory period by the activation of Na^+ K^+ pump. The action potential (AP) thus generated sets up local circuit currents which activate ionic channels at the next excitable part of the membrane (next node of Ranvier in myelinated fibre) and the AP is propagated without decrement.

Tetrodotoxin (from puffer fish) and saxitoxin (from certain shell-fish) selectively abolish

increase in Na^+ conductance in nerve fibres and thus block impulse conduction.

II. Transmitter release The transmitter (excitatory or inhibitory) is stored in prejunctional nerve endings within 'synaptic vesicles' (Fig. II.2). Nerve impulse promotes fusion of vesicular and axonal membranes through Ca^{2+} entry which fluidizes membranes. All contents of the vesicle (transmitter, enzymes and other proteins) are extruded by exocytosis (also *see* Fig. 2.6) in the junctional cleft.

While majority of the neurotransmitters are preformed, kept stored in synaptic vesicles and released on activation by exocytosis as outlined above, some mediators like NO, prostaglandins, endocannabinoids are synthesized on demand and reach their target by diffusion or by active transport.

The release process can be modulated by the transmitter itself and by other agents through activation of specific receptors located on the prejunctional membrane, e.g. noradrenaline (NA) release is inhibited by NA (α_2 receptor), dopamine, adenosine, prostaglandins and enkephalins while isoprenaline (β_2 receptor) and angiotensin (AT_1 receptor) increase NA release. Similarly, α_2 and muscarinic agonists inhibit acetylcholine (ACh) release at autonomic neuroeffector sites (but not in ganglia and skeletal muscles).

III. Transmitter action on postjunctional membrane The released transmitter combines with specific receptors on the postjunctional membrane and depending on its nature induces an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP).

EPSP Increase in permeability to cations → Na^+ or Ca^{2+} influx (through fast or slow channels) causes *depolarization* followed by K^+ efflux. These ionic movements are passive as the flow is down the concentration gradients.

IPSP Increase in permeability to anions, so that Cl^- ions move in (axonal Cl^- concentration is lower than its extracellular concentration) and tend to hyperpolarize the membrane → an IPSP is generated. Stabilization of the membrane or hyperpolarization can also result

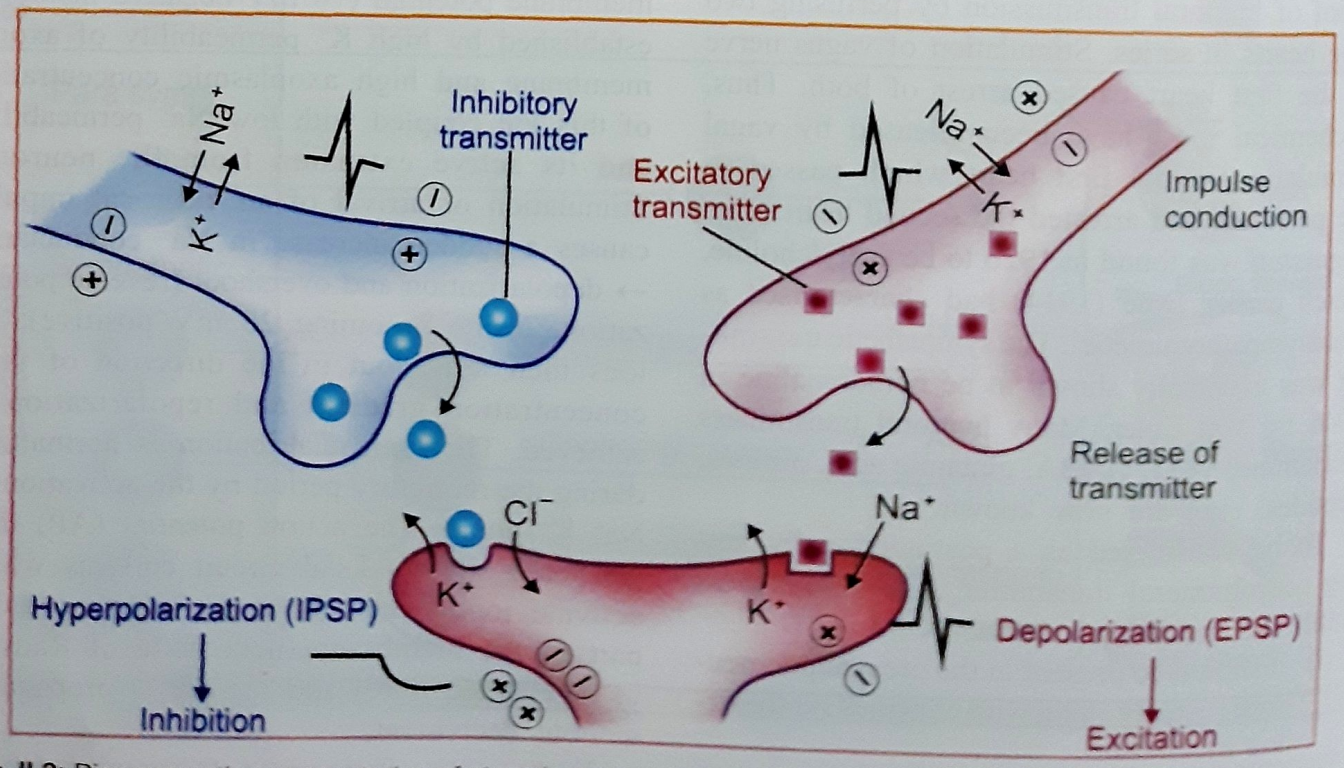

Fig. II.2: Diagrammatic representation of steps in excitatory and inhibitory neurohumoral transmission: EPSP—Excitatory postsynaptic potential; IPSP—Inhibitory postsynaptic potential

