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Clinical Implications of Membrane Receptor Function in Anesthesia

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DURING THE LAST DECADE, there have been important discoveries concerning the manner in which polypeptide hormones, adrenergic hormones, and neurotransmitters affect their target cells. From this, the membrane receptor concept has evolved to explain the mode by which a molecule can initiate a biological response following interaction with the plasma membrane of the cell.

The receptor is an integral membrane protein which can be selectively recognized by a precise hormone or neurotransmitter called a ligand (fig. 1). Ligands are known as agonists when they "activate" the receptor to transduce a response. An antagonist is a drug that interacts with a receptor, causing it to remain in the "inactive" form, and thus, by occupying the receptor, diminishes or aborts the effect of an agonist.

The biological response itself is generated by a functionally separate unit, the effector, in some cases by stimulating the production of another molecule or "second messenger." Alternatively the effector may open channels in the membrane allowing ionic fluxes to move along concentration and electrical gradients. Receptor and effector functions usually reside in separate molecules which interact in the lipid bilayer of the plasma membrane.

In the practice of clinical anesthesia, many drugs are employed which perturb receptor-ligand interaction with far-reaching effects. These are clarified by recent advances in understanding the function and regulation of membrane receptors. Certain principles of receptor function common to all receptors, will be discussed first. Specific receptors will then be dealt with individually.

Characteristics of Ligand–Receptor Binding

The interaction between ligand and receptor is a specific, reversible, saturable, and high-affinity binding process. Specificity is conveyed by the molecular configuration of the receptor which allows the ligand to fit the receptor precisely.

There are a measurable number of receptors in the membrane, all of which will be saturated when exposed to an excess of ligand. The process is reversible at conditions of equilibrium and one can describe the binding according to the law of mass action[1] as

$$[L] + [R] \underset{}{\overset{K_a}{\rightleftharpoons}} [LR]$$

where [L] is the concentration of free ligand, [R] is the concentration of receptor binding sites, [LR] is the concentration of ligand–receptor complex, and K_a is the affinity constant.

With the development of radiolabeled ligands, it has become possible to quantitatively assess the characteristics of binding. In a typical experiment, a radiolabeled ligand with a known specific activity (Ci/mole) is reacted with receptor-bearing membranes (fig. 2). The reaction mixture is centrifuged and the bound and free isotope fractions are measured. The quantity of ligand nonspecifically adsorbed to sites other than the receptors is assessed by reacting radiolabeled ligand and membranes in the presence of a 100-fold excess of unlabeled ligand. The unlabeled ligand by virtue of its high concentration will preferentially bind to all the available receptors leaving the radiolabeled ligand only the "nonspecific binding sites" to which to bind. The difference between bound radioactivity in the presence and absence of excess unlabeled ligand is a measure of the specific binding of the radiolabeled ligand. This is repeated at varying

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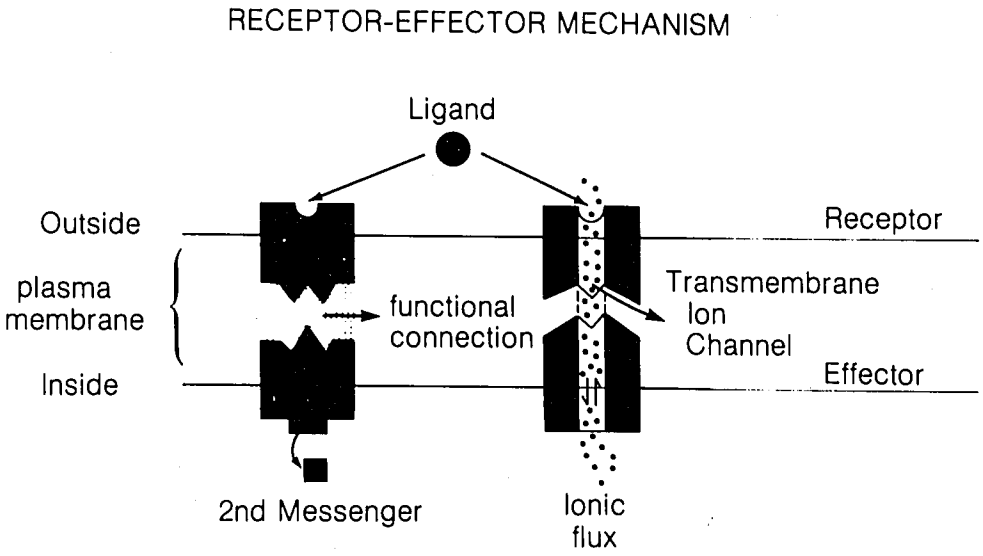

FIG. 1. Receptor-Effector Mechanism. The receptor and effector molecules are situated in the outer and inner leaflets, respectively, of the lipid bilayer of the plasma membrane. After the ligand is recognized by the externally disposed receptor, the effector is activated and initiates the cell's biological response either by release of a "second messenger" or by promoting ion fluxes through a transmembrane ion channel.

concentrations and the ratio of bound to free radio activity *vs.* bound radio activity is graphed (fig. 3). This is called a Scatchard plot[2] which if linear, indicates a single homogeneous class of receptors. A curvilinear plot suggests the presence of more than one class of receptors with different binding affinities. The affinity of the ligand for the receptor as well as the number of receptor sites can also be determined from this graph.

