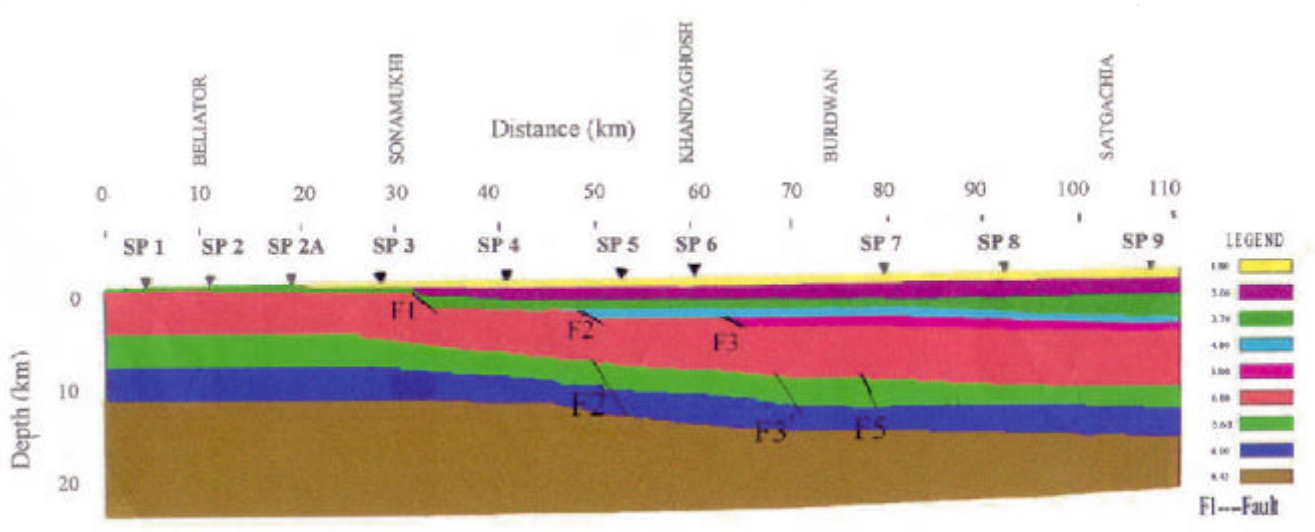

Figure 2. Velocity depth section of Beliator–Burdwan profile.

contain thick columns of recent river deposits and the deposits in and around Burdwan are saturated with shallow groundwater. A relook into the velocity–depth section in light of some specific indications in the record sections of SPs 5, 6, 7 and 8 suggests probable presence of hidden faults (F_2' F_3' and F_3) below the basement in the zone between Sonamukhi–Khandaghosh and Khandaghosh–Burdwan. The suggested fault zone of this area and other en-echelon faults (Figure 2) can be locales for release of accumulated stresses, if any. As such it is suggested that seismic surveillance could be of some definite use to understand the seismicity of this region, especially in view of its proximity to the known highly seismic north-eastern segment of the Indian continent.

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NEWS

Signal transduction in the nervous system: The 2000 Nobel Prize for physiology or medicine

P. K. Gupta

One of the important characteristics of all animal systems is their ability to respond rapidly to stimuli such as sight, sound, smell, etc. This involves intercellular communications that are often described as signal transduction. These communications between the brain cells or neurons are very fast (100 m/sec or more), and cannot be brought about due to hormones that are carried by the blood or the lymph at a much slower speed. Transfer of signal from one neuron to another through junctions called synapses is also described as synaptic transmission, which can be electrical or chemical in nature (Figure 1). This subject has been a very active area of research in recent years, due to its direct bearing on understanding the causes of several neurological disorders, which are common in human beings. Arvid Carlsson, Paul Greengard and Eric Kandel, the three Nobel Laureates in Physiology or Medicine for the year 2000, have made pioneering discoveries concerning signal transduction, that is described as *slow synaptic transmission* (*slow synaptic transmission* involves chemical synapse as against *fast synaptic transmission*, which involves electrical synapse). These discoveries have

been crucial for an understanding of the normal function of the brain and to explain how disturbances in signal transduction in brain cells can give rise to neurological and psychiatric diseases. The research conducted by these three Nobel Laureates has also resulted in the development of new drugs and therapies for these diseases.

Carlsson, Greengard and Kandel received the Nobel Prize for the following discoveries. Arvid Carlsson from the Department of Pharmacology, University of Gothenburg (Sweden) was rewarded for his discovery of the neurotransmitter dopamine, whose deficiency in certain parts of the brain causes Parkinson's disease (PD). Paul Greengard from the Laboratory of Molecular and Cellular Science, Rockefeller University, New York, USA, was rewarded for his discovery of the mechanism of action of dopamine and a number of other neurotransmitters. Eric Kandel from the Center for Neurobiology and Behavior, Columbia University, New York, USA, was rewarded for his discovery of how the efficiency of synapses can be modified for short-term and long-term learning/memory, and what molecular mechanisms are involved in this modification.

A broad outline of the general aspects of signal transduction in the nervous system, which is the subject of the Nobel Prize for Physiology or Medicine this year will be presented in this article. The subject of therapy and treatment for PD, although not a subject of the Nobel Prize, will also be dealt briefly.

