7. NEUROTRANSMITTERS AND THEIR RECEPTORS – 2003

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Much has recently been discovered and achieved in the research of neurotransmitters, and much has already been incorporated and elaborated in textbooks and handbooks. Of course, any review of these plentiful new concepts would be more or less subjective unless a longer time is allowed to elapse in-between. Like all other scientific fields, the research of neurotransmitters is characterized by the exponential growth of novel concepts. In contrast, due to the time-consuming nature of drug trials, which is dictated by the ever rising professional demands and safety requirements to be met by new drugs, this inapparent segment of these studies advances at a much slower pace, thus practicing physicians may frequently perceive the amount of novelties in the field to be rather modest. However, the possibility for novel achievements to be utilized in laboratory diagnosis lies somewhere in-between the basic discoveries and the progress in pharmacotherapy.

The last decade has witnessed considerable achievements in all fields of medical research, mostly based on the molecular biology procedures. In the 1990s, the new concepts on the nervous system included characterization of the structure of some major proteins involved in synaptic communication; enzymes that synthesize or breakdown neurotransmitters; proteins that transport them across particular membrane structures (transporters); neurotransmitter receptors, etc. Even more so, it has probably been generally known by now that molecular cloning has discovered more receptors for particular neurotransmitters than they were considered to possess; however, little information apart from their molecular structure is presently available for some of these receptors. In the 1990s, a new concept of ‘feedback messengers’ has emerged, as it was demonstrated that receptor stimulation could stimulate the synthesis of gaseous nitric oxide (NO), which is freely diffused to the surrounding tissues and as a biologically active molecule can influence the activity of presynaptic neurons.

In addition to the concepts mentioned above, which have already become part of the textbook state-of-the-art, there are numerous novel discoveries the practical value of which has occasionally been recognized, but more commonly imply dilemmas. This review is an attempt to briefly present those new concepts in the field.

7.1 Basic concepts on neurotransmitter receptors

7.1.1 The structure of ionotropic receptors – a complex puzzle of Nature

All ionotropic receptors have been shown to consist of a number of different proteins and cloning genes. However, whereas only five subunits are required for binding of functional receptors, about twenty are needed in case of the GABA-A receptor. In case of cholinergic nicotine receptors and receptors for excitation amino acids (NMDA, AMPA, kainate) there are also more subunits than it is needed to form a functional receptor. Consequently, the exact number of the forms of ionotropic receptors present in the brain remains unknown. The question is by no means irrelevant, because the receptor composition has a substantial effect on its pharmacologic properties. Thus, for example, there are GABA-A receptors upon which benzodiazepines have no effect at all, whereas other receptors sustain different effects by different benzodiazepines. In addition, some of the same subunits that form GABA-A receptor in particular regions of the brain will form a glycine receptor with substantially different pharmacologic properties.

7.1.2 Inverse agonists

Inverse agonists, according to definition, denote drugs that increase the number of receptors in inactive conformation instead of stimulating them by increasing the number of receptors in active conformation). The inactive conformation has been demonstrated to be just inactive in certain conditions, thus the inverse agonists resemble antagonists; however, with a substantial difference in that true antagonists abolish instead of summing their effect. It has been shown, however, that particular inverse agonists also possess an intrinsic effect opposite to the effects of true agonists. These findings open many new questions about the function of particular receptors. The said findings have mostly been obtained in vitro, e.g., the findings of inverse agonism for some neuroleptics, thus their
clinical relevance remains unknown. It is obvious, however, that in-depth studies of, for instance, clinical effects of various doses are needed in case of these neuroleptics, where we encounter another question, i.e. is there a clinical ‘instrumentarium’ sensitive enough for these studies?