Receptor number and affinity fluctuate in response to biologically relevant stimuli. Regulation of receptor number is an event that requires participation by other subcellular organelles beyond the plasma membrane and include changes in receptor synthesis and degradation as well as internalization of receptors into inaccessible intracellular sites.[3] Regulation of receptor affinity is a physicochemical process intrinsic to the receptor and its phospholipid environment.

Adrenergic Receptors

These receptors interact selectively with the catecholamines that are released from the postganglionic sympathetic nerve endings (norepinephrine) or are

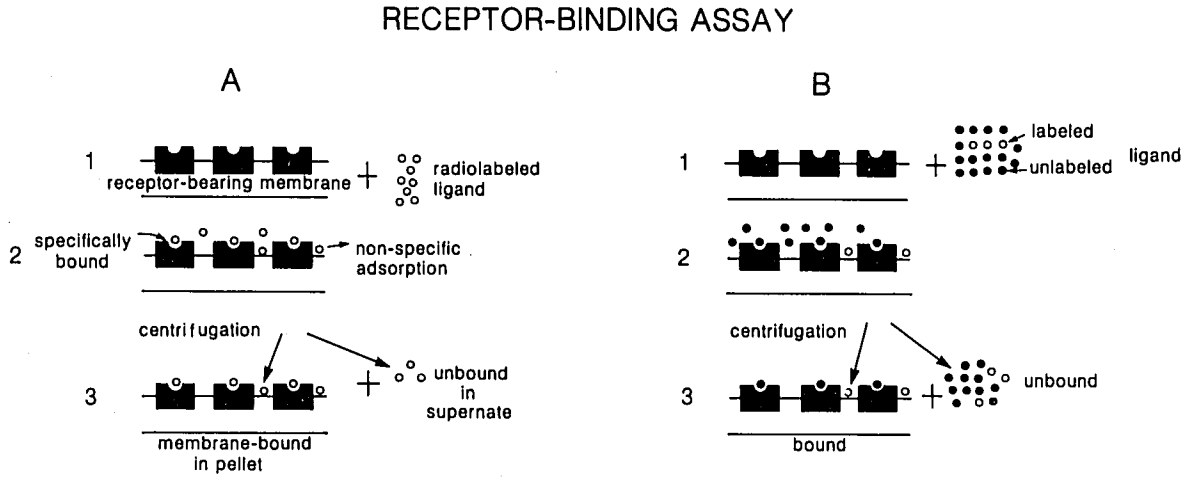

FIG. 2. Receptor-Binding Assay. (*A*). 1) The plasma membrane fraction of a cell homogenate is reacted with a radiolabeled ligand with a known specific activity (Ci/mole). 2) The ligand will specifically bind to the receptor as well as nonspecifically adsorb to the membranes. 3) The bound and free fractions of the radiolabeled ligand are separated by centrifugation. (*B*). 1) The extent of the nonspecific binding of the radiolabeled ligand to the membranes can be assessed by repeating the experiment in the presence of a 100-fold excess of unlabeled ligand. 2) The unlabeled ligand, by virtue of its high concentration, will preferentially bind to all the available receptors, leaving the radiolabeled ligand only the "nonspecific binding sites" to which to bind. 3) After the two phases are separated, the nonspecifically bound radioactivity is subtracted from the total bound radioactivity (*A*, step 3) to yield the specific binding of the radiolabeled ligand.

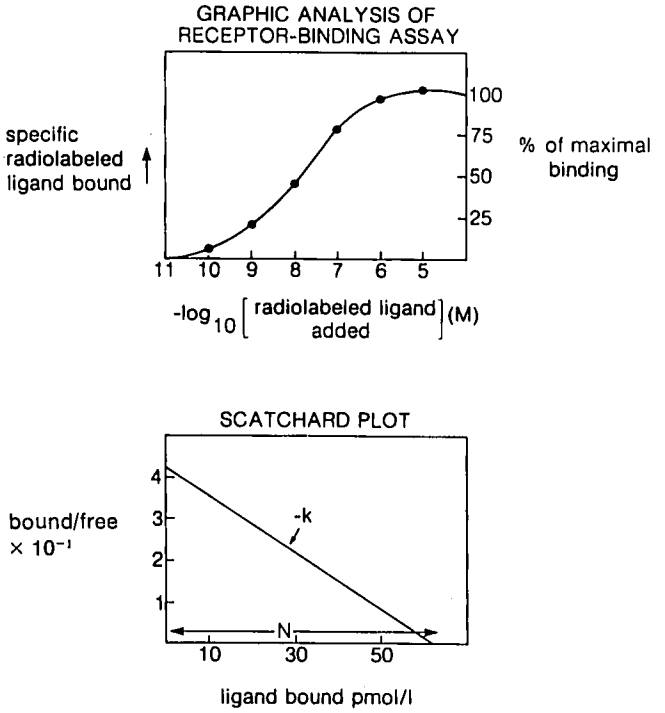

FIG. 3. Graphic Analysis of Receptor-Binding Assay. (*A*). The receptor-binding assay is repeated at varying concentrations of radiolabeled ligand to construct a dose-response curve. The characteristics of binding follow zero-order kinetics and can be displayed on a semi-logarithmic plot. (*B*). The Scatchard plot is a linear transformation which yields a line, the negative slope of which is equal to the binding affinity constant (K) and the abscissa intercept is equal to the total number of binding sites or binding capacity (N).

released into the circulation from the adrenal medulla (norepinephrine and epinephrine). Ahlquist[4] postulated that the responses to catecholamines were exerted through two different types of receptors which he named alpha-adrenergic and beta-adrenergic receptors. The beta-adrenergic receptors will be discussed first as their functional mechanism has been defined more comprehensively and can be considered a prototype for receptors in general.

