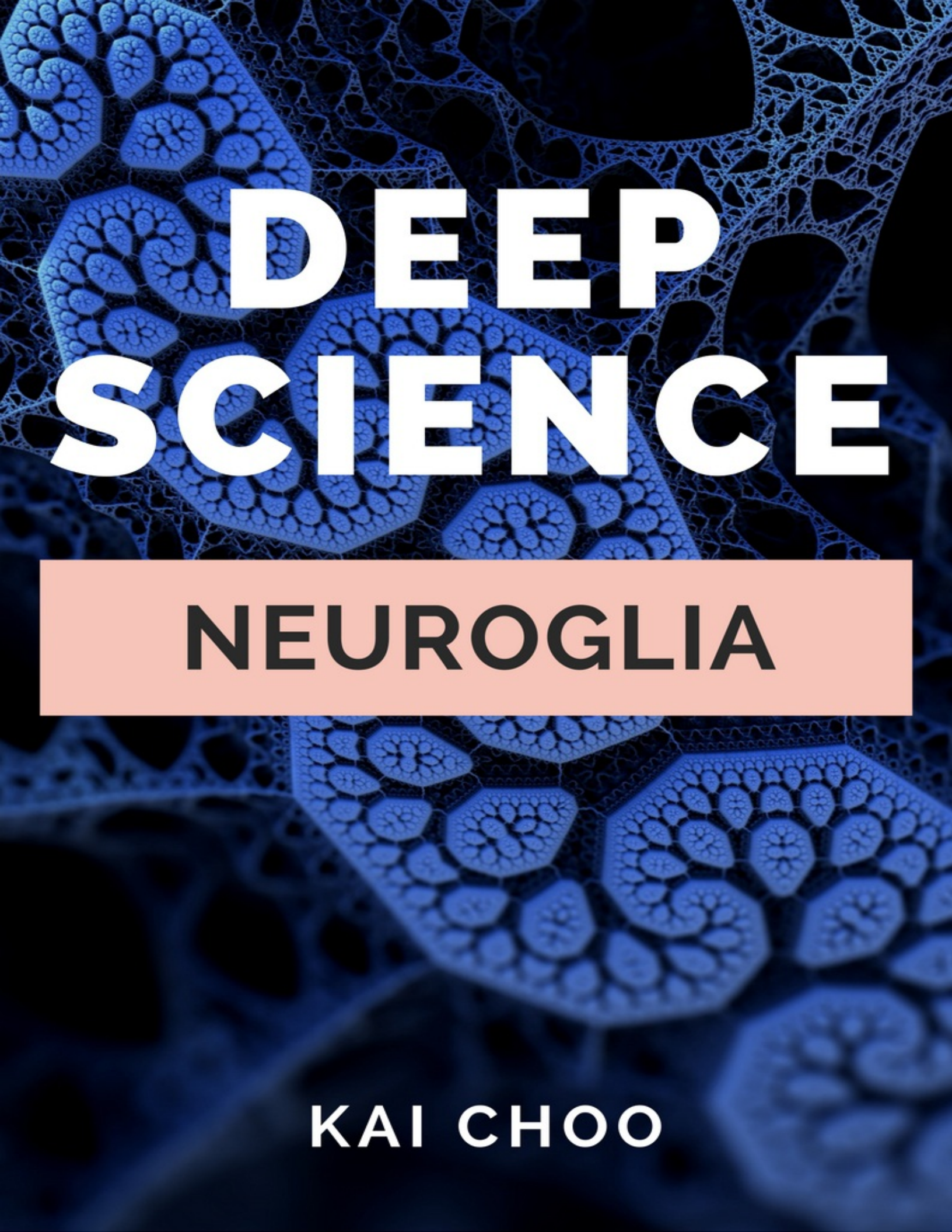
DEEP
SCIENCE
NEUROGLIA
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DEEP SCIENCE: NEUROGLIA

Notes for a deeper understanding

by

Kai Choo

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NEUROGLIAL FUNCTION

Glia, small cells that drastically outnumber their larger neighbors in the brain, neurons, account for about half the brain's weight. Traditionally, they have been characterized as mere support cells for the brain's neural network, which sends electrical impulses along complex routes to form the cellular basis for thought, learning and memory. But now, scientists are finding that glial cells may play a much greater role in the brain's communication than previously thought.