7.1.3 Dimerization

Dimerization denotes the binding of two receptors to achieve and enhance or modify their effect. The phenomenon of dimerization is known in case of tyrosine kinase receptors for particular growth factors or in intracellular receptors. Because of their specific structure (zinc fingers), intracellular receptors for steroids, thyroid hormones, hormonally active forms of vitamin D and vitamin A, cannot bind to DNA without dimerization or will have completely different effects. It is of interest to note here that there is also a phenomenon of heterodimerization, i.e. binding of various receptors, whereby substantially different effects are achieved in particular cells. The existence of dimerization of G-protein receptors characteristic of neurotransmitters has for quite long been known from in vitro studies; however, its physiologic relevance is hardly discernible at present. So, for example, the metabotropic GABA-B receptor (known as the site of baclofen action) is found in two forms, GABA-B1 and GABA-B2. The receptor monomer causes inhibition of adenyl cyclase at least in vitro, whereas binding of the two receptors also leads to opening of the K-channel, resulting in an additional inhibitory action. Does it mean that the effect of baclofen and other drugs may substantially differ in some patients? The answer to this question remains unknown.

7.1.4 Multiple intracellular signalization

At the beginning of the 1990s, most researchers believed in the existence of relatively simple pathways from receptor stimulation to the achievement of their effect. Based on such a concept, receptors were classified into ionotropic and metabotropic ones. The well known example of ionotropic NMDA receptor that also allows calcium ions to enter the cell, which may have a toxic effect in extreme cases, shows that this basic classification is not fully consistent. However, what has been subsequently discovered, mostly in in vitro conditions, indicates that particular metabotropic receptors can in different conditions follow different signal pathways that include signalization characteristic of growth factors or the one associated with apoptotic cycle.

Consequently, the so-called receptor promiscuity, cross-talk, etc., have been discussed. It should be noted, however, that the signalization and thus probably the effect can modify in different conditions. This principle is not quite new, because it has long been known that stimulation of dopaminergic receptors decreases growth hormone secretion in acromegaly patients and increases it in healthy individuals. Fundamental studies show that such phenomena may be found in a number of additional cases, posing new challenges to those dealing with pharmacology and pharmacotherapy. Accordingly, switching from phase I (healthy volunteers) to more advanced phases of clinical trials may in the future turn much more demanding.

7.1.5 Growth and differentiation control – possible role in neurogenesis

The above concepts are also related to the latest research into the effect of neurotransmitters on cell growth and differentiation. The most intriguing is the phenomenon of neurogenesis, i.e. creation of new neurones from stem cells in human brain. It has been demonstrated that certain drugs with quite specific and known actions on particular neurotransmitter receptors can considerably modify neurogenesis and thus probably also brain plasticity. Although the number of such findings is steadily increasing, it appears to be, as yet, unimply to generalize that all SSRI when administered in therapeutic doses (there are some individual data) increase the formation of new neurones in the brain. On the other hand, however, we do not know yet whether it is really good or not. The experimental findings, suggesting that neurogenesis could be initiated in the damaged parts of the brain, fire the imagination and raise hopes of the researchers that, one of these days, brain lesions will also be treatable.

7.2 ‘New neurotransmitters’ and newly recognized functions of known neurotransmitters

7.2.1 Endocannabinoids

Toward the end of 1980s, the receptors for cannabis (central or cerebral CBR-1 and peripheral CBR-2, characteristic of immune system cells) were cloned, and potential endogenous ligands of these receptors were isolated from the brain, anandamide being best known among them (arachidonyl ethanolamide, all are arachidonic acid derivatives). The highest amounts of enzymes involved in the synthesis and breakdown of anandamide were found in the regions with highest receptor density, i.e. hippocampus and globus pallidus. The functions of anandamide might prove very interesting because of the numerous pharmacologic effects of
alkaloids obtained from cannabis (antiemetic, analgesic, euphoric, immunosuppressive, etc.).

Considering the high CB1 receptor density in the hippocampus and the indicators showing that marijuana impairs memory, the research of the role of endocannabinoids in cognitive functions may prove highly intriguing. Besides its effects on specific cannabinoid receptors, anandamide also exerts an action on vanilloid receptors (VR1), thus additionally extending the possible clinical use of cannabis derivatives.