Beta-adrenergic Receptors

Agonists include isoproterenol, epinephrine, norepinephrine, and dopamine in order of decreasing potency. Beta-adrenergic receptors have been further subdivided into beta-1, which mediate the positive inotropic effects on the heart and are equally sensitive to epinephrine and norepinephrine, and beta-2 which mediate smooth muscle relaxation in the bronchus and vasculature and are more sensitive to epinephrine than norepinephrine.[5] The effects of beta-adrenergic agonist stimulation are mediated intracellularly by the cyclic nucleotide, cyclic adenosine monophosphate (cAMP).[6] Cyclic AMP is often referred to as the "second messenger", the first messenger being the water soluble catecholamine agonist which cannot cross the lipid membrane (fig. 4). Cyclic AMP activates intracellular protein kinases which in turn phosphorylate proteins in the cell thereby altering their activity. Its synthesis is controlled by the enzyme, adenylate cyclase, situated on the inner leaflet of the lipid bilayer and spatially separated from the receptor.[7] The beta-adrenergic agonist-receptor complex diffuses laterally along the membrane until it couples to adenylate cyclase, the effector molecule, which is then activated and catalyzes synthesis of cAMP.[8] The level of cAMP is further controlled by phosphodiesterase which hydrolyzes the second messenger to an inactive molecule.

Thus, the beta-adrenergic response of a target tissue can be regulated by: 1) the level of catecholamine agonist, 2) the receptor number and binding affinity, 3) factors affecting the coupling of the activated receptor to adenylate cyclase, and 4) factors affecting the activity of phosphodiesterase. It can be seen that relatively large variations may be observed between catecholamine binding and biological response because of the postreceptor events involved.

Regulation of Beta-adrenergic Receptors

Knowledge gained from radiolabeled ligand studies has led to the description of a number of clinical situations in which receptor number is altered. A perturbation in which the receptor number is elevated is called "up regulation", whereas "down regulation" refers to a decrement in the receptor concentration. In general, there is an inverse relationship between the ambient concentration of the agonist and the number of its receptors[9] and, therefore, the sensitivity of the target organ. This is the presumptive explanation for the lack of a positive correlation between the plasma catecholamine levels and the extent of blood pressure elevation in patients with pheochromocytoma,[10] and should make one wary of relating plasma catecholamine levels to biological responsiveness of the autonomic nervous system. Discordance between hormone levels and biological effects have also been noted in the non-insulin dependent (adult type) diabetic where the concentration of insulin is normal or elevated even in the presence of hyperglycemia.[11]

Since sympathomimetic drugs are frequently used in the operating room, changes in the number and function of adrenergic receptors or effectors are of obvious interest to the anesthesiologist. The following examples show how this may occur as the result