Two types of synaptic transmissions

A neuron transmits a signal to another neuron through a synapse or a synaptic cleft, characterized by the space between two adjoining neurons. The intercellular communications between neurons are facilitated by nerve impulses or action potentials moving at a speed of 100 m/sec or more. The action potentials are transmitted in the form of transient changes in potential differences across the membranes of the neurons, generated by ion gradients, involving K^+, Na^+ and Cl^- ions. The ion gradients are caused by the regular release of ions from ion channels located in the membranes of neurons. Synapses can be either electrical in nature, involving *fast synaptic transmission* that lasts for a short duration or they can be chemical in nature, involving *slow synaptic transmission* which lasts for a long duration. Only the latter is the subject of the Nobel Prize this year. The electrical synapses are small (~ 0.2 nm), in which the membranes are connected to each other with gap junction channels to allow flow of ionic current in both the directions. The chemical synapses, on the other hand, are relatively large (20–50 nm) to allow transmission of signal through a chemical substance synthesized within the nerve terminal. In electrical synapses, the arrival of the action potential at the presynaptic membrane leads directly to depolarization of the postsynaptic membrane and a new action potential is initiated in the postsynaptic cells. In chemical synapses, the action potential causes secretion of a chemical substance called neurotransmitter by the presynaptic cell, with the help of structures described as synaptic vesicles (SVs). The secreted neurotransmitter binds to its receptor on the postsynaptic membrane to initiate a cascade of events leading to a specific response[1].

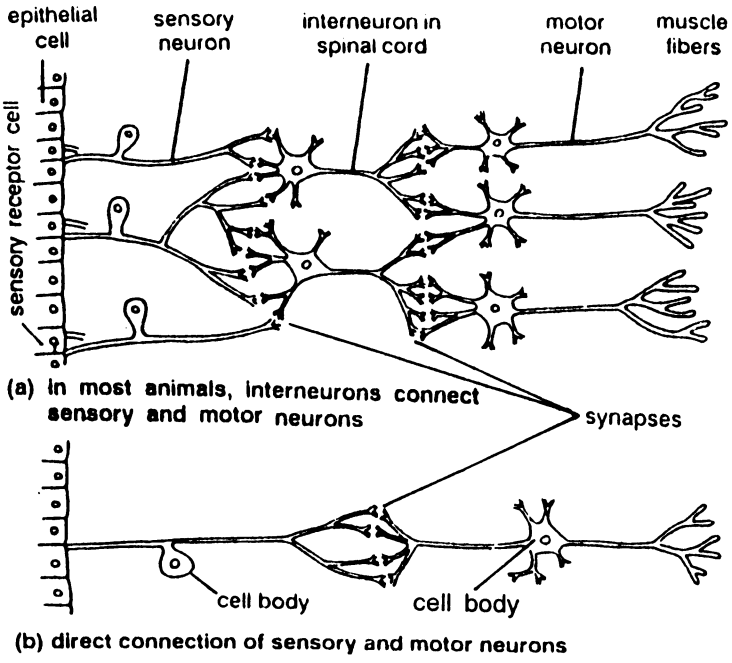

Figure 1. Formation of two different types of synapses for signal transduction in nerve terminals.

Slow synaptic transmission and the synaptic vesicle cycle

In slow synaptic transmission, an SV cycle operates at the nerve terminals. The cycle takes about a minute, and involves the following steps[2] (Figure 2). (i) SVs, filled with neurotransmitter dock at the active zone opposite to the synaptic cleft or synapse. (ii) SVs undergo membrane fusion triggered by Ca^{++} ions and release the neurotransmitter in the synaptic cleft. (iii) Empty SV membranes are internalized by formation of clathrin-coated pits, which form the coated vesicles. (iv) Coated vesicles shed their coats and fuse with early endosomes. (v) SVs are regenerated due to budding from endosomes and accumulate neurotransmitter by active transport driven by an electrochemical gradient created by a proton pump. (vi) SVs with neurotransmitter again approach the active zone for membrane fusion and release of neurotransmitter, thus starting another cycle.

Proteins involved in the formation of synaptic vesicle

The SVs consist of a variety of proteins, which include (i) *transport proteins* that facilitate uptake of neurotransmitters and (ii) *trafficking proteins* that mediate docking, fusion and budding. A number of other interacting proteins are also involved in the SV cycle (Table 1; Figure 3). Synapsins, that were identified for the first time by Paul Greengard and coworkers, account for ~ 9% of all SV proteins. However, synapsins are only peripherally associated with the cytoplasmic surface of the SVs, and bind actin with high affi-

nity, so that they may cross-link SVs with actin[3–6]. Synapsins have been classified mainly as Ia, Ib, IIa and IIb, although, recently a third type (synapsin III) has also been described by Paul Greengard and coworkers[7]. Synapsins have similar N-terminal domains, but differ at the C-terminal domains. The N-terminal domains provide sites for phosphorylation due to cAMP-dependent protein kinase A (PKA) and Ca^{++}/calmodulin-dependent protein kinases (CaMKI, CaMKII)[8,9].