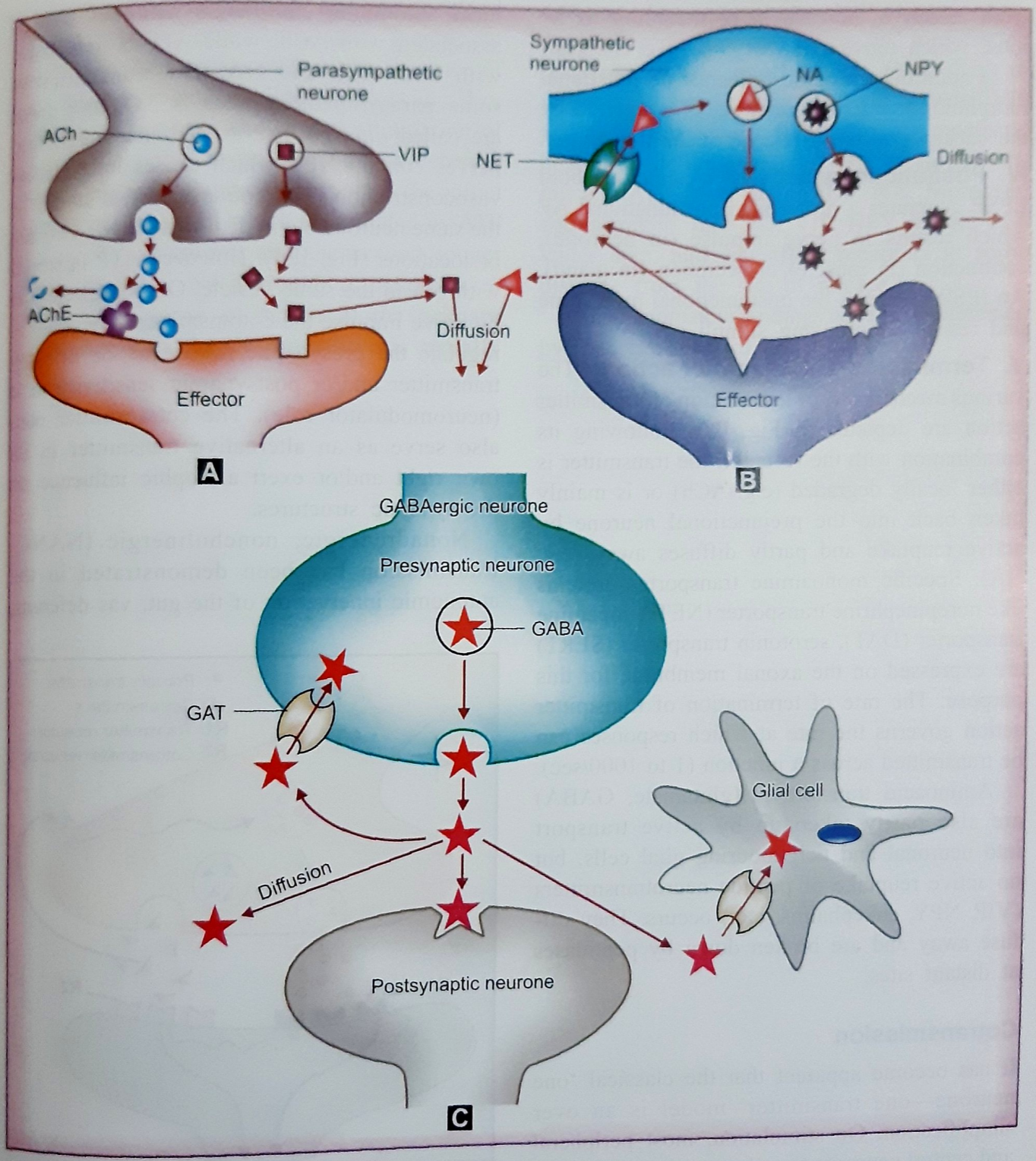

Fig. II.3: Mechanisms of termination of transmitter action
A. Parasympathetic neurone: The primary transmitter acetylcholine (ACh), which is an ester, is rapidly hydrolysed by a specific enzyme acetylcholinesterase (AChE) located strategically on the synaptic membrane. A common co-transmitter is vasoactive intestinal peptide (VIP), which on release diffuses slowly to be degraded by peptidases at distant sites. It may act on the same as well as neighbouring effectors.
B. Sympathetic neurone: The primary transmitter, an amine, noradrenaline (NA) is largely taken back into the neurone by membrane-bound norepinephrine transporter (NET) and recycled. A minor fraction diffuses away. One of the cotransmitters is neuropeptide Y (NPY), which on release meets the same fate as VIP.
C. Gabaergic neurone: The amino acid transmitter gamma-aminobutyric acid (GABA) released into the synaptic cleft is partly taken up into the neurone by GABA transporter (GAT), as well as into neighbouring glial cells. Some of it dissipates by diffusion.