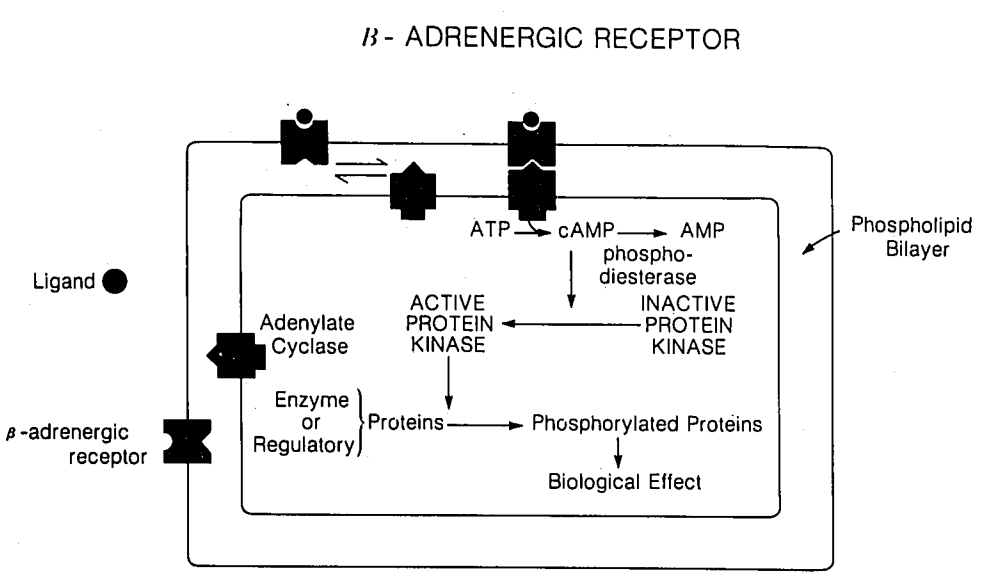

FIG. 4. Beta-Adrenergic Receptor. The externally disposed receptor molecule in the plasma membrane of the target cell is recognized by the catecholamine agonist. After binding, the agonist-receptor complex diffuses laterally along the membrane until it couples to its effector molecule, adenylate cyclase, situated on the inner leaflet of the lipid bilayer. This enzyme is activated converting ATP into cAMP ("second messenger"), the level of which is further controlled by phosphodiesterase which hydrolyzes the second messenger to an inactive molecule. cAMP activates intracellular protein kinases which phosphorylate regulatory proteins in the cell thereby altering their activity and causing the observed biological effect.

of drug therapy, disease states, or administration of anesthetic agents themselves. After acute or chronic exposure to beta-adrenergic agonists, such as terbutaline in the treatment of asthma, the receptor number will decrease, resulting in tachyphylaxis.[12] It is now conjectured that guanine nucleotides can in some way reverse the decreased beta-adrenergic binding that follows prolonged exposure to catecholamines[13] and clinical application of this finding may be expected in the future. Conversely, treatment with beta-adrenergic antagonists such as propranolol will increase the receptor concentration after a relatively short interval of five days.[14] If the antagonist is abruptly withdrawn, the concentration of beta-adrenergic receptors remains elevated for several days and this may result in adrenergic hypersensitivity with catastrophic results in susceptible patients.[15] For this reason, it is inadvisable to withdraw propranolol before surgery in patients with ischemic heart disease.

Several other examples illustrate the clinical importance of receptor-drug interactions. The use of the ophthalmic solution containing the beta-adrenergic receptor blocker, timolol, for treatment of glaucoma should alert the anesthesiologist to the possibility that systemic beta-blockade may have occurred,[16] and of the need to maintain the therapy perioperatively. The characteristic features of ethanol withdrawal after chronic administration resemble a hyperadrenergic state. Recently, this has been shown to be due to a specific increase in beta-adrenergic receptors[17] exaggerating the biological response to catecholamines, and has been successfully treated with beta-adrenergic blockade.[18]

Thyroxine has been shown to increase receptor concentration[19] and the clinical signs and symptoms of hyperthyroidism can be aborted by beta-adrenergic blockade. Conversely, in hypothyroidism,[20,21] receptor number is diminished. Amphetamines,[22] guanethidine,[23] and excess sodium intake[24] all increase receptor number and responsiveness to administered catecholamines.

Drugs can also change target organ responsiveness at the postreceptor level. For example, since the receptor and effector molecules are spatially separated in the membrane, factors affecting membrane fluidity will change the lateral mobility[25] and coupling-collision frequency of activated receptor and adenylate cyclase and therefore modify the response. Halothane sensitizes the myocardium to the arrhythmogenic effects of catecholamines.[26] The mechanism by which it does so may involve change in target responsiveness at the postreceptor level rather than changes in the number or binding affinity of the beta-adrenoceptors.[27] This hypothesis has been strengthened by the finding that some anesthetic agents affect the specific activity of enzymes that change the methylated phospholipid composition of the lipid bilayer.[28] Thus, the membrane fluidity[29] and consequently the diffusion-controlled coupling process[30] will also be influenced.

In patients with excessive beta-blockade due to inadvertent overdosage with beta-adrenoceptor blockers, glucagon has been used as an alternative to isoproterenol in efforts to reverse the effects of the blockade. Cardiac glucagon receptors are also coupled to adenylate cyclase and it can generate cAMP production and achieve the same biological effects of beta-agonist stimulation even in the presence of intense