7.2.2 Agmatine

Agmatine was discovered in the 1990s as a potential endogenous ligand of imidazole receptors in the brain, among others influenced by the well-known antihypertensive clonidine. Since that time, studies provide ever more convincing evidence that it probably is a newly discovered neurotransmitter system in the brain, its functions being ever more extensively investigated.

7.2.3 Is there an endogenous ligand for GHB receptors?

Gamma hydroxybutyrate (GHB) is an endogenous substance used as an illegal drug depem (so-called ‘liquid ecstasy’), and recently also as a medicine (see below). As a ‘drug’, it is usually categorized among ‘designer drugs’ or ‘club drugs’; however, it induces an alcohol- or sedative-like effect. Most intriguing is its completely different mechanism of action. So, specific GHB receptors have been found in the brain. According to current analogy (detection of opiate, benzodiazepine or cannabinoid receptors first, then detection of their endogenous ligands), it might be expected that in the near future we will face convincing data on the existence of endogenous ligands, potential neurotransmitters acting upon GHB receptors.

7.2.4 Newly detected functions of glutamate receptors

It has been assumed for a dozen years now that glutamate and NMDA receptors in the hippocampus are of special importance for memory formation. This is substantiated by the NMDA receptor specificity, having the characteristics of both ion channel and ionotropic receptor, so, depolarization is required to render the receptor capable of reacting to glutamate, thus acting as a sort of ‘coincidence’ detector. This, along with the role of NO secreted from the neurones stimulated via NMDA receptors, enables the classic ‘Hebb’s synapse’ to explain as a theoretical model of key importance for memory processes. Recent data on the issue are in a way spectacular. Mice with excessive or deficient NMDA receptors in the hippocampus were obtained by genetic manipulations. The former were found to learn and master cognitive tests for the hippocampus; the latter were found to learn and master cognitive tests for the hippocampus. The latter were found not to learn and master cognitive tests for the hippocampus.

In addition to these latest discoveries, some of the ‘classic’ ones have not yet been fully elucidated. One of the most important is that agonists of ionotropic glutamate receptors can be ‘excitotoxic’, i.e. can cause cell damage and cell death. A too intensive stimulus leads to excessive entry of Ca++ and other ions into the cell, thus leading to changes in osmolarity and toxic effects of Ca++ ions. This stimuli toxicity underlies the belief that excessive activity of these neurones may be involved in the pathogenesis of a number of disorders. In contrast to this, in experimental conditions, all antagonists of the receptors for excitation amino acids have certain antiepileptic, ischaemia-protective and other properties. That is why the great number of studies investigating the pathophysiologic relevance of these receptors are no surprise.

Excitotoxic amino acids are also found in nature. Glutamate itself, used as a spice, does not cross the blood-brain barrier. However, lethal poisoning with shellfish, caused by the presence of domoic acid, has been reported. Neurotoxicity, which is endemic in the Indian subcontinent, develops as a consequence of dietary intake of seeds of Lathyrus sativus, which contains the excitotoxic amino acid β-N-oxyl aminoalanine. The Pacific amyotrophic lateral sclerosis, which is usually accompanied by Parkinsonism and dementia, is considered to be consequential to dietary intake of flour made from the fruits of the cycad palm (Cycad circinalis) containing β-N-methylaminoalanine in which reaction with CO2 also becomes excitotoxic. The ‘pantherine syndrome’ in mushroom poisoning (Amanita pantherina and others) can be explained by the presence of ibotenic acid. A rare congenital disorder of sulphite oxidase deficiency leads to the formation of endogenous excitotoxic amino acids (5-sulphohysteine), degeneration of various parts of the brain and very early death. An enhanced activity of excitation neurones appears to be almost logically associated with the pathogenesis of epilepsy. The strongest evidence for this is that practically all antagonists of excitation amino acid receptors have certain antiepileptic properties. It is considered that various stimuli, primarily ischaemia (CVI, perinatal asphyxia, etc.), can lead to the pathologic activity of excitation neurotransmitters, i.e. to their excitotoxic action and death of innervated neurones.

