Human brain biochemistry

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Abstract: The human brain that serves as a center of the nervous system is structurally unique. It is extraordinarily complex and highly specialized in its distinct heterogeneous anatomical regions as its function remains a great challenge. The neuron is the functional unit that depends on special anatomical and chemical connections with other units of the system. The essential biochemical connections of the nerve cell have special morphological features: synaptic contact that is mediated by chemical molecules ensures sequential propagation of neurotransmission of electrical pulses through units of the system. The chemical energy expended in maintaining the distribution gradients of cations across cellular membranes, and the chemical neurotransmission causes an alteration in cation distribution. The energy utilization mechanisms that underlie cations re-distribution are not peculiar to the nervous system, but they are of particular importance to neural function because the mechanisms of chemical transmission are peculiar to the nervous system. Human nerve cells have the ability to generate electrical impulses that can travel through the body without a significant loss of impulse strength. Such unique features are based on semi-permeable excitable membranes that alter permeation to small chemical molecules and to cations. The biochemical function of the brain is demonstrated in the efficient production of energy required to accomplish the processes mentioned above, and it is essentially ATP that is stored and produced from glucose oxidation to carbon dioxide and water. The brain has virtually no reserves of chemical energy (glucose 1-2 µmoles/g and ATP 3 µmoles/g) to function for minutes only, considering that this organ is 2% of total adult weight that consumes 20% of the whole body glucose through a constant blood supply. Yet, the various factors that regulate glucose uptake and its utilization in the central nervous system are not well understood. This review is an attempt to update the rapidly expanding information on human brain neurotransmission biochemistry, though the adaptive processes of learning; cognitive performance and memory in the brain have subtle relationships.

Keywords: Human Brain, CNS-Central Nervous System, Neurotransmitters, ATP-Adenosine Triphosphate, Cognition, Alzheimer's Disease, Dopamine, Cerebral Blood Flow

1. Introduction

Biochemists are often study the brains of small mammals and they then extrapolate to what might take place in the human brain [1,2,3,4]. Yet, the "mammalian" brain of a rat, guinea pig, rabbit, dog or a monkey is obviously far different in appearance and many functions from that of man [5].

Homo sapiens' brain with its neural network is the legacy of billions of years of evolution in terms of molecular, cellular, multicellular, vertebrate, mammalian, and primate evolution [6,7,8]. Evolution has left a distinctive mark on the human brain which is shown in Fig.1: (a) the brainstem structures provide functionality for controlling vital life processes and overall modulator functions for cortical and limbic system systems, (b) the limbic system provides quick response functionality for rapidly-changing environmental challenges, and (c) the cortex provides more-deliberate responses that provide refined behavior, which augments and modulates social interactions, cognitive interpretations, historical perspective, decision-making, and future planning [9,10].
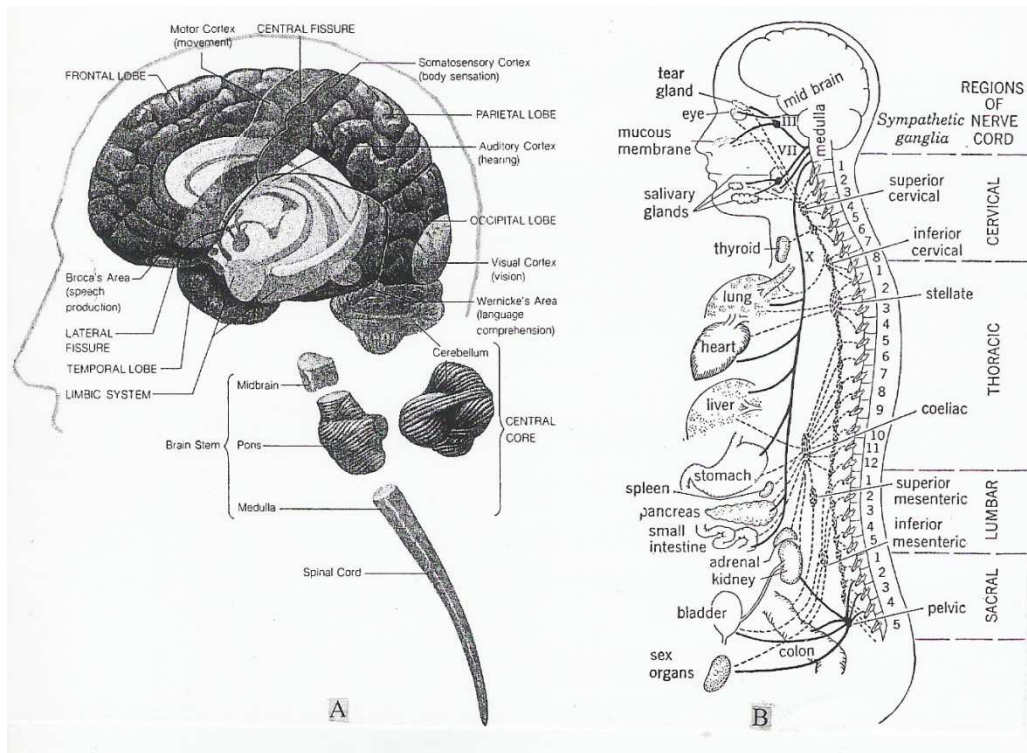
Fig. 1. *Human nervous system. (A) The left hemisphere of the human brain. The diagram shows major two fissures and the four lobes of the cerebral cortex; regions of cortex involved in speech, hearing, vision, sensory and motor function are identified. (B) The human autonomic nervous system. The connections of the nervous system with central nervous system and the internal organs; diagrammatic and simplified. Source: Bootzin, R.R., Bower, G.H., Crocker, J. and Hall, E. (1991) Psychology Today: An Introduction, 7th edn., p.62. New York, NY: McGraw-Hill, Inc. ; Storer, T.I., Usinger, R.L. and Nybakken, J.W. (1968) Elements of Zoology, 3rd edn., p.137. New York, NY: McGraw-Hill Book Company.*