Synapsin I (but not synapsin II) also contains proline-rich C-terminal domains that function as phosphorylation sites for CaMKII. The different synapsins and their phosphorylation regulate SV-traffic, but they may not be essential for either the SV-development or the SV-traffic. Through the use of synapsin I knockout mice also, it has been shown that for the basic process of neurotransmitter release at the synapse, synapsin I is dispensable. Synapsins have actually been shown to control only the availability of SVs for release of the neurotransmitter. For instance, it has been shown that small pools of ready-to-fuse docked SVs are always present at the presynaptic terminals. However, it is only with the help of synapsins, that a large reserve pool of SVs becomes available, to be used when strong stimulation needs large quantities of neurotransmitter. The human synapsin III gene has also recently been identified as a candidate gene for schizophrenia[7].

Phosphorylation of proteins and alterations in the function of nerve cells

Paul Greengard and coworkers had shown for the first time that slow synaptic transmission involved phosphorylation of certain proteins (particularly synapsins), thus altering their function[10–13]. Greengard's discoveries concerning protein phosphorylation have increased our understanding of the mechanism of action of several drugs, which specifically affect the phosphorylation of proteins in different nerve cells. For instance, he demonstrated that when dopamine stimulates a receptor in the cell membrane, it causes an elevation in the level of cyclic AMP (a second messenger) in the cell, thus activating a Protein Kinase A (PKA), bringing about phosphorylation of certain proteins in the nerve cells (Figure 4). One important group of such proteins form ion channels in the membrane of the cell. They control the excitability of the nerve cell and make it possible for the nerve cell to send electrical impulses along its axons and terminals. Each nerve cell has different ion channels, which determine the reaction of the cell. When a particular type of ion channel is phosphorylated, the function of the nerve cell may be altered by, for example, a change in its excitability. Several other proteins that have been shown to undergo phosphorylation at the nerve terminals include synapsin, synaptophysin and synaptobrevin[14,15] (Figure 3).

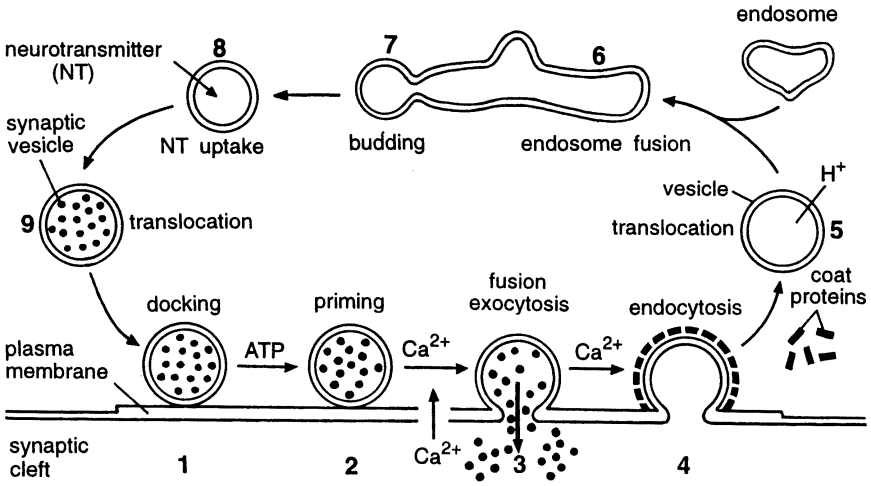

Figure 2. Different steps (1–9) of the synaptic vesicle cycle in the presynaptic nerve terminal (modified from ref. 2).

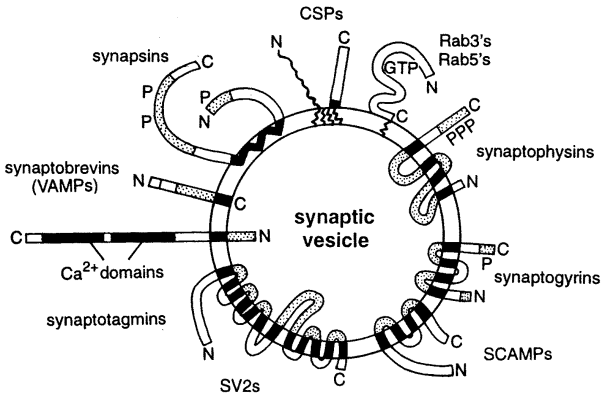

Figure 3. Structure of some major proteins of synaptic vesicles. In each protein, the N terminus is marked by N, the C terminus is marked by C and phosphorylation sites are marked by P; for abbreviations, see Table 1 (modified from ref. 2).

Neurotransmitters and their receptors

Neurotransmitters (including dopamine)

A variety of small molecules, including acetylcholine, glutamate, GABA and dopa-

Table 1. Summary of synaptic proteins involved in the release of neurotransmitter

SV proteins: CSPs (cysteine string proteins), cytochrome b561, *abg* (secretory carrier membrane proteins), SV2s, synapsins Ia, Ib, IIa, IIb, synaptobrevins (VAMPs), synaptogyrins, synaptophysins, synaptotagmins, transport proteins (channels) for chloride and zinc, vacuolar proton pump

SV associated proteins: Amphiphysin, AP2 and clathrin, CaMKI and CaMKII (Ca^{2+}, calmodulin-dependent kinases), dynamin 1, dynein, GDIs (GDP associated inhibitors), kinesins, MSS4, $pp60^{SPC}$