Experimentally, virtually all ionotropic receptor antagonists (from the classic antitussic dextromethorphan, however, AMPA antagonists are more efficient) reduce ischaemic lesions (‘penumbra’). The neuroprotective effect of deprenyl has also been associated with the metabolism of polyamines acting on NMDA receptors. Studies are also under way of memantine in Alzheimer’s disease, characterized by both acetylcholine and glutamate deficiency. In Huntington’s chorea, destruction of GABA neurons is most pronounced, however, there is also a NMDA receptor deficiency. According to some hypotheses, GABA neurons are being destroyed by these very receptors, and the administration of excitotoxic amino acids (kainate, quisquialate, etc.) into the striatum of experimental animals has been a generally accepted animal model of the disease.

The latest studies have shown that there is a deficient glutamate uptake in the specifically damaged segments of the nervous system in amyotrophic lateral sclerosis. Therefore, glutamate may accumulate in excitotoxic concentrations. Patients’ CSF specifically induces neuronal death in cell culture, which can be prevented by ionotropic receptor antagonists. Initial clinical trials with riluzol, which seems to block the secretion of glutamate, are quite promising.

Recent studies have related glutamate to Rasmussen syndrome (encephalitis). It is one of the most severe chronic and progressive forms of epilepsy in children with hemiparesis, hemianopia, aphasia, etc. Because the disease is refractory to classical antiepileptics, radical procedures like hemispherectomy have to date been used in the treatment. Antibodies to GluR3 receptor subunit were found in patient plasma. Removal of these antibodies by plasmapheresis reduces the frequency of epileptic seizures. The antibodies activate ionotropic glutamate receptors, which can be prevented by the experimental drug CNOX that blocks the AMPA/kainate receptors.

7.2.5 Recent concepts on nicotine receptor.

All nicotine receptor subunits (α, β, δ, γ and ε) and their subtypes were cloned in the 1990s. Muscarinic receptor subtypes (M1 – M5)
were also cloned. Cholinergic system impairments underlie a number of diseases; classical concepts refer to myasthenia and congenital myasthenic syndromes, Alzheimer’s disease, Lambert-Eaton syndrome, Parkinsonism and various poisonings (poison gases, botulism, insecticides, drugs, araneism). Mutations of the α- and/or δ-receptor subunit have recently been demonstrated to underlie congenital myasthenic syndrome with impaired acetylcholine binding and/or nicotine receptor regulation. Furthermore, it has been shown that cholinergic deficit in Alzheimer’s disease is not just a consequence of Aβ-peptide neurotoxicity; namely, Aβ inhibits acetylcholine synthesis and muscarinic receptor binding to Gq/11 proteins. In pharmacotherapy, attention has been especially attracted by the use of several inhibitors of acetylcholine esterase in the management of Alzheimer’s disease.

### 7.2.6 Some recent concepts on catecholamines

Synaptic importers that selectively transmit dopamine (DAT) or norepinephrine (NAT) from the synaptic cleft to presynaptic nerve endings, and nonselective vesicular importers for monoamines that store monoamines in synaptic vesicles of presynaptic ending, have also been cloned. Synaptic transporters for a particular catecholamine are the site of action for drugs such as antidepressants (NAT), benzotropine (DAT), or cocaine (DAT). Vesicular carriers are found in two isoforms: VMAT1 (in chromaffin and enterochromaffin cells, the inhibitor is fenfluramine) and VMAT2 (in central, peripheral and enteric neurons, catecholamines have higher affinity for them, and potent inhibitors are amphetamine, rezerpine, etc.). Gene expression for DAT and VMAT2 is decreased in Parkinson’s disease, for DAT in Lesch-Nyhan disease, and for NAT in Alzheimer’s disease.