Glia make up approximately 90 percent of the cells in the human brain, and yet researchers have assigned mainly passive functions to them. Some glia wrap around nerve cells and insulate them with a protein called myelin. Glia at synapses act both as a physical barrier that prevents crossed wires and as a disposal unit that mops up extra messenger molecules released by nerve cells.

NEUROGLIA: POSSIBLE ROLES IN NEUROLOGICAL DISORDERS

Until recently the most abundant cells in the central nervous system, the neuroglia, received relatively little research attention with regard to their possible roles in the aetiologies of CNS disorders. However, many lines of evidence indicate that the neuroglia not only play crucial roles in normal CNS function, but also may be involved in the development of major neurological disorders.

Neuroglial cells of the central nervous system include the astrocytes, oligodendrocytes, and microglia. Their counterparts in the peripheral nervous system are the Schwann cells. The term neuroglia comes from an erroneous concept originally coined by Virchow (1850), in which he envisioned the neurons to be embedded in a layer of connective tissue or 'nevroglie' (nerve glue). Subsequently, Deiters and Golgi identified glial cells as making up the 'nevroglie' and distinguished them from neurones. The term, or its shortened form - glia, has persisted as the preferred generic term for these cells. A reciprocal relationship exists between neurons and glia, and this association is vital for mutual differentiation, development, and functioning of these cell types. Therefore, perturbations in glial cell function, as well as glial metabolism of chemicals to active intermediates, can lead to neuronal dysfunction.

There are many more glial cells than there are neurones in the CNS (in the human brain it has been estimated that 90% of brain cells are glial). They occupy the space between neurones and neuronal processes and separate neurones from blood vessels. Depending on their anatomical position they are classified as follows:

Central glia – comprising four cell types, i.e. astrocytes, oligodendrocytes, microglia and ependymal cells. The latter form the epithelial surfaces lining the walls of the cerebral ventricles and the central canal of the spinal cord, whereas the first three main glial cell types are interstitial (occupying the spaces between neurones).

Peripheral glia – comprising one cell type; the Schwann cell.

Several features clearly distinguish glia from neurones:

- Glia do not generate or conduct action potentials
- Glia do not establish chemical synapses
- Glial cells are capable of division for several years postnatally.

Astrocytes

Astrocytes are small star-shaped cells with numerous ramified processes covered with varicosities. They often have enlarged terminals in contact with neurones or non-neuronal tissue (e.g. walls of capillaries). There are two main types of astrocyte – fibrillary astrocytes containing numerous cytoplasmic filaments (found mainly in white matter), and protoplasmic astrocytes found mainly in grey matter. Although they do not form chemical synapses, astrocytes do form junctional complexes between themselves (gap junctions and desmosomes) such that they form a vast cellular network (syncytium) extending from neurones to blood vessels and the external surface of the brain. Normally, three main functions of astrocytes may be recognized:-

(i) *maintenance of the blood-brain barrier* – astrocytic processes terminate on the walls of capillaries in astrocytic end-feet, which are joined by junctions forming a barrier between the blood and brain neurones. This is not, however, the 'blood-brain barrier', which is formed by vascular endothelial cells which have characteristic ‘tight’ intercellular junctions. The astrocytic end-feet appear to be responsible for maintaining these tight endothelial junctions.

(ii) *regulation of the composition of the extracellular fluid* – the fluid bathing the neurones in the CNS must have a controlled composition to allow correct brain function. For example, potassium concentration must not be allowed to build up or uncontrolled neuronal depolarization would follow. Astrocytes appear to play a crucial role in ‘mopping up’ excess potassium and releasing potassium ions via their end-feet into the blood stream.