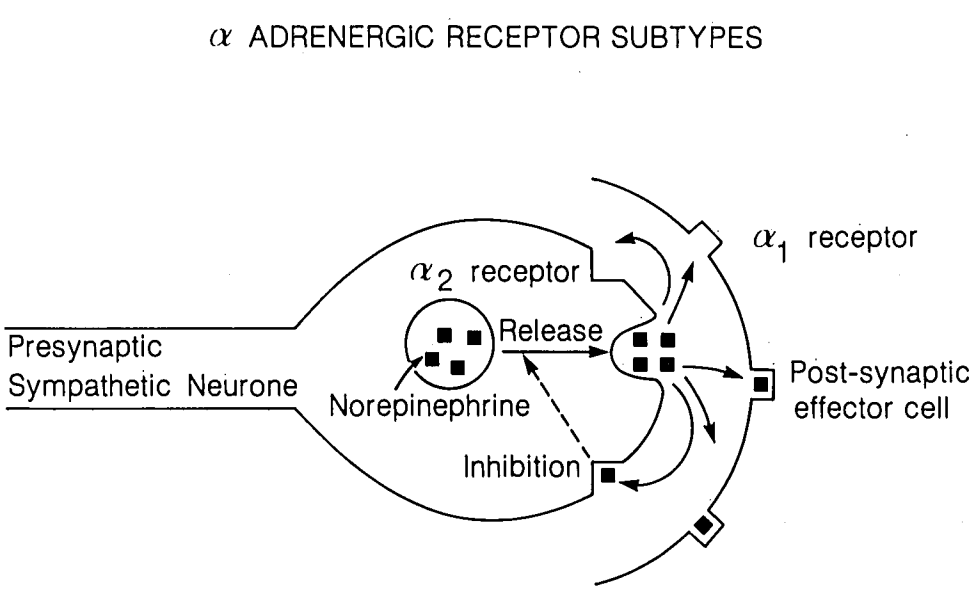

FIG. 5. Alpha-Adrenergic Receptor Subtypes. Quanta of stored norepinephrine molecules are released at the synapse in response to stimulation of the presynaptic sympathetic neurone. These neurotransmitters will bind to the α-1 receptors transducing the alpha-adrenergic effect on the post-synaptic target cell. The alpha-2 receptors on the presynaptic membrane are further sites for norepinephrine binding, which, when occupied, will inhibit further neurotransmitter release.

beta-blockade. However, severe nausea is a profound side effect of this form of therapy.[31]

ALPHA-ADRENERGIC RECEPTORS

These receptors mediate contraction in the smooth muscle of the vasculature, uterus and gastrointestinal tract. The typical order of potency of the agonists is epinephrine > norepinephrine > isoproterenol.[32] With the advent of alpha-antagonists, it is now evident that there are two classes of alpha-receptors, alpha-1 and alpha-2 (fig. 5). The alpha-1 adrenoceptors are postsynaptic, mediate constriction of smooth muscle cells, and are selectively blocked by prazosin. Alpha-2 receptors are found on presynaptic sympathetic nerve terminals, mediate feedback inhibition by norepinephrine of further neurotransmitter release[33] and are selectively blocked by yohimbine. Alpha-2 receptors are also found on platelets where they mediate platelet aggregation. Phenoxybenzamine is a selective alpha-1 antagonist while phentolamine is equipotent at both alpha-1 and alpha-2 receptors. For the agonists, it has been suggested that both methoxamine and phenylephrine are alpha-1 selective, and clonidine is alpha-2 selective.

Thus far, a physically and genetically separate effector molecule has not been recognized for the alpha-adrenergic receptor; consequently there is no identifiable "second messenger." Nevertheless, it is widely assumed that the combination of the alpha-agonist with the alpha-adrenoceptor generates a transmembrane message which initiates early intracellular events.[11] Calcium flux has been mentioned as a possible mechanism.[34] Activation of alpha-2 adrenergic receptor on platelets results in a decrease in intracellular cAMP through inhibition of adenylate cyclase.[35]

The endogenous level of alpha-agonist can regulate the number of receptors on the surface of target cells. Chemical sympathectomy with 6-hydroxydopamine, results in a significant increase in alpha-adrenoceptors in the rat salivary gland.[36] Conversely, in the presence of excess alpha-adrenergic catecholamines, there is "down regulation" of the alpha-receptor binding sites.[37] Other humoral influences known to regulate alpha-adrenoceptor concentration include estrogen (up regulation), progesterone (down regulation), and thyroxin (down regulation).[3] Of particular interest to the anesthesiologist would be the effect of alpha-blocking agents on receptor number. If the situation is analogous to that for beta-adrenoceptors, then one would expect an elevation in the alpha-adrenergic state following treatment with alpha-adrenergic antagonists.

Demonstration of the presynaptic auto-inhibitory alpha-2 receptor has helped to explain the apparent paradox of the observed increase in inotropic and chronotropic action that occurs after treatment with phentolamine. This drug is a potent antagonist at both postsynaptic alpha-1 receptors and presynaptic alpha-2 receptors. When the normal negative inhibition of norepinephrine on further norepinephrine release is antagonized at the alpha-2 receptor, there is increased secretion of norepinephrine stimulating beta-adrenergic receptors in the heart.[32] Prazosin, on the other hand, while effectively blocking alpha-1 receptors does not antagonize alpha-2 receptors, and therefore does not interfere with the feedback inhibition of norepinephrine release. The absence of beta-adrenergic effects makes prazosin a more effective drug to

selectively reduce blood pressure. Another way to overcome the unwanted beta-adrenergic effects produced by nonselective alpha-adrenergic blockade is to incorporate a beta-blocker in the same preparation. Labetalol is just such an agent and has been successfully used for the treatment of hypertensive patients with angina pectoris.[38]

Dopamine Receptors

Since 1959[39] it has been recognized that dopamine is not only a precursor in the synthesis of epinephrine and norepinephrine but is a neurotransmitter of considerable importance. Defining specific dopamine receptors and physiological responses has been difficult because dopamine also acts directly on alpha- and beta-adrenergic receptors. With the judicious use of alpha- and beta-adrenergic blockade, the selective hormonal, metabolic and cardiovascular effects of dopamine are now established.[41]

There are multiple classes of dopamine receptors in the central and peripheral nervous system. These have been separated according to pharmacological and biochemical criteria.[42] Both acetylcholine and dopamine act as neurotransmitters in basal ganglia. These exert opposing actions and a disturbance in the balance explains many symptoms of basal ganglion disease.[43] In Parkinson's Disease, there is a deficiency of dopamine which leads to the unopposed action of acetylcholine. Therefore, dopamine replacement therapy in the form of levodopa (a precursor of dopamine) or treatment with anticholinergic drugs, will both result in clinical improvement.