Synaptic membrane proteins: Munc13s, neurexins, SNAP-25, syntaxins, (originally named HPC-1), voltage-gated Ca^{2+} channels

Proteins that associate with plasma membrane proteins reversibly: Complexins, Munc18s, NSF (N-ethylmaleimide sensitive factor), *a*/*b*/*g*-SNAPs

mine, can serve as neurotransmitters[16] (Table 2). Each of these chemicals can serve more than one function. For instance, a chemical which functions as a neurotransmitter can also be released in the bloodstream to serve as a hormone. By definition, a substance functions as a neurotransmitter when the chemical is synthesized in the neuron. It is present in the presynaptic terminals and is released in the synaptic cleft to bring about a short-distance signalling effect on the postsynaptic neuron. From the synaptic cleft, the presynaptic terminal also reuptakes the neurotransmitter to be utilized in another SV cycle. It has also been shown that a neurotransmitter administered as a drug in comparable concentrations exerts the same effect as the native neurotransmitter does *in vivo* at the sites of synapses[1].

Towards the end of the 1960s, although it was known that dopamine, noradrenaline and serotonin were used as neurotransmitters in the central nervous system, knowledge about the mechanism of their action was lacking. Paul Greengard shares the 2000 Nobel Prize for elucidating the mechanism of their action at the synapses. Neurotransmitters such as dopamine, noradrenaline, serotonin and certain neuropeptides transmit their signals by what is referred to as *slow synaptic transmission*. The resulting change in the function of nerve cells may last from seconds to hours. This type of signal transmission is responsible for a number of basic functions in the nervous system and is of importance in, for example, alertness and mood. Slow synaptic transmission can also control fast synaptic transmission, thus enabling actions like speech, movements and sensory perception.

Catecholamine neurotransmitters and biochemistry of neurological disorders

Catecholamines are utilized as neurotransmitters in the brain and as hormones in the circulatory system. They are synthesized from tyrosine, both in sympathetic neurons and in the adrenal glands. Tyrosine is hydroxylated by tyrosine hydroxylase to form 3,4-dihydroxyphenylalanine (L-dopa), which gives rise to dopamine (Figure 4), by the enzyme aromatic amino acid decarboxylase (AADC) or dopa decarboxylase. Subsequent hydroxylation of dopamine results in the formation of norepinephrine (noradrenaline), which on methylation forms epinephrine (adrenaline). Defects in catecholamine processing are responsible for many neurological disorders, including clinical depression involving norepinephrine (NE) and Parkinsonism involving dopamine (DA). NE and DA are packaged in SVs and are released in synaptic clefts, where they bind to their receptors in the postsynaptic membranes, to elicit specific responses. After performing their function, they are removed from the synaptic cleft and are taken up either by the presynaptic membranes or by other glial cell membranes, with the help of membrane transporters or uptake proteins available in these membranes. In the presynaptic neuron, the catecholamine is packaged again in the SVs with the help of H^+-ATPase/H^+-ligand exchange mechanism to start another SV cycle. The catecholamine neurotransmitters can also be metabolized and inactivated by two enzymes, catechol-O-methyl-transferase in the synaptic cleft and monoamine oxidase (MOA-B) in the mitochondria[16]. For the treatment of clinical depression, AADC/MOA-B inhibitors and tricylics such as desipramine are used as antidepressants, leading to either an increase

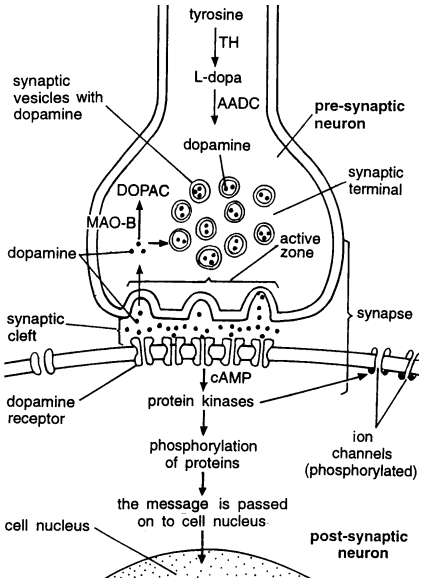

Figure 4. Prototypic dopaminergic terminal with cycle of synthesis, storage, release and removal of dopamine; TH = tyrosine hydroxylase, AADC = aromatic amino acid decarboxylase (modified from ref. 33).

Table 2. Different classes of neurotransmitters with suitable examples (modified from ref. 16)

Class of neurotransmitter	Family of different neurotransmitters
Cholinergic agents	Acetylcholine
Catecholamine	Norepinephrine (noradrenaline), epinephrine (adrenaline), L-dopa, dopamine, octopamine
Amino acids and derivatives	*g*-aminobutyric acid (GABA), alanine, aspartate, cystathione, glycine, glutamate, histamine, proline, serotonin, taurine, tyrosine
Peptide neurotransmitters	Cholecystokinin, enkephalins and endorphins, gastrin, gonadotropin, neurotransin, oxytocin, secretin, somatostatin, substance P, Thyrotropin Releasing Factor (TRF), vasopressin, Vasoactive Intestinal Peptide (VIP)
Gaseous neurotransmitters	Carbon monoxide (CO), nitric oxide (NO)

in the level of catecholamines in the brain or to facilitate more prolonged stimulation of post-synaptic NE receptors.