(iii) *mediation of neurotransmitter metabolism* – excess neurotransmitter which diffuses out of synapses can be taken up by astrocytes – this is

particularly true for glutamate. Astrocytes have a particularly large capacity for glutamate uptake, thereby preventing neurotoxic levels of the amino acid from accumulating. Furthermore, astrocytes participate in glutamate and GABA neurotransmitter metabolism by converting uptaken glutamate into glutamine, which is then passed back into the neurones for conversion to glutamate and GABA. It has also been suggested that astrocytes can release glutamate in a calcium-dependent manner, possibly indicating that the astrocytes can also participate in signaling mechanisms.

Astrocytes are now known to be involved in the most integrated functions of the central nervous system. These functions are not only necessary for the normally working brain but are also critically involved in many pathological conditions, including stroke. Astrocytes may contribute to damage by propagating spreading depression or by sending proapoptotic signals to otherwise healthy tissue via gap junction channels. Astrocytes may also inhibit regeneration by participating in formation of the glial scar. On the other hand, astrocytes are important in neuronal antioxidant defense and secrete growth factors, which probably provide neuroprotection in the acute phase, as well as promoting neurogenesis and regeneration in the chronic phase after injury.

Oligodendrocytes

There are two main types of oligodendrocyte – (a) the interfascicular (or myelinizing) oligodendrocytes which are found in white matter where they make up axonal myelin sheaths, and (b) the satellite oligodendrocytes which surround neuronal stomata in the grey matter. The interfascicular cells are so-called because they lie between bundles (or fascicles) of axons, and are responsible for the formation of myelin sheaths around neuronal axons. The myelin sheath is formed by flattened processes, extending from the oligodendrocytes, which wrap themselves around the axon for up to 40 turns. Each oligodendrocyte can form myelin segments around many different axons (20-70), so that degeneration or dysfunction of a single oligodendrocyte can have disastrous consequences on the function of many different neurones. Each section of myelin is about 1 mm long such that the axon is covered by a discontinuous or segmented myelin sheath, with the

segments separated by unmyelinated gaps (the nodes of Ranvier).

Microglia

Ramified microglial cells are scattered throughout the CNS and comprise 5-12% of all cells which are derived embryologically from monocytes. During embryology these monocytes are active macrophages which dispose of unrequired, dead or dying cells together with tissue fragments. They differentiate into ramified (many processes extending out from the cell body) microglia which are usually quiescent during adulthood. However, as a result of injury or infection of the CNS these quiescent microglia become activated, and can become amoeboid, phagocytosing damaged tissue.

Other Glial Cells

In addition to the three main types of CNS neuroglia described above, there are two further types which require brief description. These are the ependymal cells of the CNS and the peripheral Schwann cells. The ependymal cells form a continuous epithelium lining the walls of the cerebral ventricles. In the choroid plexuses of the lateral ventricles the ependymal cells form tight junctions with each other such that they form a barrier between the blood capillaries and the cerebrospinal fluid (CSF). This is important as the blood-brain barrier in these regions is ‘leaky’. In addition to this role, the ependymal cells of the choroid plexus regions are also involved in CSF production. Outside the choroid plexus regions, the ependymal cells lining the ventricles are ciliated, presumably to aid movement of the CSF, and do not form tight junctions.

Schwann cells are the glial cells of the peripheral nervous system, and their main role is to myelinate the axons of peripheral neurones. There are also Schwann cells which do not myelinate neurones – these cells encapsulate non-myelinated axons, or surround and protect neuronal cell bodies in ganglia. In addition to these insulating and protective roles, Schwann cells also appear to play an important part in the regeneration of injured peripheral nerves (central axons are not capable of any regeneration).