Concerning Parkinson’s and Alzheimer’s disease, the neuroprotective treatment based on the effect of seleagine (a selective irreversible MAO-B inhibitor) that prevents the development of MPTP Parkinsonism attracted much attention in 1990s. According to the ‘oxidative stress’ hypothesis, the free radicals formed by auto- and enzymatic (MAO-B) oxidative dopamine degradation, have a cytotoxic effect on striatal dopaminergic neurones. Studies are under way of a novel, reversible MAO-B inhibitor, lazabemide, which, in contrast to seleagine, is not metabolized into active metabolites and has short action. Therapeutically, in addition to dopaminomimetics and anticholinergics, particular NMDA receptor antagonists (e.g., memantine, similar to amantadine) have been emerging, which is considered substantial for their efficacy.

### 7.2.8 GABA

GABA is the most frequent inhibitory neurotransmitter in the brain (about 30% of all neurons). GABA-A receptor is an ion channel, pentameric protein composed of 2α, 2β and 1γ, or p subunits that modulate the chloride channel opening between them. At least 18 isoforms of the main subunits have been cloned: α1-6, β1-4, γ1-4, δ, and ρ1-2, encoded by different genes, which can bind variably and form (theoretically) hundreds of combinations. The molecular heterogeneity of these receptors is the reason for different binding of particular ligands and their variable pharmacologic effect. The best-investigated binding sites on the GABA-A receptor are those for GABA, benzodiazepines, barbiturates and picrotoxin, ethanol and neurosteroids. A homomer receptor composed exclusively of p subunits has been detected in the retina, proposed to be named GABA-C receptor. It is characterized by absence of the characteristic benzodiazepine and bicuculline effect. GABA-B receptor acts via G protein, and there are two forms, B1 and B2 receptor. As mentioned above, it seems that it is only by dimerization that these two receptors achieve their full biochemical effects, classically considered to be characteristic of GABA-B receptors. The genes for 4 carriers (GAT1-3, BGT1 transporters) that transmit GABA from the synaptic cleft to the presynaptic neuronal endings and surrounding glia cells, were also cloned in the 1990s. Furthermore, new antiepileptics acting on GABA-ergic transmission were synthesized in the 1990s. Vigabatrin is an irreversible GABA-transaminase inhibitor, efficacious in the treatment of complex partial (more potent) and generalized tonic/clonic (less potent) seizures in patients refractory to classical antiepileptics, and possibly also in the management of stiff-man syndrome. However, there also are reports on the occurrence of intramyelin oedema with its use. Gabapentin increases the release of GABA. Felbamate indirectly enhances the effect of GABA and also inhibits the excitatory effects mediated by NMDA receptors. It is efficacious in the management of complex partial seizures and Lennox-Gastaut syndrome; however, there is the risk of aplastic anaemia. Levetiracetam is a potential ligand of GABA-A receptor. Topiramate is a carbonic anhydrase inhibitor, its anticonvulsant effect being based on potentiating the effect of GABA by binding to α, as yet, unidentified site. Clinical trials with triazole based drugs, e.g., loreclezol, which binds to β, or β subunit of GABA-A receptor, are under way. Tiagabine is a potent inhibitor of GAT1 GABA
transporter in neurones and glia cells, which is currently in phase III clinical trials.

Baclofen is a selective GABA-B receptor agonist that has recently been tried to administer intrathecally in the form of an implanted programmed pump. It is efficacious in spinal level spasticity, whereas in cerebral lesions intrathecal administration of baclofen led to epileptic seizures.

Studies have pointed to the presence of antibodies to glutamic acid decarboxylase, GAD65 (the enzyme is found in two isoforms, GAD65 and GAD67) in stiff-man syndrome, with consequential decrease in GABA synthesis.