Table 1. *Human brain limbic system.*

Structure	Proportion by volume (100%)
Cerebral cortex:	77:
Frontal lobe	31.6%
Temporal lobe	16.9%
Parietal lobe	14.6%
Occipital lobe	13.9%
Diencephalon	04
Midbrain	04
Hindbrain	02
Cerebellum (142g/60kg body weight)	10
Spinal cord	02

Sources: Swanson, L.W. (1995) "Mapping the human brain: past, present and future", Trends in Neurosciences, vol. 18 (11), pp.471-474; Kennedy, D.N., Lange, N., Makris, N., Bates, J. and Caviness, V.S. Jr. (1998) "Gyri of the human necortex: an MRI-based analysis of volume and variance", Cerebral Cortex, vol. 8, pp.372-384; Toga, A.W. and Mazziotta, J.C. (2000) Brain Mapping the Systems. San Diego, CA: Academic press.

The first part of the illustration shows the lateral aspect of the whole brain and some of the internal parts which are seen if the brain is divided into the two hemispheres. The whole brain has been divided into four main parts for convenience: cerebrum, cerebellum, mid-brain and brain stem; it is the latter one that contains a large number of specialized parts [11]. Fig. 1 also illustrates the somatic nerves of ganglia and fibers connecting to all smooth muscles, glands and viscera, deals with the internal environment of human body. It controls routine functions such as the rate of metabolism, the action and tone of internal muscles, and the maintaining of a constant state (homoeostasis) of components in the blood, lymph and tissue fluids.

The increase in surface area per unit volume of the cortex (Table 1) has been affected by the increased folding, so that the convolutions of the cerebral cortex are considerably extensive [12,13]. The individual intelligence and malformations on the surface folds in a brain region that includes "Broca's area". Pierre Paul Broca (1824-1880) described "le grand lobe limbique" that refers to the cortical structures that form a border around the inner structures of the diencephalon and midbrain on the medial surface of the cerebral hemispheres [14]. It is the main region underlying language within humans might be modulated by the degree of folding in certain cortical regions [15,16,17]. The more intelligent individuals may have the more complex folding in left parietal lobe, for example, deeply and frequently convolution of sulci (hills and valleys) and gyral shape during thinning of cortical thickness [18,19,20,21,22, 23]. The function of the cortex has altered, but the areas that were devoted to higher functions of learning and decision-taking have significantly increased [12,24]. Other areas, such as the limbic (border, Latin) system that is concerned with more primitive functions of homeostasis, motivation and emotion [25, 26], are phylogenetically older and they have changed little in relative size [28,28,29] . The major areas of the human

brain are shown in Fig.1 and its chemicals composition is illustrated in Table 1.

One prominent feature of human brain anatomy is its extensive blood supply and oxygen delivery to an adult brain mass of 1300-1400g, i.e. brain to body ratio is 1:40 magnitude [30]. The brain uses approximately 20% of five liter blood of healthy body and it needs 25% of the body's oxygen supply to function optimally. Blood flow in a healthy body is 54 ml/kg of brain mass per minute [31] . There are 740 ml of blood circulating in the brain every minute; oxygen consumption is at a rate of 3.3 ml.kg^{-1}.min^{-1} of brain tissue; this means that approximately 46 ml of oxygen are used by the entire brain in one minute [32, 33, 34,35]. The blood flow to the brain is increased during sleep, but the rate of oxygen consumption remains the same [36].

Table 2. Composition of human cerebrospinal fluid-CSF.