Dopamine receptors have also been identified in the hypothalamus and are principally involved in the regulation of prolactin release from the anterior pituitary. Dopamine suppresses prolactin secretion whereas dopamine antagonists such as metoclopramide may result in hyperprolactinemia which is often accompanied by galactorrhea and hypogonadism.[44]

Three dopaminergic systems connect the limbic cortex, basal ganglion, and hypothalamus integrating various aspects of behavior and are thought to be involved in the pathogenesis of schizophrenia.[45] Neuroleptic drugs, such as the phenothiazines and butyrophenones block dopamine receptors. They also ameliorate schizophrenia and other psychoses. The efficacy of the various neuroleptic drugs correlates closely with the affinity of these drugs for dopamine receptors *in vitro*.[46] Another central action of dopamine is to stimulate the chemotrigger zone of the medulla oblongata producing nausea and vomiting. Conversely, dopamine antagonists are clinically effective in suppressing nausea and vomiting.[47] The importance of dopamine as a neurotransmitter in the peripheral autonomic nervous system has only recently been appreciated.[48] In the cardiovascular system it has weak pressor effects on adrenoreceptors only 1/35 and 1/50 as potent as epinephrine and norepinephrine, respectively, but also excites specific dopamine receptors and thus can be classified as both dopaminergic and sympathomimetic. Dopamine receptors have been identified in renal, mesenteric, coronary,[49] and cerebral vessels.[50] Dopamine dilates arteries in these tissues but in contrast has minimal effect on skeletal muscle vasculature. The overall hemodynamic responses are dose-dependent. In doses less than 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, dopamine lowers systemic vascular resistance via selective vasodilation but at higher infusion rates (20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) the pressor responses due to excitation of alpha-adrenergic receptors predominate.[51]

Dopamine receptors have also been identified on the presynaptic membrane of postganglionic sympathetic nerves[52] and in sympathetic ganglia, but their physiologic role, if any, in these sites remains controversial.

Finally, there is evidence for the presence of specific dopamine receptors in the esophagus, stomach, small intestine, pancreas, and submandibular glands.[40] Dopamine diminishes gastrointestinal tone and motility and enhances secretion. Metoclopramide, the dopamine antogonist, reverses these effects.

The mechanism of the physiological response to dopamine in the renal artery is mediated by the adenylate cyclase-stimulated intracellular accumulation of cAMP.[53] However, in other sites, the receptor is not coupled to adenylate cyclase; in the hypothalamus and anterior pituitary, the response to dopamine does not involve cAMP.[42]

Pharmacologic evidence also indicates that there may be several classes of dopamine receptors since separate antagonists are not equally effective at different dopamine receptors. Furthermore, dopamine itself displays a considerable range of potencies at its receptors in different tissues as evidenced by the wide range in affinity constants ascertained by radiolabeled ligand binding studies.[54]

Despite the widespread use of dopamine agonists and antagonists for various behavioral, endocrinological, gastrointestinal, and cardiovascular disorders, the effects of these drugs on regulation of receptor number and binding affinity remain largely unknown. However, estrogen is now known to increase dopamine receptor sensitivity and this is postulated to be the mechanism for the occurrence of chorea in pregnancy and in women taking oral contraceptives.[55]

Acetylcholine Receptors

Acetylcholine is the neurotransmitter present at three distinct classes of receptors which explains the diverse physiological effects attributable to this small molecule. All the receptors appear to work by translating the binding of acetylcholine into opening of discrete channels in excitable membrane, allowing Na^+ and K^+ ions to flow along their electrochemical gradients. Depending on the particular ions that move through the channels, the electric charge they carry, and the direction of their movement, acetylcholine produces excitatory or inhibitory effects.[56] Normally, the action of acetylcholine is terminated by its hydrolysis induced by acetylcholinesterase, and to a lesser extent by diffusion out of the synaptic cleft.[57]

Three classes of peripheral cholinergic receptors can be differentiated by their anatomical location and their binding affinity to various agonists and antagonists. One class is located at the terminals of postganglionic parasympathetic nerves. They are selectively stimulated by muscarine and mediate a variety of responses depending on the target cell. Muscarinic cholinergic receptors have also been identified in non-neuronal locations such as the red blood cell membrane where their function has not yet been elucidated.[58]

The other two classes are agonized by nicotine. Preganglionic nerves of the autonomic nervous system release acetylcholine which interacts with nicotinic receptors at both sympathetic and parasympathetic ganglia. The nicotinic receptor at the postsynaptic membrane mediates skeletal muscle contraction. This receptor has been the most widely studied because of its abundant source in the electric organs of fish which develop embryologically from the same type of tissue that gives rise to striated muscle and has similar acetylcholine receptors.[59]

A current model of the functional mechanism of the acetylcholine receptor proposes that the receptor complex consists of separate macromolecular units,[60] namely a binding site for agonists and antagonists and a site functioning as a selective ion gate or ionophore.[61] Receptor site and ionophore can exist in the resting, active, or desensitized states. Agents can also bind to the ionophore and block ion translocation. This is the proposed mechanism by which local anesthetics produce neuromuscular blockade.