Dopamine theory of Parkinson's disease

Parkinsonism, characterized by tremors, rigidity and hypokinesia (reduced ability for spontaneous movements), is caused by the degeneration of dopaminergic neurons. It was previously believed that dopamine was only a precursor of another neurotransmitter, noradrenaline, but during the 1950s, it was conclusively shown for the first time by Arvid Carlsson that PD is caused by a deficiency of dopamine. This is popularly described as 'dopamine theory of Parkinson's disease'. A series of pioneering studies conducted by Carlsson during the late 1950s had shown that within the brain, high concentration of dopamine in basal ganglia (exercising control on the motor behaviour), not only causes PD, but also leads to psychosis and schizophrenia (Figure 5).

In a series of experiments, Carlsson also used a naturally occurring substance, reserpine, which depleted the storage of several synaptic neurotransmitters, including dopamine. When reserpine was given to experimental animals, they lost their ability to perform spontaneous movements, presumably due to depletion of dopamine. Subsequently, Carlsson showed that the animals which lost normal motor behaviour, if subjected to treatment with L-dopa (a precursor of dopamine) resumed normal movements associated with the normal levels of dopamine in the brain. In contrast, animals that received a precursor of the neurotransmitter serotonin did not improve the motor behaviour.

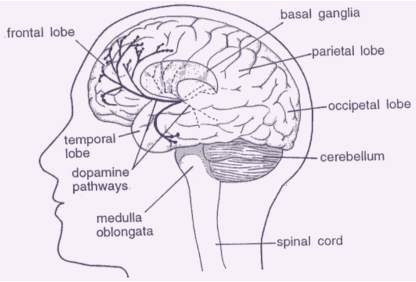

Figure 5. Major neural pathways in normal and Parkinsonian basal ganglia (the thickness of the arrows represents the strength of the signal).

Receptors for neurotransmitters (including dopamine receptors)

Postsynaptic membranes generally have neurotranmitter receptors, associated with ion-pumps. A neurotransmitter that is released by the SVs in the synaptic cleft, binds to these receptors and influences the membrane potential of the postsynaptic neuron, directly or indirectly, by several different mechanisms. However, the signal to open or close ion-pumps is not determined by the chemical properties of this neurotransmitter alone, but also by the type of receptor involved. One type of receptor has ion channels associated with its areas, to which the neurotransmitter may bind directly and bring about a conformational change, leading to opening of the channels immediately. The second type of receptors gate these ion channels indirectly with a second messenger system. A neurotransmitter bound to such a receptor causes, in several steps, the release of regulatory proteins within the cell membrane, that act on a family of ion channels (Figure 4). Both receptors serve different functions. The direct stimulation is relatively fast (though slower than electric stimulation), lasts only a few milliseconds, and is used in the circuitry that produces behaviour. The second messenger system is slower and often involves lasting changes in connection strength and alterations in excitability of neurons. This makes it possible to learn new behaviour. It has also been shown that depending on the properties of the receptor, the same neurotransmitter, for example dopamine, can both inhibit and excite neurons. A reduction in the number of postsynaptic receptors also leads to a number of neurological disorders, but little is known about the cellular and molecular mechanisms which control the number of receptors in a synapse.

Receptors also differ in the pathways that they follow for phosphorylation. For instance, neurotransmitter serotonin activates two types of receptors in the sensory neurons, one of which is coupled to the cAMP/PKA pathway and the other to the inositoltriphosphate/protein kinase C (PKC) pathway. Eric Kandel and coworkers have recently also isolated a gene for octopamine receptor that couples selectively to cAMP/PKA pathway[17].

Dopamine receptors

There are at least three different dopamine receptors (D_1, D_2 and D_3), which are homologous to one another, each being a 7-transmembrane segment (7-TMS) protein of 446 residues. In the third transmembrane segment of each of these receptors a conserved Asp residue is found and in the fifth segment Ser residues are found, which are critical for the recognition of agonist ligands possessing catechol group. It has been shown that dopamine release actually excites a direct pathway by stimulating the receptor D_1 and inhibits the indirect pathway by stimulating the receptor D_2. D_1 receptors stimulate adenyl cyclase, while D_2 and D_3, in addition to inhibiting, adenyl cyclase, also inhibit phosphatidylinositol turnover and activation of K^+ and Ca^{2+} channels. Although the function of D_1 receptors was known for some time, the function of D_2 receptors has been elucidated only recently. In a recent study conducted by Greengard and coworkers, it was shown that D_2 receptors can activate mitogen-activated protein kinase (MAPK) and cyclic AMP response element-binding protein (CREB)[13]. Hypersensitivity of dopamine receptors, may also cause psychosis and schizophrenia.