Substance (37 $^\circ$C)	CSF	Plasma	R=[C$_2$] / [C$_1$]	$\Delta\Psi_d$ =RT/F.lnR (mV)
Water (%)	99	93	1.06	
Protein (mg/l)	3.5	700	5.0 x 10^{-3}	
Glucose (mg/l)	6	9	0.67	
Urea (mg/l)	1.2	1.5	0.80	
Creatinine (mg/l)	0.15	0.12	1.25	
Uric acid (mg/l)	0.15	0.50	0.30	
Lactic acid (mg/l)	1.8	2.1	0.86	
Cholesterol (mg/l)	0.02	17.5	1.0x10^{-3}	
Osmolality(mOsm/l)	295	295	1.00	
Na$^+$ (mEq/l)	147	150	0.98	- 5.4 x 10^{-1}
K$^+$(mEq/l)	2.8	4.5	0.62	- 12.76
Ca^{+2} (mEq/l)	2.1	4.8	0.44	- 21.92
Mg^{+2} (mEq/l)	0.3	1.7	0.18	- 45.79
Cl^{-1} (mEq/l)	113	99	0.88	- 3.41
HCO$_3$$^{-1}$ (mEq/l)	25.1	24.8	0.99	- 2.7 x10^{-1}
Inorganic P (mg/l)	0.34	0.47	0.73	- 8.40
pH (-log [H$^+$]$_{active}$)	7.33	7.41	0.99	- 2.7 x10^{-1}
P$_{CO2}$ (mmHg)	50.2	39.5	1.28	

Where R= distribution ratio; R=universal gas constant (8.314 JK-1mol-1); T=absolute temperature (273+37=310 oK); F=the Faraday (96485 Cmol-1); $\Delta\Psi$d=diffusion potential (mV) Resources: Davison, H. (1967) Physiology of the Cerebrospinal Fluid. London: Churchill; Fishman, R.A. (1980) Cerebrospinal Fluid in Disease of the Nervous System. Philadelphia, PA: Saunders; Bannister, R. (1992) Brain and Bannister's Clinical Neurology, 7th edn. New York, NY: Oxford Medical Publications.

Exchange of solutes between the various fluid compartments (Table 2) exhibits unique features; endothelial cells of blood capillaries of the brain are most studied site for 'blood-brain' barrier features [37, 38]. This concept arose from the limited penetration of injected drugs, dyestuff and toxins from the blood stream to the brain substance; also this phenomenon was found with a variety of small highly water-soluble chemicals, such as: fructose, sucrose, thiocyanate and most amino acids [39, 40]. Microscopic examination of the endothelial cells of the

blood of the brain indicated that they were packed more tightly together than in capillaries outside the brain, i.e. there is a physical permeation barrier at the capillary wall [41,42,43]. This suffices for large molecules like proteins, but it does not explain the apparent limited permeability of substances such as glutamate [44]. If a radioactive glutamate is present in the blood-stream, it equilibrates rapidly with the glutamate within the brain, but a massive increase in concentration of the external glutamate does not alter its internal concentration, i.e. glutamate concentrations have been reported to be: in plasma 50-100 μM , in brain 10,000-12,000 μM , but in extracellular fluids at 0.5-2 μM [45] . The 'blood-brain' barrier could be regarded as a homeostatic mechanism whereby the internal concentration is sustained by active efflux process of extrusion [46]. The brain must regulate glucose, glutamine and ketone bodies (β-hydroxybutyrate) for energy under normal circumstances and especially during development and aging [47, 48] .

The 'blood-brain' barrier can impede potential treatment of brain disorder by virtue of difficulty to cause internal accumulation of drugs or metabolites, due to its inherent role in protecting a highly sensitive brain [48]. Such a difficulty might be resolved by appreciating the biochemistry of the system [11]. For example, Parkinson's disease which is a degenerative and progressive disorder associated with weakness, rigidity, muscular tremor and bradykinesia due to failure of basal ganglia at the output that showed degeneration of certain nerve tracts and histochemical analysis in parallel to the loss of dopamine [49, 50]. Dopamine is neurotransmitter in the brain that plays vital roles in a variety of different behaviors [51]. The major behaviors dopamine affects are movement, cognition, pleasure, and motivation [52] , abnormalities in brain dopamine are associated with many neurological and psychiatric disorders including Parkinson's disease, schizophrenia and substance abuse [53,54]. Dopamine (L-2,4-dihydroxyphenylethylamine) is not easily transported into the brain [55], whereas its immediate, Dopa (L-3,4-dihydroxyphenylalanine), is readily taken in [37,56,57]. Hence, a marked improvement has been achieved in Parkinson's treatment with L-Dopa [58,59].

