INTERNATIONAL ATOMIC ENERGY AGENCY
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SMR/111 - 24

SECOND SUMMER COLLEGE IN BIOPHYSICS

30 July - 7 September 1984

1. DNA Damage and Repair Mechanisms
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DNA Damage and Repair Mechanisms

DNA is subject to damage by chemical (mutagenic) and physical (radiation, heat) agents in the environment, and by free radicals generated in metabolism and also by the occasional insertion of virus DNA into chromosomes. DNA also suffers errors during its replication and in the course of other metabolic processes. Damage to DNA has more severe implications for the functional integrity of the cell than does damage to most other cellular components.

The early studies focused on the radiation-induced alterations in DNA and their biological consequences, a field of interest for radiobiologists and photobiologists, but it is now abundantly clear that the plethora of chemical agents that "contaminate" our environment constitute a major source of biologically significant damage to genetic material in living cells. A major proportion of human cancer is of environmental origin. There are approximately 3,000 chemical compounds for which there is alleged some degree of evidence of tumorigenicity or carcinogenicity; 10% of them are confirmed carcinogens based on human data.

Approximately, 1000 Roentgen (R)(~10 Gy) units increase the frequency of lethals in Drosophila from the spontaneous level of about 0.2% to about 3%. The nuclear weapons are now familiar and terrible sources of ionizing radiation. It has been estimated that in a generation (30 years) we each receive a dose of about 3.0 R to our

gonads from natural background (0.01 mR/h) and an additional 0.2 R from the nuclear-weapons tests already performed.

Most physical and chemical agents reacting with DNA induce a large variety of products. In many cases products produced by different agents are structurally related and are expected to have similar effects on the local conformational structure of DNA helix, e.g., base elimination as a consequence of exposure of DNA to ionizing radiation ($E \geq 10$ eV), heat or alkylating agents; interstrand cross-linking by alkylating agents or by psoralen plus light; ring-saturation products by UV and ionizing radiation. Most, if not all, reactions of exogeneous agents with sugar residues of the DNA backbone result in strand breakage.

The classes of lesions with common structural features are repaired by common repair pathways than that specific enzymes exist for individual lesion or for a specific damaging agent. Structurally related lesions are also expected to have similar biological effects regardless of the agents responsible for their formation.

While long-term survival of a species may be enhanced by changes in its genetic inheritance, its short-term survival absolutely demands that the genetic material be adequately maintained. An accurate mechanism for DNA replication (error in the range of 1 in 10^9) but also a mechanism for repairing the many accidental damages that occur in DNA are essential for the survival. Sufferers from xeroderma pigmentosum, in which DNA repair mechanisms are defective, have a high risk of skin cancer, the actual direct cause being the UV component of sunlight.

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Accuracy in Protein Synthesis

Heraclitus expounded the proposition that all "things" are in a continual flux or change which can be translated into a modern biological term as "the dynamic state of body constituents". Recently, there has been a growing interest in processes and mechanisms whereby cellular constituents are replaced continuously, not only the mechanisms of regulation of synthetic processes, but also the mechanisms and regulation of degradative processes. The concentration of a protein in a cell is determined by the balance between the rate of its synthesis and the rate of its degradation. As a result, there is a constant protein turnover. The rate of protein synthesis is usually controlled by regulating the amount of its mRNA available for translation. The average degradation times for particular proteins range from several minutes to months or even years. Most of the proteins that are subject to rapid degradation within a cell are enzymes that catalyze a rate-determining step in a metabolic pathway. The rates of synthesis of these key proteins are usually regulated according to environmental conditions so as to promote the most efficient use of the metabolic pathway. Only if they are continuously and rapidly degraded can the concentrations of these enzymes adjust rapidly to the new levels determined by a change in their rate of synthesis.

Erythrocyte (red blood cell) has a finite life span of 120 days and travels 250 km. There are 4×10^8 hemoglobin molecules/erythrocyte and 3×10^6 erythrocytes are produced and broken down per second, i.e.,

approximately 10^{15} hemoglobin molecules are synthesized per second or 2.3 Kg/year.

Because cells possess a "house cleaning system", an efficient degradation mechanism for the elimination of defective (denatured, abnormal) proteins, protein synthesis is more relaxed compared to a high fidelity of replication maintained in DNA, and the error observed is in the range of 1 in 10^4. The accuracy of protein synthesis seems to come in part from the direct stereochemical discrimination of simple Michaelis-Menten enzymatic process, and in part from the way the overall kinetic scheme allows proofreading of small discriminations to occur at the expense of extra energy consumption.

The biological solution to the accuracy problem seems to be not the manufacture of a super-discriminating enzyme, but rather the assembly of a system which together is more accurate than its individual steps or component parts.