Signal transduction for learning and memory: Sea slug, a model system

Using the nervous system of a sea slug (a fish, *Aplysia*) as an experimental model, Kandel demonstrated how changes in shape and function of the synapse are central to learning and memory (Figure 6). Kandel had initially started to study learning and memory in mammals, but realized that the conditions were too complex to provide an understanding of basic memory processes. He therefore decided to investigate a simpler experimental model, the nervous system of the sea slug, *Aplysia*. It has comparatively few nerve cells (around 20,000), many of which are rather large. It has a simple protective reflex that protects the gills, which can be utilized to study basic learning mechanisms. Starting in mid-1970s, Kandel published a series of papers[18–29] and had shown that while reversible protein phosphorylation in the synapse is needed for short-term memory, synthesis of new proteins is required for the development of a long-term memory (Figure 6). It was also shown that a neurotransmitter binds its receptor on the postsynaptic cell surface and triggers a

cascade of reactions, which through phosphorylation of certain 'key proteins', regulate a variety of functions affecting learning/memory.

Kandel found that certain types of stimuli resulted in an amplification of the protective reflex of the sea slug. This strengthening of the reflex could remain for days and weeks and was thus a form of learning. He could then show that learning was due to an amplification of the synapse that connects the sensory nerve cells to the motor nerve cells, thus activating the muscles forming the protective reflex.

Short- and long-term memory

Kandel showed initially that weaker stimuli give rise to a form of short-term memory, which lasts from minutes to hours[18]. The mechanism for this 'short-term memory' involves alterations in ion channels, leading to release and entry of more calcium ions in the nerve terminal. This leads to an increased amount of transmitter release at the synapse, and thereby to an amplification of the reflex. This change is due to phosphorylation of certain ion channel proteins[19]. A more powerful and long-lasting stimulus results in long-term memory that can remain for weeks. The stronger stimulus will give rise to increased levels of the messenger molecule cAMP and PKA. These signals will reach the cell nucleus and lead to increase in the synthesis of some specific proteins (Figure 6). If this synthesis of new proteins is prevented through the use of some inhibitors, only the long-term memory is blocked and the short-term memory is not affected.

Synaptic plasticity: A precondition for memory

Synapses differ in strength and their ability to undergo alterations is described as synaptic plasticity. It involves restructuring of synapses for long-term changes, and depends partly on phosphorylation of proteins (e.g. synapsins) at the nerve terminal (Figure 6). It is also characterized by changes in neurotransmitter release, caused either by changes in Ca^{2+} influx, or by direct effects on fusion machinery. Using sea slug and mice as models, Kandel demonstrated that short-term as well as long-term memories are located at the synapse and are governed by synaptic plasticity. The fundamental mechanisms that Kandel elucidated are also applicable to humans. Consequently, our memory can be said to be 'located in the synapses' and changes in synaptic function are central, when different types of memories are formed. It is now possible to study how complex memory images are stored in our nervous system, and how it is possible to recreate memory of earlier events. Since we now understand important aspects of the cellular and molecular mechanisms that make us remember, the possibilities to develop new types of medication to improve memory function of patients with different types of dementia may be increased.

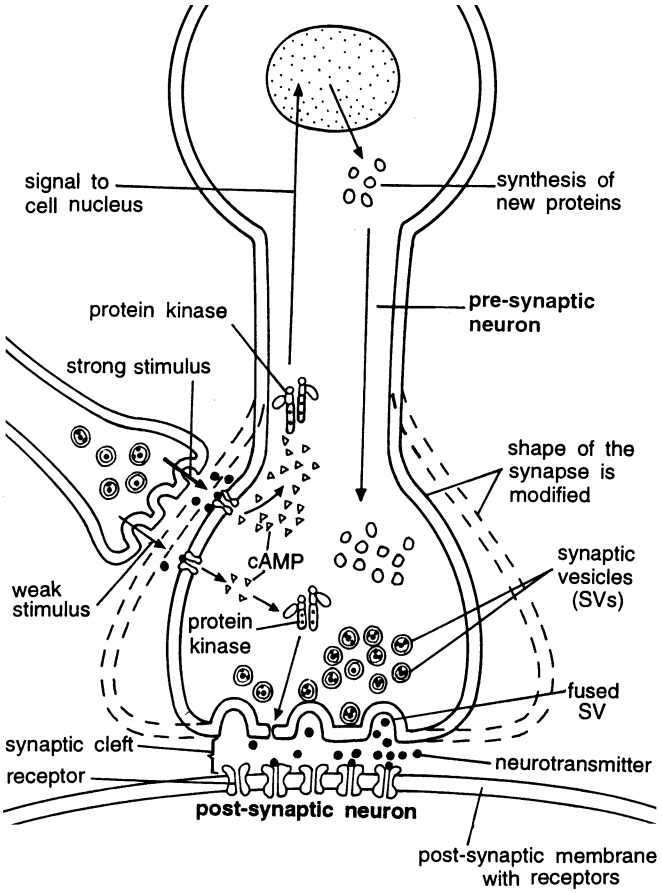

Figure 6. Different pathways at the nerve terminal for weak and strong stimuli, involving modification of the shape of the synapse.

Possible therapy for Parkinson's patients

PD is marked by the death of brain cells that make the neurotransmitter dopamine. Therefore, any treatment that may eventually lead to a long-term normalization of the concentration of dopamine in the basal ganglia of the brain, without any serious side-effects, should help PD patients. Following are some of the treatments that have been tried, although none of them proved effective in curing the disease on a long-term basis.