Hajjawi [60,61] has reported that all cells have a difference in electrical potential across their outer cell membranes that were resulted from the relative distribution of ions between the intracellular and extracellular compartments (Table 2). Cell plasma membranes define compartments of different compositions; the fundamental building blocks of all cell membranes are phospholipids (amphipathic molecules) which are spontaneously form a stable bilayer barrier in aqueous solutions [62]. Proteins are the other major constituent of cell membranes; the current model of membrane structure is a fluid mosaic in which proteins are inserted into a lipid bilayer [63] . Molecules transported by either channel or carrier proteins cross membranes in the energetically favorable direction, as determined by concentration and electrochemical gradients ,so , the diffusion potential arises from

permeating ions in Goldman-Hodgkin-Katz equation [64,65,66]. The Goldman equation is derived from the Nernst equation. It gives the equilibrium potential due to the asymmetric distribution of each ion across the semi permeable membrane:

$$\Delta\Psi_d = \frac{RT}{F} \cdot \ln \frac{[P_K K^+_{in} + P_{Na} Na^+_{in} + P_{Cl} Cl^{-1}_{out}]}{[P_K K^+_{out} + P_{Na} Na^+_{out} + P_{Cl} Cl^{-1}_{in}]},$$

where $\Delta\Psi_d$ is diffusion potential, R is universal gas constant, T is the absolute temperature, F is the Faraday, and P the permeability constants for the individual ions that are normally calculated from radioisotopes flux measurements. This contributes to the electrical properties of the neuron. At rest, neurons maintain a difference in the electrical potential on either side of the plasma membrane. A typical value of the membrane potential at rest is −65 mV; but it can range between −40 mV and −80 mV [67]. The electrical impulse can be utilized as a signaling mechanism [68].

There are three different types of muscle: skeletal or striated, smooth or visceral and cardiac [69] ; these three types are differentiated on the basis of their distinct control system, namely: anatomic location, cellular structural specialization, function, and biochemistry[70]. The neurons which are the core components of the nervous system that includes the brain, and spinal cord of the central nervous system, and the ganglia of the peripheral nervous system ; they do not run directly from the periphery to the brain. All neurons are electrically excitable, maintaining voltage gradients across their membranes by means of metabolically driven ion active pumps, which combine with ion channels embedded in the membrane to generate intracellular-versus-extracellular concentration differences of ions such as sodium, potassium, chloride, and calcium. [71] put the human brain at $\sim 10^{11}$ neurons and 10^{14} synapses.

There are two types of phenomena at action in processing the nerve impulse: electrical and chemical. The electrical events propagate a signal within a neuron, whereas the chemical events transmit the signal from one neuron to another or to effectors cells at the end of axon in synapse [70]. A single neuron has from a few 100s up to ≥20,000 synapses , and the average adult human brain contains ~86 billion neurons [72].

The initiated signal is normally relayed by several intermediate neural cells. The synapse, an interconnection between neurons, behaves as a simple switch, but it also has a special role in information processing. The function of the synapse is to transfer information in the form of electric activity from one cell to another; the transfer can be from nerve to nerve (neuro-neuro), or nerve to muscle (neuro-myo). The synaptic cleft, a region between the pre- and postsynaptic membrane is very narrow (30-50 nm). A chemical mediator is utilized to bridge communication between pre- and post-junction cells. The sequence of events is as follows: (a) an action pulse reaches the terminal endings of the presynaptic cell, (b) a neurotransmitter (e.g.

glutamate and GABA- γ amino butyric acid) is released, which diffuses across the synaptic gap to bind to receptors in specialized membranes of the postsynaptic cell, then (c) the transmitter acts to open channels of one or several ion species, resulting in a change in the transmembrane potential. If it is depolarizing, it would be an excitatory postsynaptic potential and if it is hyperpolarizing, it would be an inhibitory postsynaptic potential [11,73].

The unique feature of nerve cell is seen when the 'resting state' distressed and the cell appears to be physiologically stimulated where a series of events ensues [74]. The membrane potential undergoes a rapid alteration from about -60mV to -70mV (K$^+$ equilibrium potential -90mV), but this does not continue in the same way as it is the case in the non-excitable cell: there is a rapid overshoot to the extent that the membrane potential become positive, to some +10mV to 30mV; this rapid change of depolarization last about half a millisecond and it is known as the action potential [75] . This is associated with movement of cations: the membrane becomes more permeable to Na$^+$, the Na$^+$ equilibrium potential is +60mV [64]. It is likely that macromolecules constituting lipo-protein matrix of the membrane have changed to reduce Na$^+$ permeability restrictions and a rapid flux of Na$^+$ can occur. Sodium flows into the cells and potassium out until near electrochemical equilibrium is reached. The increase in permeability to Na$^+$ and K$^+$ are not simultaneous (K$^+$ equilibrium potential is -90mV): Na$^+$ permeability increases at first to a greater extent, and subsequently K$^+$ permeability increases as that of Na$^+$ decreases [75,76]. This process becomes self-limiting and the potential difference returns to its original value [11].