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Excitable Membranes

The regulation of complex multicellular organisms depends heavily upon chemical messages sent between cells. The secretion of hormones into the circulating system is one major type of communication. Less well understood is the chemical transfer of information through communicating cell junctions. The phenomenon is best established for nerve cells (neurons). The nervous system, a network of neurons (nerve cells) is in active communication. While many invertebrates (e.g., leeches, insects, & snails) have brains containing approximately 10^4 to 10^5 neurons, the human brain contains roughly 10^{11}. Each of these neurons interconnects through synapses with hundreds of thousands of other neurons.

A typical neuron consists of a cell body, ranging from 5 to 100 μm in diameter, from which emanate one major fiber, the axon, and a number of fibrous branches, the dendrites. The axon may give off branches near its beginning and it often branches extensively near its end. The dendrites and the cell body receive incoming signal; the cell body combines and integrates them (i.e., it averages them) and emits outgoing electrical signals, and it also serves for the general upkeep of the cell; the axon transports the outgoing signals to the axon terminals, which distribute the information to a new set of neurons.

The signaling system is a double one: electrical and chemical. The signal generated by a neuron and transported along its axon is an

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electrical impulse, but the signal is transmitted from cell to cell by molecules (transmitter substances) that flow across a specialized contact, the synapse, between a supplier of information (presynaptic cell) and a recipient of information (postsynaptic cell). One neuron is generally fed by hundreds or thousands of other neurons and in turn feeds into hundreds or thousands of still other neurons.

How does a single neuron generate electrical signals and convey information to other cells. The concentration of certain ions, mainly Na^+ and K^+, on one side of the cell membrane differs from that on the other side. Consequently, the entire neuron is polarized so that the interior of the axon is approximately 70 mV negative with respect to the exterior. These ions can traverse the lipid bilayer (membrane) only by passing through special protein channels which are selectively permeable, i.e., one type of channel lets Na^+ pass through and largely excludes K^+, whereas another type of channel does the reverse. When the ion channels open or close, the charge distribution shifts and the membrane potential changes. An electrical signal that exceeds a certain threshold strength (threshold voltage) triggers an explosion of electrical activity that is rapidly propagated along the neuron's plasma membrane. The "all-or-none response" or "firing" is a characteristic of neurons. This traveling wave of electrical excitation is known as an action potential or nerve impulse. It can carry a message without attenuation from one end of a neuron to the other at a speed of up to 100 m s^{-1}. The frequency of the impulses from neurons varies from a few per sec to a maximum of about 200.

Neuronal signaling thus depends on channels whose permeability is regulated, the so-called gated channels. Two classes of gated channels are of crucial importance: (1) voltage-gated channels which open and close in response to voltage differences across the cell membrane (voltage-gated Na^+ channels play the key role in the explosion of electrical activity by which action potentials are propagated along a nerve cell process); and (2) ligand-gated (chemically-gated) channels, which respond when a particular organic molecule (transmitter) binds to a receptor region on the channel protein in the receptive membrane of synapses. It converts extracellular chemical signals into electrical signals. They play a central role in the operation of synapses, e.g. acetylcholine-activated channels.

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Molecular Basis of Memory

Learning is the ability to modify behavior in response to experience. Memory is the ability to store that modification over a period of time. The capacity to learn is widespread in nature; it has evolved in many invertebrate animals and in all vertebrates. The similarity of some of the learning processes suggests that the neuronal mechanisms for a given learning process may have features in common across phylogeny. There appear to be no fundamental differences in structure, chemistry or function between the neurons and synapses in man and those of other organisms.

Two decades ago the notion was advanced that memories might be recorded in the form of large molecules, with the information encoded in a sequence of smaller molecules, as genetic information is encoded in DNA. Also, it was thought that nucleic acids or proteins could have information content high enough to be involved in such a role. This idea was taken seriously and much time was consumed in experiments like "transfer of memory through cannibalism". This fad has died out.

An understanding of memory will probably involve two quite different components. One component is the change that most likely take place in synapses as a result of the repeated use of neural circuits, i.e., efficacy altered. Neurons are connected to certain other cells in a definite, orderly manner and the pattern of connections is practically the same from one individual animal to another. This strength of the

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connections can be changed by experience (learning). The second component, far more difficult to pursue, is to understand what goes on when animals perceive, act, think and experience.

Although it has been known since 1962 that the specific activity of adenylated cyclase is higher in the nervous system than in any other tissue of the body, because of the heterogeneity of nervous tissue, it has been difficult to specify a precise role of cyclic AMP (cAMP) in neuronal function.

During the 1970's the role of cAMP-mediated protein phosphorylation as a general regulatory mechanism became apparent in animal cells, and it is very likely that a similar mechanism is operating in neurons and serving as a mechanism for memory.

In genetics, the observation of the breeding pattern of a plant led to the information about chromosomes. It is very likely that a real breakthrough in this field will come from the studies at the level of the overall control of the system.