7.2 Glycine

Glycine is an inhibitory neurotransmitter found in the spinal cord and brain stem. The receptor consists of 5 subunits with a chloride channel in-between. The few recent studies of the management of nonketotic hyperglycaemia, a rare metabolic disease characterized by an increased level of glycine in CSF and serum, and neuropsychically by motor dysfunction, indicate that besides striatone, the use of dextromethorphan and ketamine (NMDA receptor blockers) that also possess a binding site for glycine, is therapeutically efficient; however, the physiologic role of this receptor differs substantially from that of glycine. One case of optic nerve atrophy with consequential blindness has been recorded in this disorder. There are two literature case reports of a new form of hereditary metabolic disease, deficiency of 3-glycerate dehydrogenase, an enzyme involved in serine synthesis. The disease is characterized by low plasma and CSF levels of serine, and low CSF glycine. Cerebral atrophy and impaired myelination, and clinically congenital microcephaly, severe psychomotor retardation, hypotonia, hypogonadism and epilepsy have been described. The occurrence of seizures was prevented by peroral administration of serine.

7.2.10 Neuropeptides

Among a dozen of opioid polypeptides, new ones such as nociceptin or orphanin FQ with strongest expression in the brain and spinal cord have been identified. Orphanin receptor, ORL1, structurally similar to opiate receptors but without opioid effects, has also been identified. The role of endogenous opioids in the control of pain sensation, mood, hypothalamic hormone release and coughing reflex as well as their peripheral effects have been recognized. Over the past few years, the existence of a peptide ‘antiopioid’ system in the body has been demonstrated. Nociceptin, CCK and especially neuropeptide FF exert a pronociceptive (‘antiopioid’) action. The development of tolerance to the analgetic effect of opiates is associated with the increase in the number of neuropeptide FF-immunoreactive neurones in the spinal cord, medulla oblongata and hypothalamus. Hyperstimulation of the opioid system (opiate abuse) is considered to activate ‘antiopioids’, which then mediate the development of tolerance and withdrawal syndrome.

The calcitonin gene-related polypeptide (CGRP) is synthesized by specific sensory nonmyelinated neurones and brain neurones. The effects of CGRP include vasodilatation and increased vascular wall permeability. Neural CGRP has been demonstrated to accelerate wound healing, contribute to the occurrence of idiopathic persistent coughing syndrome, favour inflammation and cause cerebrovascular dilatation, whereas its deficiency is associated with the occurrence of spasms and vascular malformations. Neuropeptide Y (NPY) is most abundantly present in arcuate and paraventricular nuclei of the hypothalamus and peripheral sympathetic nerves. There is ever more evidence for the importance of NPY in the central metabolic regulation, also showing that hypothalamic NPY impairments are crucial in the development of obesity and cachexia.

In the author’s opinion, orexins or hypocretins belong to most intriguing neuropeptides discovered in recent years. These are hypothalamic polypeptides which are especially important for their, as it seems, central role in the regulation of eating and sleep. Great attention is paid to the studies in knockout experimental animals and studies indicating ever more tighter association between these neuropeptides and narcolepsy. Interestingly enough, orexins were discovered by a procedure denoted as reverse pharmacology. Starting from the existence of codes for 7 transmembrane (lipophilic) segments characteristic of G-protein-bound receptors, such ‘orphan’ receptors had been formed in vitro, whereas their endogenous ligands were searched for in tissue extracts.

7.3 New drugs – drugs under development

Attempts have been made at pharmacologic manipulation with all those mentioned above, and new drugs are probably tried to create. Unfortunately, keeping the results secret until drug registration is an ever more pronounced characteristic of the research in the pharmaceutical industry. Therefore, it is now quite difficult to state what and how intensive the research is. For instance, in the case of sildenafil (Viagra) the professional public was informed on relevant results only upon the drug had been registered in the United States. Immediately after the registration, a document on its effects and other features could only be found on the Food and Drug Administration (FDA) web site.