The system remains is excitable for ~200ms of a refractory period where temporarily changes in membrane permeability allows K$^+$ freely [77, 78]. The excitable membranes are able to transmit the generated action potentials along their surfaces, and they are showing the essential features for the basis of cable properties [11,56,79].

2. Methodology

The development of techniques that allow the high fidelity measurement of small scale ionic currents ushered in a new era of investigation into the role of ion channels in the physiologic and pathophysiologic function of excitable tissue. The resting state of the membrane is 50-75 times more permeable to K+ than to Na+ ; thus the magnitude and polarity of the resting potential are due entirely to the efflux of K+ from the intracellular medium [80] . So, the control of membrane voltage and membrane current measurements is of strong interest for the study of numerous aspects of skeletal muscle physiology and pathophysiology [11,81,82] . Hence, the use of 'voltage-clamp' technique (Fig.2) enables the investigator to prevent the uncontrolled explosive occurrence of the action potential, and to control changes in the membrane potential ,

during which current and ion flux rates could be measured though the capacitive current is zero if the derivative of the voltage is zero [83]. Voltage-clamp mode is best-suited for recording cell firing activity, and current-clamp mode is best-suited for recording resting membrane potential and synaptic potentials [84,85,86]. The process is stipulated in Fig. 3 as follows: (a) excitation causes first an increase in permeability of Na+ by ~600-fold , so, more sodium ions rush into the cell and thus the membrane potential decreases with an eventual reverse of polarity, i.e. becoming positive at the intracellular membrane and negative at extracellular membrane, (b) the increase in the permeability to Na+ is turned off (sodium inactivation) , coupled with a simultaneous increased permeability to K+ over its resting level, (c) these two events of Na+ inactivation and increased K+ permeability allow K+ flux to regain predominance over Na+ flux and the membrane potential rapidly restored to its resting level, yet a small hyperpolarizing overshoot of membrane potential is due to permeability of K+ greater than normal [80]; the cell has many repeated depolarization before its cations balance reach equilibrium phase without change in concentration gradient, and further excitation is discontinued [86] . This does not happen in normal circumstances, because energy is continually being expended to return the cations to their original distribution which is effected through the Na+/K+-ATPase [60, 61].The action potential has certain clear characteristics such as the critical size of the stimulus that is produced: smaller stimuli having no effect whereas larger stimuli producing no greater effect [87]. The critical size is the threshold and the process is 'all-or-none' (Fig. 3), i.e. the size of the action potential is independent of the size of the stimulus, as long as it is above the threshold , though this does not imply that the 'signal' is uncontrolled .
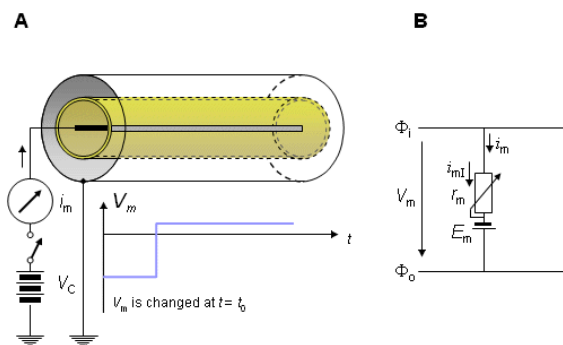

Fig. 2. Voltage clamp experiment.

(A)The simplified principle of the experiment, and (B) Electric model of the transmembrane axon in voltage clamp experiment.

V_m denotes membrane voltage, V_m the transmembrane voltage, is taken as the intracellular potential, Φ_i, relative to the extracellular potential, Φ_o,V_c: clamp potential, i_m: total current per unit length, i_{ml}: ionic current per unit length. A desired voltage step is switched between the inner and outer electrodes, and the current flowing between these

electrodes (i.e., the transmembrane current) is measured.

Source: Hodgkin AL, Huxley AF, Katz B (1952) "Measurement of current-voltage relations in the membrane of the giant axon of Loligo", J. Physiol. (Lond.), vol.116, pp.424-48.

However, control at the nerve cell that is depolarized may be exerted by a sequence of stimuli in terms of frequency and of size, i.e. the interval of time between stimulation and action potential might be decreased with a repeated increase in size and in frequency stimuli that can effect post synaptic response [90,91]. Other variables are operational, such as the properties of the axon that conducts the signal, the chemical transmitter at nerve endings, and the post synaptic system.