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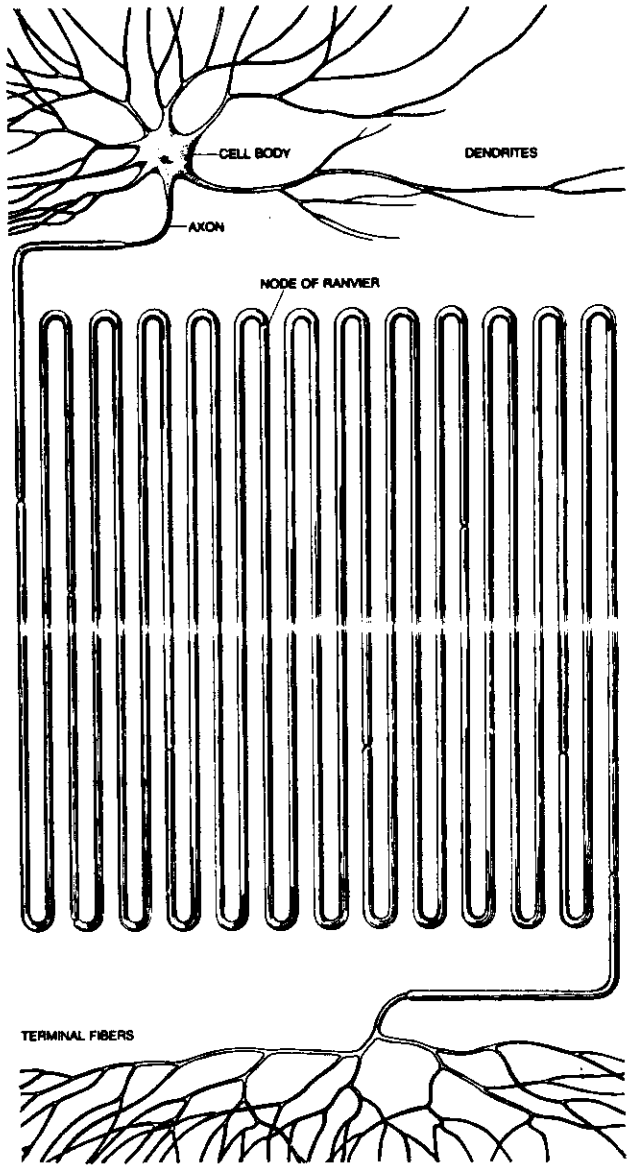

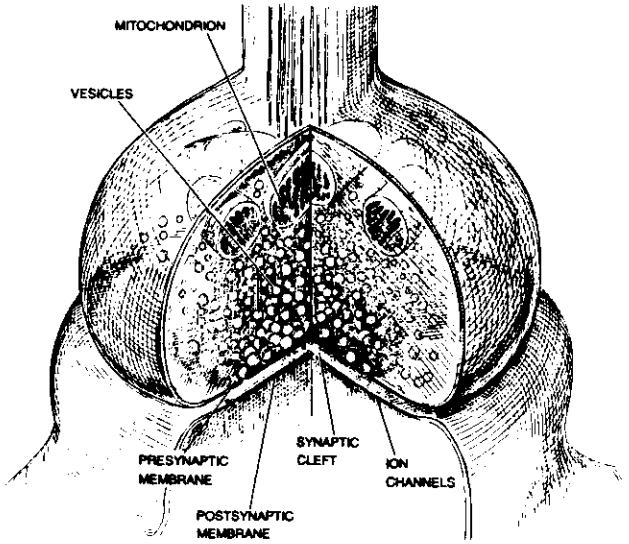
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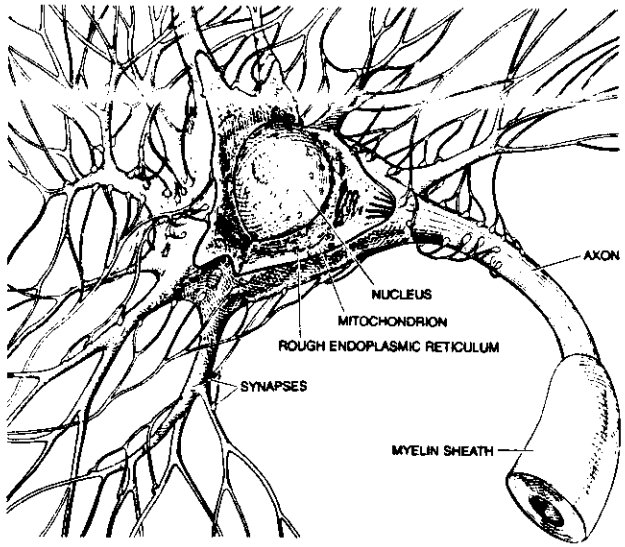
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