NEUROGLIAL RESPONSES TO CNS INJURY AND INFECTION

It was mentioned above that the main function of microglial cells is to react to CNS injury and to mediate repair/disposal of damaged tissue and invading pathogens. However, in addition to the microglia, astrocytes also become activated by CNS trauma. Injured neurones rapidly change their gene expression and secrete cytokines and growth factors to stimulate nearby glial cells.

NEUROLOGICAL DISORDERS

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder that results in mental deterioration in the elderly (usually over 65) and was described by Alois Alzheimer in 1907. It can be categorized into five stages: normal, normal aged forgetfulness, mild cognitive impairment, mild AD, moderate AD, moderately severe AD and severe AD. The mean age from diagnosis to death is usually 8-9 years.

The neuropathological aspects of AD include the gradual, progressive destruction of higher brain centers which includes the neocortex and limbic systems (hippocampus and amygdala). As the hippocampus is involved in learning and memory, it should come as no surprise that the pathology generates in the entorhinal cortex region of the hippocampus and then spreads to the amygdala and cortical regions. There is extensive neural atrophy in the hippocampal regions as well as the cortex where the gyri and ventricles appear enlarged.

The histopathological changes including intracellular neurofibrillary tangles (NFT) and extracellular senile plaques. The neuronal cytoskeleton is made up of microfilaments as well as microtubules. Specific TAU proteins facilitate and maintain tubulin. However, in AD, hyperphosphorylation of TAU leads to formation of paired helical filaments which disrupt microtubule assembly and the cytoskeletal structure, replacing them with NFT. The amount of NFT is correlated with the severity of dementia. On the other hand, beta amyloid is a soluble protein that is usually made via the breakdown of amyloid precursor protein (APP) by beta and gamma secretase enzymes. Mutation in either the APP gene, which is located on chromosome 21 or secretase enzymes, leads to the formation of a novel beta amyloid consisting of 42 AA. This version is insoluble, highly toxic and deposits as senile plaques. The plaques resist degradation by neprilysin and plasmin. These plaques are also thought to initiate inflammatory reactions via the activation of microglia and astrocytes which release cytokines and inflammatory mediators such as NO and reactive oxygen species as well as proteins such as apolipoprotein 4 (APOE), which are normally involved in cholesterol carrying in the blood but in AD in aggravate senile plaque formation.

A common feature of Alzheimer's disease pathology is the abundance of reactive astrocytes and activated microglia surrounding the characteristic neuritic plaques containing amyloid peptide which are deposited in brain tissue. The precise relationship between neurodegeneration and glial activation remains unclear, although it is known that the cytokines and other inflammatory mediators released by the glia have the potential to initiate or exacerbate the progression of neuropathology. It is believed that the abnormal deposition of amyloid triggers the activation of neuroglia leading to an abnormal chronic inflammatory reaction. The inflammatory mediators released by activated glia 'recruit' and activate more glial cells and promote further amyloid deposition resulting in a self-propagating cascade of neuronal destruction.

Currently clinical diagnosis of AD focuses on biomarkers found in the cerebrospinal fluid. TAU protein is found to be elevated while insoluble 42AA fragments of the β-amyloid peptide is found to be reduced. APP and acetylcholinesterase are also elevated. In mouse models, increasing the latter two, enhanced neuronal survival during development.

AD is 15% familial and 85% sporadic. Several theories have been speculated as to the cause of AD. These are: genetic factors, neuropathology and changes in gross of the brain and several neurotransmitter hypotheses.

Four genes have been conclusively shown to affect the development of Alzheimer's disease: the APP gene on chromosome 21, the PS1 gene on chromosome 14, the PS2 gene on chromosome 1, and the apoE gene on chromosome 19. APP is a 695 residue protein encoded for by a gene on the long arm of chromosome 21. Down's syndrome is a pathology that consists of trisomy 21, which often displays AD characteristics. However, it is found that point mutations in the gene lead to abnormal processing of APP. PS1 and PS2 are responsible for the manufacturing of the secretase enzymes. The ApoE gene encodes ApoE4 which is found in AD patients, it promotes beta-amyloid production.