Axons are the primary transmission network lines of the nervous system, and as bundles they form nerves. Some axons are large and can extend up to 100 cm or more. Other axons are short and they extend as little as 1 mm in length, thin (<1μm across) and they are non-myelinated, i.e. they are without myelin covering that may cause some dissipation of impulse amplitude [92]. The myelin sheath acts as an efficient insulator that preserves the strength of signal between the 'nodes of Ranvier' in the axon; the signal is renewed at the gaps in the myelin sheath between the nodes , providing the action potential (Fig. 3) reaching the node is still above the threshold, so, depolarization re-occur [11]. The action potential can therefore be propagated throughout the entire length of a myelinated axon without decreasing in size; the speed of conduction is subject to the diameter of the axon and the thickness of the myelin sheath [90].
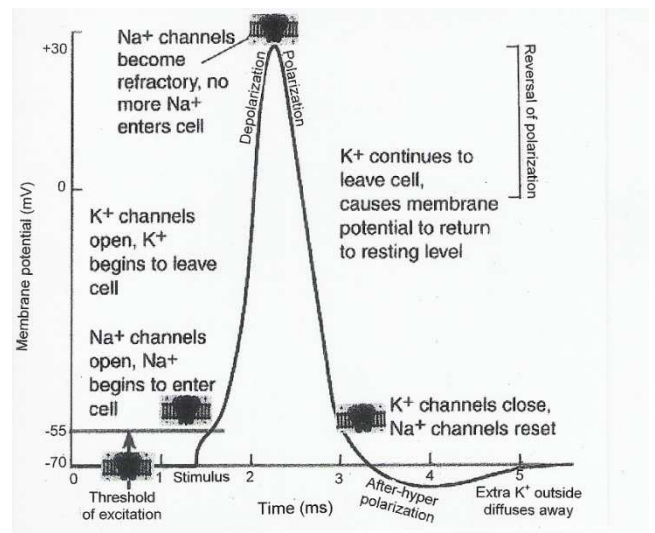

Fig. 3. Changes in membrane potential during an action potential.

Depolarization of an axon membrane results in an action potential. The change in Na^+ and K^+ time course flux.

Adopted from: Bers, J.M., Tymoczko, J.L. and Stryer, L. (2002) Biochemistry, 5th edn. New York, NY: W.H.Freeman and Company; Barrett, K., Barman, S.M., Boitano, S. and Brooks, H.L. (2012) Ganong's Review of Medical

Physiology, 24th edn. New York, NY: McGraw-Hill Lange, Inc.

Otto Loewi (1873-1971) and Henry Dale (1875-1968) were the first to identify acetylcholine as a neurotransmitter in the central nervous system [93].

In despite of the remarkable resolution of the above patch-clamp recording techniques, its process is difficult and laborious for drug development [94]. Consequently, a newly automated planar silicone-clamp technique has demonstrated considerable advantages of using silicon micromachining [95,96] that makes use of a conventional patch-clamp apparatus to achieve whole-cell voltage clamp of a restricted portion of a fully differentiated adult skeletal muscle fiber [97,98] .

Histochemical, immunologic and radioisotopic methods are widely used to map the distribution of specific transmitters, their associated enzyme systems and their receptors [99].

Other procedural techniques were developed to investigate the function and structure of human brain constituents (Fig 1), namely:

(1) The effects of brain damage that produces different behavioural and psychological

impairments. Hans Berger (1893-1941) recorded the first electrical signals on ElectroEncephaloGram-EEG from a human brain [100]. The intelligence is linked to how well and to how fast information passes through a constantly changing circuitry of the 100 billion brain cells as a function of experience [101]. There are major hubs that seem to be linked to sequential processing of information that involves involve attention, memory and language [102, 103]. (2) The effects of electrical stimulation at selective different places in the brain affect specific psychological processes. Intra-cranial electrophysiology technique is used for example of epilepsy patients [104]. Electrical electrodes are implanted the brain and pulses were monitored to determine which parts of the brain could be removed to treat epilepsy while leaving all other functions intact [105,106]. (3) The effects of chemical stimulation to measure concentration and change in concentration of medication, e.g. cerebral edema which is a swelling of brain tissue in response to injury or electrolyte imbalances [107]. (4) The effects of magnetic stimulation, using radio frequency pulses and a strong magnetic field. Magnetic Resonance Imaging-MRI looked to the brains of dyslexics and to intelligence as a function of gray matter of brain cells [108, 109]. (5) The Computerized Axial Tomography-CAT (or CT) scans technique for rotating X-ray measurements in a large doughnut-shaped tube [110] . The scan shows the brain structure to locate blockages, lesions and other abnormalities [111] . In schizophrenia, the scan shows a smaller than normal sized-area in front of the brain [54,112]. (6) The Positron Emission Tomography- PET scan technique shows the brain metabolic activity at cellular level, i.e. analyzing the amount of glucose processed in each region of the brain.PET scan detects metabolic imbalances that are responsible for epilepsy and nervous system disorders [113]. It also differentiates between benign and malignant brain tumors [114]. It predicts Alzheimer's [115] and it identifies strokes and transient ischemic attacks [116,117,118]. (7) The Single Photon Emission Computed Tomography-SPECT imaging technique allows noninvasive investigation into events of physiology and physiopathology of human brain when neurological or psychiatric symptoms cannot be explained by structural neuroimaging findings. A good example in the application of this perfusion SPECT in the differential diagnosis of dementias [119,120,121].