L-dopa treatment

Since dopamine cannot pass the blood–brain barrier between the blood vessels and neurons, it cannot be used for treatment of PD patients. Therefore, supply of L-dopa (a precursor of dopamine) to the few remaining healthy dopaminergic neurons is one of the best available remedies to ease the lives of Parkinson patients. However, it does not stop further deterioration of dopaminergic cells, and hence does not work well in the long term, so that the therapeutic effect gradually fades away and serious side-effects, including further motor impairment and psychiatric complications develop.

Dopamine receptor agonists

To bypass the problem of the side-effects of L-dopa treatment, dopamine receptor agonists such as *bromocriptine* have also been used to counter the degeneration of dopaminergic neurons in the brain. These compounds would take over the role of dopamine, thus eliminating the need of L-dopa, so that the side-effects induced by large amounts of L-dopa would be countered. However, increasing the dose of these agonists beyond a threshold leads to other serious side-effects such as psychotic reactions. A combination of low doses of L-dopa with an agonist has, however, been accepted as a better alternative, although even this will not cure the patients.

AADC and/or MOA-B inhibition

In the early 1970s, the first AADC inhibitors which inhibit conversion of dopamine in other compounds, were introduced. Although they could not pass the blood–brain barrier, the dopamine levels in the brain increased due to selective inhibition of the conversion of extra L-dopa in the peripheral organs. Another way to increase dopamine levels is to block the enzyme MOA-B that converts norepinephrine to DOPAC (3,4-dihydroxyphenylglycolaldehyde). It is demonstrated that the administration of AADC/MAO-B inhibitors slows down the progression of PD, and increases the life expectancy.

Use of engineered dopaminergic cells

Since 1980, several studies have been conducted to find out if dopamine-producing cells can be injected into the brains of PD patients[30–32]. For instance, at the Neuroscience Annual Meeting held during October 1999, results of a study were presented which suggested that foetal cells can produce dopamine, thus reducing patients' tremor and paralysis[30]. An increase of 20% in dopamine activity was observed in the treated patients and this improvement persisted for several years. Mouse embryonic stem (ES) cells have also been shown to give rise to a high yield of dopaminegic neurons *in vitro*[32].

Genetically modified L-dopa- or dopamine-secreting cells were also produced for grafting. For this purpose transgene producing the enzyme tyrosine hydroxylase (TH) was initially tried, but a permanent high level of transgene expression could not be obtained. More recently, transgene for Nurr 1, a transcription factor that mediates induction and/or survival of dopamine neurons was tried, and procedures were developed, which could generate unlimited number of neurons suitable for transplantation in PD patients[31]. These experiments may eventually lead to a successful therapeutic treatment of the disease using genetically modified ES cells for therapy.

Conclusions

Signal transduction has been an important area of research in the field of cell and molecular biology, and has been chosen for several Nobel Prizes during the last decade. The roles of reversible phosphorylation, G-proteins and nitric oxide in signal transduction are some examples of these Nobel Prize-winning discoveries. Signal transduction within the cell plays several roles, the most important role being in the regulation of gene expression. However, signal transduction in the nervous system, which is the subject of Nobel Prize this year, has its own special significance. Research in this area led to an understanding of the mechanisms involved in several neurological disorders and consequently helped in the development of new drugs and therapies for the treatment of these disorders. The neurological disorders investigated by this year's Nobel Laureates included PD and the loss of learning/memory, which are rather common in old age and for which no cure is available so far. Hence, any progress made in this area is a significant step forward towards the amelioration of human sufferings due to these neurological disorders. Future research in these areas will certainly lead to the development of new drugs and therapies that will provide a permanent cure for these disorders.

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Indo-US High Level Roundtable on Science and Technology: The second phase

The second Indo-US High Level Roundtable on Science and Technology (S&T) was hosted by the U.S. government on 15 September 2000, coinciding with Indian Prime Minister A. B. Vajpayee's visit to that country. The Government of India hosted the first roundtable on 24 March 2000 in Hyderabad. This set the ball rolling for the launch of the Indo-US S&T Forum, a significant effort towards closer links in S&T co-operation between the two countries.

A public meeting of the US President's Committee of Advisers (PCAST) on S&T was held on 14 September this year and an Indian delegation was invited where V. S. Ramamurthy, Secretary, Department of Science and Technology addressed the gathering on 'borderless science, sustainable technologies and equitable development'. The official report published on the occasion states that Ramamurthy's address highlighted the 'changing S&T scenario in India'. The meeting had presentations by several distinguished scientists, science-administrators and policy makers. According to one of the participants, 'the vibrancy of the meeting came through carefully planned presentations that highlighted aspects such as how to build S&T capacity abroad, and new opportunities for capacity building, from first hand experiences'. The salient points of the meeting included a 'technology driven 'push' and market driven 'pull' for accelerating technology-based development for developing countries, the programme of CISCO network academy covering 84 countries, pivotal role of USAID in bringing about a partnership between University of Oklahoma, USA and Chulalongkorn University, Thailand, in petrochemicals and polymer science. Points raised included 'new administration and how any agency/scientific community need to position itself to maximize the benefits which are expected over the next 3 years in the form of increased allocations'.