Sporadic cases are thought to arise due to Ach deficits. There are two constellations of cholinergic neurons in the brain. The 'basal forebrain' constellation is located in the telencephalon and includes the basal nucleus of Meynert, which provides cholinergic innervation to the entire neocortex,

amygdala, hippocampus and thalamus. This constellation is involved in learning and memory and dramatic loss of cholinergic neurons in this area has been implicated in AD which explains the dementia. Animal studies are consistent with this hypothesis. Additional evidence of the cholinergic hypothesis is based on the finding of a marked deficit of choline acetyltransferase in postmortem brains of AD patients reported in 1976. Nonetheless, this does not alleviate all symptoms which is why mechanisms of neuronal degeneration in AD must involve multiple transmitter systems. Serotonin and the death of pyramidal cells have also been investigated. There is a loss of 5HT1A receptors in the human brain.

ALS

Motor neurone disease or ALS (amyotrophic lateral sclerosis) is a degenerative disease characterised by progressive paralysis usually leading to death within 3-5 years. This is due to the highly selective degeneration of motor neurones. It has been proposed that an important factor in the pathogenesis of ALS may be excitotoxicity due to excess glutamate resulting from a deficiency in astrocyte glutamate uptake. This, in turn, has been suggested to be a result of the excessive release of reactive oxygen species from the neurone damaging the astrocytes and inhibiting their capacity to 'mop up' glutamate in the extracellular fluid.

Pathological Pain

Recent evidence indicates that spinal cord astrocytes and microglia may be involved in the creation of at least some forms of neuropathic pain. In an animal model of neuropathic pain it was discovered that spinal astrocytes became activated. It has now been confirmed that spinal astrocytes and microglia become activated in response to a wide variety of conditions that produce hyperalgesia. Also, prevention of glial activation attenuates the exaggerated pain induced by a variety of conditions (inflammation etc). Glial activation also appears to reduce the effectiveness of opiate analgesics suggesting that the glia release substances which somehow counteract the effects of opiates. Activated glia release several mediators which are known to act as transmitters in synapses transmitting pain signals or which 'sensitize' pain neurones, e.g. excitatory amino acids, nitric oxide, prostaglandins, cytokines, growth factors etc. It is particularly significant that activated glia release pro-inflammatory cytokines such as TNF and

interleukins (IL-1 and IL-6) which play no part in normal pain transmission but which are released as a result of injury or infection to create a state of hyperalgesia. Malfunctions in the control of the release of these agents may be at least partly responsible for states of abnormal pathological pain. For example, it has been suggested that pathological pain, having no obvious cause, which occurs in conditions of chronic infection (e.g. AIDS) may be due to chronic abnormal activation of neuroglia by viral or bacterial pathogens.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disorder affecting movement, sensation, and bodily functions. It is caused by destruction of the myelin insulation covering nerve fibers (neurons) in the central nervous system (brain and spinal cord). Despite considerable research, the trigger for this autoimmune destruction is still unknown. One important factor which has been suggested is the involvement of a slow-acting virus, one that is acquired early on but begins its destructive effects much later. Slow viruses are known to cause other diseases, including AIDS. In addition, viruses have been implicated in other autoimmune diseases.

The two main mechanisms whereby viral infection could lead to autoimmune destruction of the oligodendrocytes responsible for myelination in the CNS are: - (a) the immune system is actually attacking a virus (one too well-hidden for detection in the laboratory), and the myelin damage is an unintentional consequence of fighting the infection, and (b) the immune system mistakes myelin for a viral protein, one it encountered during a prior infection. Primed for the attack, it destroys myelin because it resembles the previously-recognized viral invader. As has been suggested for Alzheimer's disease, the underlying problem in MS may be an abnormal chronic CNS inflammation mediated by microglia and astrocytes, which then 'attack' the oligodendrocytes leading to gradual destruction of myelin sheaths.