3. Findings and Conclusions

The nervous system that uses chemicals for the transmission of information, has the ability to influence processes in distant regions of the body [70] . Chemical transmission that occurs between nerve cells and between nerve cells and their effectors cells, takes place through the release of small amounts of neurotransmitter substances from the nerve terminals into the synaptic cleft [122]. There are thousands of neurotransmitters that cross the cleft by concentration gradient diffusion and activate or inhibit the postsynaptic cell by binding to a particular receptor molecule in response to signals from the brain [15,123]. By using drugs that mimic or block the actions of chemical neurotransmitters, many autonomic functions can be selectively modified [38, 124] . These functions involve a variety of effectors tissues, including cardiac muscle, smooth muscle, vascular endothelium, glands, epilepsy , presynaptic nerve terminals and semantic dementia [89,122,124,125] , as well as somatic nervous cells (nonautomatic) that have consciously controlled functions such as posture, movement, respiration, emotional empathy and other psychological and physiological occurrences [38,99,126].

The brain is a highly integrated complex system, in which the total number of neurotransmitters is not known, but it is well over 100 [127]. A typical neuron receives 1000s of synaptic contacts [128]. A number of small chemical molecules have been isolated from brain and studies suggest that these chemical agents may be neurotransmitters. Despite this diversity, these neurotransmitters can be classified into four categories, namely: acetylcholine, biogenic amine neurotransmitters, peptide neurotransmitters and amino acid neurotransmitters (Table 3).

Substance P* is an undecapeptide (monodecapeptide) of the tachykinin neuropeptides family;

P* has eleven amino acids with the sequence: Arginine-Proline-Lysine-Proline-Glutamine-Glutamine-

Phenylalanine-Phenylalanine-Glycine-Leucine-Methionine.

Table 3. *Major categories of neurotransmitters in the central nervous system*[1,2,3].

No.	Neurotransmitter (IUPAC name)	Anatomy	Association
1	Acetylcholine4 (2-Acetyl-N,N,N-trimethylethanaminium)	Cell bodies at all levels; long and short connections. Motoneuron-Renshaw cell synapse.	Cholinergic pathways appear to play an important role in cognitive functions, especially memory. Presenile dementia of the Alzheimer type is reportedly associated with a profound loss of cholinergic neurons.
2	Monoamines5,6,7: 2.1.Dopamine (4-(2-aminoethyl)benzene-1,2-diol)	Cell bodies at all levels; short, medium and long connections.	
	2.2. Norepinephrine (4-[(1R)-2-amino-1-hydroxyethyl]benzene-1,2-diol)	Cell bodies in pons and brain stem project to all levels.	The therapeutic action of levodopa-carbidopa drug to treat Parkinson's disease is associated with dopamine pathways linking substantial nigra to the neostriatum and ventral segmental to limbic structures.
			When noradrenergic input applied to neurons, norepinephrine can hyperpolarize them by increasing K+ conductance. Behavioral processes thought to involve noradrenergic pathways, e.g. mental arousal and elevated mood.
	2.3.Serotonin (3-(2-aminoethyl)-1H-indol-5-ol; 5-Hydroxytryptamine)	Cell bodies in midbrain and pons project to all levels.	It has often been speculated that serotonin pathways may be involved in the hallucination induced by lysergic acid diethylamide. Other functions include sleep, temperature, appetite and neuroendocrine control.
			The central nervous system cocaine and amphetamine are believed to act primarily at epinephrine synapses.
	2.4.Epinephrine (adrenaline; catecholamine) (4-[1-Hydroxy-2-(methylamino)ethyl] benzene-1,2-diol)	Hormone and a neurotransmitter.	
3	Peptide neurotransmitters8: 3.1.Opioid analgesic drugs (Enkaphalin, Endophrine, Morphine) 3.2.Neurotensin 3.3.Somatostatin 3.4.Cholesystokinin 3.5.Neuropeptide Y	Immunohistochemical techniques mapped a great many central nervous system peptides that produce dramatic effects on behavior and on the activity of individual neurons.	Substance P* has defined the role of peptides in CNS and its association with sensory fibers. It is present in some of the small unmyelinated primary sensory neurons of the spinal cord and brain stem. Presenile dementia of Alzheimer type is also associated with the decrease levels of putative transmitters, e.g. somatostatin.