Myasthenia gravis was one of the first disorders in which a membrane receptor abnormality was demonstrated to be a major pathogenetic factor. Myasthenic muscle fibers have diminished sensitivity to acetylcholine at the postsynaptic region because of a reduced number of acetylcholine receptors.[62] This is a consequence of interaction of these receptors with antireceptor antibody[63] which then enhances their degradation rate.[64] Once the immunologic basis for this disease was established, treatment modalities have focused on ways in which receptor concentration could be preserved. Thus, clinical exacerbation may often be controlled with prednisone, azothioprine, thymectomy, or plasmaphoresis.[65] In this manner, sensitivity to acetylcholine is enhanced at the postsynaptic membrane without the use of long-term anticholinesterase therapy.

It has long been known that denervation of skeletal muscle enhances its sensitivity to acetylcholine. Denervated muscle develops a diffuse distribution of acetylcholine receptors over the extrajunctional surfaces and the total number of receptors increases more than 20-fold.[66] Thus, there will be an exacerbated response to stimulation by agonists such as succinylcholine as more receptors are activated. The excessive movement of intracellular potassium through the ion channels results in life-threatening hyperkalemia.

Histamine Receptors

Histamine is stored in tissue mast cells and circulating basophils and is released in response to many stimuli, including antigen-antibody interaction. The heterogeneity of the receptors which mediate this amine's physiologic response is analogous to the heterogeneity of beta-adrenergic receptors. Thus far, two classes of histamine receptors have been identified. H1 receptors mediate contraction of smooth muscles in various organs including the gut and the bronchi. This effect can be suppressed by low concentrations of an H1 antihistaminic such as diphenhydramine.[67] H2 receptors stimulate the secretion of acid by the stomach, increase the heart rate, and inhibit contractions in the rat uterus. These effects cannot be prevented by H1 antihistaminics but are suppressed by the H2 receptor antagonists of which cimetidine is the clinical prototype.[68] Histamine-induced vascular effects, including increased vascular permeability, are mediated by both H1 and H2 receptors.[69] In certain instances, H1 and H2 receptors mediate opposing effects in the same tissue; for example, pulmonary H1-mediated vasoconstriction and H2-mediated vasodilation.

Histamine is present in large quantities in cardiac tissue, mainly in mast cells. Its physiologic role[71] is unclear because of the difficulty of distinguishing direct from reflex actions of histamine on the heart. Histamine increases the sinus rate (chronotropic effect), increases the amplitude of ventricular contraction (inotropic effect), impairs A-V conduction, increases

coronary blood flow, and at high concentrations induces ventricular arrythmias. Only impaired conduction is mediated by the H1 receptor. All the other cardiac effects act via H2 receptors[72] and are expressed through the intracellular accumulation of cAMP.[73]

A role for histamine as a neurotransmitter in the brain has also been proposed,[74] although the evidence is circumstantial. There are H1, H2, and possibly a third type of histamine receptor[75] in the brain, but it is not known whether they act synergistically or antagonistically. H2 receptors in the brain are blocked by the hallucinogen, D-lysergic acid diethylamide (D-LSD) which is equipotent to cimetidine at this site.[76] This may explain the profound confusional states noted in patients with compromised renal function treated with high doses of cimetidine.[77]

Thus far, data concerning regulation of receptor number and binding affinity of histamine receptors have not been reported, but with the increasing use of H1 and H2 receptor antagonists, the finding of "up regulation" in receptor number with enhanced sensitivity to circulating histamine is to be expected.

Benzodiazepine Receptor

There are many drugs which mediate control of behavior. One class of these which has gained wide acceptance and application in clinical anesthesia are the benzodiazepines. They are thought to act at specific synapses in the spinal cord and central nervous system at which the neurotransmitter is gamma-aminobutyric acid (GABA).[78] GABA receptors are coupled to a membrane channel through which chloride ions pass and inhibit nerve impulse conduction. Benzodiazepines selectively facilitate GABA action at these synapses, however, without directly activating GABA receptors nor preventing uptake and metabolic inactivation of this neurotransmitter.

How do they work? There is now evidence for the existence on neural tissue of benzodiazepine binding sites[79] which fulfill all the criteria for receptors (saturability, stereospecificity, and high affinity for a series of benzodiazepine derivatives). The endogenous ligand for these "benzodiazepine receptors" has now been isolated[80] and is thought to compete with diazepam for a regulatory site on the GABA receptor.[81] When the regulatory site is occupied by the endogenous inhibitor, the affinity of the receptor is reduced. When the site is occupied by diazepam, the affinity for GABA is enhanced, thus resulting in inhibition of nerve conduction at the synapse.[82]

This innovative concept could revolutionize ideas regarding drug action in anesthesia, for it is the first example in which a drug competes with an endogenous inhibitor for a binding site which, when occupied, alters the affinity of a neurotransmitter for its receptor.