According to the author’s opinion, most interesting of the virtually new drugs that have appeared on the market (USA) are the following:

Atomoxetin – a new drug for the treatment of attention disorders, hyperkinetic syndrome in children, also called minimal brain dysfunction (and usually attention-deficit disorder). According to available data, atomoxetin is a blocker of norepinephrine reuptake and therefore similar to antidepressants. It has no major psychostimulatory properties and should not cause dependence, as differentiated from classical psychostimulants (methylphenidate being most frequently used). Pharmacodynamic differences between antidepressants and psychostimulants are not adequately recognized in our setting, thus they are briefly explained below.

The drugs acting on the release/secretion of neurotransmitter are currently classified into two groups:

1) Transporter (reuptake) blockers, inhibitors that simply retain neurotransmitters in the synaptic cleft. Excessive retaining is self-regulated by the inhibitory presynaptic receptors. Numerous antidepressants belong to this group.

2) Substrate-like secretors are also bound to the synaptic transporter and enter the presynaptic cleft, however, changing the synaptic transporter in a manner not yet fully explained, to make it a neurotransmitter ‘exporter’ instead of ‘importer’. There are some indices that vesicular transporter is also blocked by some of these drugs. This results in nonvesicular neurotransmitter secretion into the synaptic cleft. Vesicular secretion is being controlled by presynaptic inhibitory receptors, whereas nonvesicular secretion
has no self-control. Such an action is elicited by sympathomimetics and some other substances that differ substantially from antidepressants by their central and peripheral effects.

Gamma-hydroxybutyrate (GHB) has been presented above as a ‘drug’ with specific receptors. In 2002, FDA approved the use of this substance (Xyrem) for the treatment of a small number of patients suffering from narcolepsy accompanied by cataplexy (muscular weakness and hypotonia). The mechanism of action is not fully clarified; however, GHB abuse in sports, allegedly to improve physical ability, has been reported.

Buprenorphine and combination of buprenorphine and naloxone in the treatment of opiate dependence. Buprenorphine is a long-acting agonist of opiate receptors, which has in some countries been used instead of methadone in the treatment of opiate dependence. The novelty in the preparation of buprenorphine is a low dose of naloxone for sublingual use. Sublingual buprenorphine is well resorbed, while naloxone is primarily added to prevent the drug appearing on the illegal market, because as such it is absolutely inappropriate for intravenous abuse, which generally poses great problems in methadone maintenance therapy (the introduction of methadone maintenance programs is frequently accompanied by an increased number of lethal methadone intoxication which has thus reached illegal market).

7.4 Conclusion

Neurosciences have beyond doubt grown into one of the most dynamic fields of scientific research. The intention of this presentation is to provide a review of most significant recent discoveries that have major impact on our understanding and management of neurologic diseases. Although neuroscientific research may seem distant from the viewpoint of practicing physicians, and too slow from the patients’ standpoint, the great number and credibility of the new discoveries related to neurotransmitters raise more hope than ever before. The way from a basic discovery to its practical implementation and verification is very demanding and both time- and money-consuming. In neurosciences, the time has obviously come for well-designed and organized clinical trials. Of course, basic research will by no means be abandoned. For example, it has been calculated that current drugs act on 417 ‘pharmacologic receptors’ in the human body (receptors, enzymes, ion channels, etc.). In contrast, analysis of the Human Genome Project has shown that there are 3,000 to 10,000 molecules, the possible sites of drug action. At present we know that among these molecules there are hundreds of ‘orphan’ G-protein receptors with as yet unidentified endogenous ligands – that among these molecules there are hundreds of ‘orphan’ G-protein receptors with as yet unidentified endogenous ligands – including neurotransmitters, hormones, autacoids. Evidently, the time of neuropharmacology and clinical biochemistry of neurologic and psychiatric disorders is yet to come.

References


Schematic picture of GABA A receptor with its binding site

http://homepage.psy.utexas.edu/homepage/Class/Psy301/Salinas/sec2/Brain/37.GIF