No.	Neurotransmitter (IUPAC name)	Anatomy	Association
4	Amino acid neurotransmitters9: 4.1.Neutral Amino Acids: GABA (4-aminobutanoic acid) Gycine 4.3.Acidic Amino Acids: Glutamate Aspartate	Supraspinal interneuron, spinal interneuron involved in presynaptic inhibition. Glycine concentrations are high in the gray matter of the spinal cord, and it is directly proportional with the destruction of the neurons in this area. Relay neurons at all levels.	Picrotoxin, gabazine and bicuculline are prototypic antagonists of the activity of neural GABAA receptors that open Cl- channels; They cause generalized convulsions. Baclofen activates GABAB receptors and coupled to K+ channels for treating spasticity in multiple sclerosis. Virtually all neurons are strongly excited by glutamate and aspartate. This excitation is caused by the activation of receptiors: iontropics directly gate Na+, K+ and Ca2+ selective channels, while metatropics act on intracellular enzymes. The dissociative anesthetic ketamine and the hallucinogenic drug phencyclidine block these receptors that play a critical role in synaptic plasticity.

Adopted from:

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Table 4. Human ailment as a function of cerebral fluid protein elevation

No.	Clinical condition	Protein Average (g/L)	Range (g/L)
1	Epilepsy	0.31	0.07- 2.00
2	Acute alcoholism	0.32	0.13- 0.88
3	Multiple sclerosis	0.43	0.13- 1.33
4	Neurosyphilis	0.68	0.15-42.00
5	Brain abscess	0.69	0.16- 2.88
6	Aseptic meningitis	0.77	0.11- 4.00
7	Brain tumor	1.15	0.15-19.20
8	Bacterial meningitis	4.18	0.21-22.20

Source: Steaman, M. and Southgate, H.J. (1994) "The use of cytokine and C-creative protein measurements in cerebrospinal fluid during acute Infective meningitis", Ann. Clinc. Biochem., vol.31, pp.255- 261; Seehusen, D.A., Reeves, M.M. and Fomin, D.A. (2003) "Cerebrospinal fluid analysis", Am. Fam. Physician, vol.86 (6), pp. 1103-1108.

Knowledge of the entire protein content, the proteome, of normal human cerebrospinal fluid that is produced from arterial blood, would surely enable insights into neurologic and psychiatric disorders [122]. The cerebrospinal fluid acts as a cushion that protects the brain from shocks and supports the venous sinuses (primarily the superior sagittal sinus, opening when cerebrospinal pressure exceeds venous pressure); it also plays an important role in the homeostasis and metabolism of the central nervous system [62,123,129], i.e. it provides a basic mechanical and immunological protection of the brain inside the skull [11] . Unfortunately, technologic hurdles and access to true normal samples hindered until now attaining this goal, yet 2630 cerebrospinal and 3654 plasma proteins were identified [130]. Table 4 shows that the examination of the cerebrospinal fluid has become an integral part of the assessment of the critically ill neurological and neurosurgical [131,132].

The neurological and psychiatric disorders of human brain are subject to the structure and function of the brain, whereby the clinical diagnostics are evident in, for example cerebrovascular diseases, epilepsy, Alzheimer's disease and related disorders, other neurodegenerative conditions, brain infections, multiple sclerosis, headache and chronic pain, neurosurgery, anxiety and related disorders, mood disorders, schizophrenia and related psychoses, psychoactive substance and addiction [124] . Deep brain stimulation at high frequency is now considered the most effective neurosurgical therapy for movement disorders, especially in neurodegenerative disorder of Parkinson's disease [133] ,

whereas further investigation into apomorphine-induced stereotypes and sensorimotor gating in anxiety, autism, posttraumatic stress disorder, substance disorders, and Huntington's disease might be effective [134]. The sensorimotor gating, measured as prepulse inhibition of the acoustic startle reaction, is disturbed in certain neuropsychiatric disorders, such as schizophrenia, obsessive compulsive disorder, and Tourette's syndrome [135].

The processing of information in human brain depends on 1000s of unique neurotransmitter- receptor interactions, in which their understanding is not only a theoretical imperative, but it is also a practical necessity [127] . The apparent complexity of neurotransmitter signaling process would not be readily detectable if conjugated receptor interactions are investigated in isolation. It is therefore difficult to make cause-and effect statements regarding a single neurotransmitter and a behavior due to the sheer number of possible combinations of neurochemicals within a single synapse.

Thus, investigators have been able to associate behavior and disease states to receptors when research has been focusing on the dominant neurotransmitter at any one synapse [38, 122] .

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