Opiate Receptors

These receptors were discovered[83] almost five years before their endogenous ligands were first identified.[84] The opiate receptor is strategically located in the regions of the brain and the spinal cord in which pain transmission is thought to occur, and are also found in areas associated with emotion and behavior.[85]

The endogenous ligands for the opiate receptors are two pentapeptides (leu-enkephalin and met-enkephalin) which in turn are products of proteolytic digestion of a 91 residue polypeptide chain, beta-lipotropin synthesized in the pituitary gland.[86]

This protein, also referred to as an endorphin, is devoid of opiate-like activity as the active amino acid sequences (the enkephalins) are inaccessible in the larger polypeptide chain. Proteolytic digestion into smaller chains exposes the enkephalin sequences resulting in peptides called beta-endorphins which have high affinity for opiate receptors.

These ligands appear to mediate an endogenous system of pain inhibition, although the factors activating their release have not been identified.[87] The intravenous administration of synthetic β-endorphin has no analgesic effect in humans, [88] as the polypeptide is unable to cross the blood-brain barrier. Knowledge of the existence of opiate receptors in the substantia gelatinosa of the spinal cord has prompted trials with intrathecally administered β-endorphins. In some cases, this has resulted in an early onset of profound and long-lasting analgesia without the usual side effects of narcotics such as respiratory depression, hypotension, hypothermia, or catatonia.[89] Because of this, it is postulated that there are different subpopulations of receptors which mediate the various pharmacologic effects of opiates. In the future, opiates may conceivably be developed which bind specific subpopulations of receptors to elicit analgesia without respiratory depression.[90]

The mechanism of opiate addiction has vexed the minds of scientists over the years. Theoretical models to explain the observed tolerance to, and physical dependency on narcotics have proposed a decrease in the number of opiate receptors or the proliferation of inactive receptors.[91]

Opiates are known to inhibit adenylate cyclase activity and cAMP production.[92] After withdrawal of opiates from the medium of opiate receptor-bearing cells in culture, there is a striking increase in

the level of cAMP. Thus, there were hopes that treatment with beta-adrenoceptor blocking drugs would provide useful relief of withdrawal symptoms[93] but this has not proved useful.[94] Another finding in opiate withdrawal is an elevation in brain noradrenergic activity,[94] and this has also been postulated as the cause for the signs and symptoms of opiate withdrawal. Clonidine, a central alpha-2 adrenergic agonist, diminishes the release of norepinephrine and hence central beta-adrenergic stimulation, and has been used successfully for the treatment of opiate withdrawal.[95]

Conclusions

Until recently, the receptor concept was mainly of theoretical significance. With the development of techniques for the qualitative and quantitative assessment of receptor function and knowledge of the biological responsiveness of neurotransmitter-mediated pathways, the effects of many drugs used in medicine may now be more accurately predicted. The response of a patient to a drug does not only involve the concentration of the drug in blood and tissues; number and function of receptors are also important factors. Just as advances made in understanding the pharmacokinetics of anesthetic agents permitted development of more rational regimens for their use, the stage is now set for the application of new knowledge of receptor function and regulation to the advancement of the practice of clinical anesthesia.

The author is indebted to Dr. Will Spiegelman for his helpful comments in preparing the manuscript.

Appendixes

Appendix 1. Factors Affecting Beta-adrenergic Receptor Effector Mechanism.

Condition	Effect		Reference
	Number	Coupling	
terbutaline	−		12
propranolol	+		14
alcohol withdrawal	+		17
hyperthyroidism	+		19
hypothyroidism	−		20,21
hypothyroidism (liver)	+		96
amphetamine withdrawal	+		22
guanethidine	+		23
excess Na^+ intake	+		24
isoproterenol	−		97
pseudohypoparathyroidism		−	98

A decrease is indicated by a negative sign (−) and an increase by a positive sign (+).

Appendix 2. Classification of β-adrenergic Receptor Agents.

	β-1	β-2
Agonist	Isoproterenol Epinephrine Norepinephrine Dobutamine Salbutamol Metaproterenol Dopamine	Isoproterenol Epinephrine Norepinephrine Salbutamol Metaproterenol Terbutaline Dopamine
Antagonist	Metaprolol Propranolol	Propranolol

Appendix 3. Factors Affecting α-adrenergic Receptor Number.

Condition	Effect	Reference
chemical sympathectomy	+	36
epinephrine excess	−	37
estrogen	+	99
progesterone	−	99
thyroxin	−	100

Appendix 4. Classification of α-adrenergic Receptor Agents.

	α-1	α-2
Agonists	methoxamine phenylephrine norepinephine epinephrine dopamine	clonidine norepinephrine epinephrine
Antagonists	phentolamine prazosin phenoxybenzamine phenothiazine butyrophenones	phentolamine yohimbine

Appendix 5. Classification of Dopamine-receptor Agents.

Agonist	Antagonist
apomorphine bromocryptine dopamine	phenothiazine butyrophenone metoclopramide sulpiride

APPENDIX 6. CLASSIFICATION OF ACETYLCHOLINE-RECEPTOR AGENTS.

	Agonist	Antagonist
Muscarinic	bethanecol	atropine glycopyrrolate
Nicotinic		
Ganglionic		hexamethonium trimethaphan dopamine (?)
Postsynaptic	succinylcholine	dt curare pancuronium gallamine dm curare

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