At the second roundtable meeting, co-chaired by Neal Lane, Assistant to the President for S&T and V. S. Ramamurthy, USA and India agreed 'to seek greater co-operation to advance the frontiers of S&T', states the official communique of the Office of S&T Policy, the White

Table 1. List of Indo-US Science & Technology Forum Governing Body Members

Name	Affiliation
Indian members	
V. S. Ramamurthy	Department of Science and Technology, Government of India
R. A. Mashelkar	Department of Scientific and Industrial Research, Government of India and Council of Scientific and Industrial Research, Government of India
Manju Sharma	Department of Biotechnology, Government of India
P. V. Jayakrishnan	Ministry of Information Technology, Government of India
G. Mehta	Indian Institute of Science, Bangalore, India
Anji Reddy	Dr Reddy's Laboratories, India
P. N. Tandon	National Brain Research Centre Trust, India
US members	
Frank E. Loy	Under Secretary for Global Affairs, US Department of State
Ernest J. Moniz	Under Secretary, US Department of Energy
I. Miley Gonzalez	Under Secretary, Research, Education and Economics, US Department of Agriculture
Rita L. Colwell	National Science Foundation, USA
Kenneth L. Shine	Institute of Medicine, National Academy of Science, USA
Arun Netravali	Bell Labs, USA

House, released on 19 September 2000. The release states that Lane called upon 'the scientific community to voice the importance of international collaboration in S&T'. It further notes that 'one determinant of the US success in the knowledge-based economy will be how well the US manages its S&T partnerships with countries like India in order to mutually benefit from each other's strengths'. Ramamurthy underlined 'the importance of the roundtable as a mechanism for transforming the current donor–recipient model prevalent in S&T to one of mutual partnership and cooperation'.

On the occasion of the second Indo-US High Level Roundtable on S&T a Roundtable Joint Communiqué was presented by Lane and Ramamurthy to the Indian Prime Minister. The joint statement listed collaborations in S&T in five areas, namely genomics, agricultural biotechnology, nanoscale science and engineering, computer modelling, mainly weather prediction and energy. In genomics, both sides agreed that 'they were poised for greater co-operation and accomplishment in the global fight against diseases; especially joint activities that would contribute to understanding how genetic polymorphism and gene expression influence susceptibility or resistance to infectious or chronic diseases'. For agricultural biotechnology, attention was brought to the role which 'biotechnology can play in ensuring food safety and environmental protection'. As part of the programme on nanoscale science, areas of joint collaborations would be advanced optical, electronic, magnetic and micro-mechanical devices, and also nanobiostructures and nanobiotechnology. Possible co-operation in setting up two centres of excellence, one for modelling and visualization and the other in engineering design analysis was considered. The formation of a 'worldwide digital library' was also envisaged. Energy development, both sides felt must be 'without environmental degradation'. The 'Jai Vigyan' mission and the Indian Millennium Mission 2020 by the Government of India, for integrated rural and small town development with 'physical and electronic connectivity', as well as energy-related areas of biomass utilization, etc. was discussed.

The Forum will comprise seven members from each side. While seven members from the Indian side now constitute the Governing Body of the Forum, as yet only six from the US have been identified (Table 1).

Finally, both sides agreed to hold roundtables on a regular basis. It was further decided to hold the first Governing Body meeting concurrent with an Indo-US workshop in two of the five identified areas to begin with, genomics and nanostructures, towards the end of the year, in India.

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RESEARCH NEWS

The future of flat panel displays

Nirupa Sen

The technology of electronic displays used in the area of televisions, personal computer screens and the like has been galloping at an amazing pace. The visual image obtained by conversion of electronic signals on the electronic display screen, aids information transfer between man and machine. Individual picture elements called pixels create a pattern by an 'on and off mechanism', including play in brightness and contrast. The pixel array visually enables the data transfer in the form of pictures, symbols or graphs.

Today's display screens are primarily based on old vacuum tube technology, first conceptualized in the mid nineteenth century. The technology has a basketful of woes that include manufacturing expenses, a fragile product and possible risk to human safety. What hide behind the screen are high voltages, as electrons are accelerated at large potentials to illuminate the screen. Large screens, with dimensions of about 10 feet by 8 feet with the desired resolution are yet out of reach technically.

How distant is research from achieving a cost-effective product, a screen both cheaper and safer to use, circumventing the cathode-ray tube technology? Existing flat panel displays are basically motivated from an idea to hang a television receiver on the wall, as would a painting. These displays are designed both on emissive and non-emissive phenomena. Emissive displays have gas discharge, plasma panel and electroluminescence as examples and non-emissive displays include liquid crystalline, electrochromatic and electroactive solid types. In a consumer-driven environment, the costs do still remain high and out of bounds. There are other problems as well. As any laptop owner would vouch for, the user finds it difficult to view his screen from any angle with zero distortion of the image. Liquid crystal displays (LCD) are ridden with slowness, in addition to poor visibility of the monitors as a commonly experienced problem.

So, where is the solution? The solution is to have a quantum change in technology. The next generation of display screens would be flat and could-you-believe-it, cheap too. Liquid crystal technology meets the need in a limited way in terms of cost and power requirement. Desktop personal computers still remain the exclusivity of cathode-ray tube design. Flat panel displays on the shelf are expensive.

The traditional display screens are generally made up of a luminescent material such as zinc sulphide (ZnS). ZnS has an inherent problem. A screen coated with this material requires electrons of about 25 keV energy to illuminate and brighten up the screen. Nanoparticles with large quantum efficiencies have already