Epilepsy

Decades of research in epileptogenesis have focused on the intrinsic properties and network connections of neurons. Glial cells, although long considered to be merely supporting cells in the central nervous system, may

also have an important role. Glia perform key buffering functions that help to maintain the uptake of potassium and glutamate and other aspects of the extracellular milieu of neurons. Theoretically, disruption of these glial functions could cause neuronal hyperexcitability, since increased levels of extracellular potassium decrease the threshold for neuronal firing and increased levels of glutamate could increase neuronal activation. Preliminary evidence from an animal model of cortical malformation indicates that astrocytes near the epileptic focus have a profound reduction in inward potassium currents. Thus, a change in the neuronal microenvironment may be another mechanism of epileptogenesis.

Investigations into basic mechanisms of epilepsy established that potassium homeostasis plays an important role in the control of neuronal excitability. Astrocytes are located in strategic proximity to neurons (and vasculature) to support the homeostatic regulation of the neuronal microenvironment. It has been suggested that glial dysfunction is a key factor in seizure generation. Evidence linking astrocytic physiology to potassium homeostasis is based on recordings from glia, neurons, and direct measurements of extracellular and intracellular potassium. Glia may play a specific role in the regulation of neuronal excitability by controlling the potassium concentration in the extracellular space.

(i) *Epilepsy as a neuro-immunological problem*

Epilepsy is one of the most frequent and devastating neurological disorders, estimated to afflict 7 to 20 per 1000 population in the world. More than 100,000 patients are diagnosed with epilepsy every year in the U.S. Epilepsy is a disorder that may be the result of injury to the brain produced by different factors or it may be associated with genetic predisposition. Despite the variability of etiological factors, common neuronal and neuroglia cell responses appear to be involved in processes associated with epileptogenicity. Extensive investigation of neuronal mechanisms involved in epilepsy have been done but little attention have been given to the role of neuroglial and neuroimmune reactions in the pathogenesis of epilepsy.

(ii) Neuroglia and neuroimmune mechanisms in epilepsy

Neuroimmune responses are comprised by cellular and molecular

> mechanisms that protect neurons and modulate inflammatory reactions during normal and dysfunctional stages of the CNS. The main mechanisms of modulation of immune responses within the CNS are facilitated by neuroglial-neuronal interactions and the blood brain barrier (BBB). The neuroglia, mostly astrocytes and microglia, have crucial roles in the regulation of the CNS immune response as they participate in the detoxification of excess excitatory amino acids, are fundamental to the integrity of the BBB, contribute to the functional stability of synapses, and produce a number of cytokines and chemokines necessary for maintaining CNS homeostasis.

In epilepsy, it is clear that a number of neuronal-neuroglial interactions are disrupted and an increase in the magnitude of activated astroglia and microglia occur in areas involved in epileptogenesis. Recent studies in our laboratory have focused in the role of neuroglial dysfunction and neuroimmune reactions in pediatric epilepsy. We have collected an extensive repository of brain tissues obtained from surgical resections and hemispherectomies performed as treatment of pharmacologically resistant epilepsies in children. Three major groups of disorders have been identified: Rasmussen's syndrome (RS), an inflammatory disorder thought to be of autoimmune etiology, cortical dysgenesis, and post-stroke epilepsy. We have demonstrated that in all three groups of disorders, activation of neuroglia and inflammatory pathways occurs in areas of the brain involved in epileptogenesis. Our lab also collaborate with researchers at the Sturge-Weber Syndrome Center in the characterization of the pathological mechanisms associated with this disorder.

Psychiatric disorders

In addition to the neurological disorders mentioned above, it has also been suggested recently that at least some of the pathology of schizophrenia and possibly other psychiatric disorders may be due to abnormal neurone-glial interactions. Although this is at present rather speculative, it is feasible that viral infection, particularly in the developing organism, could cause activation of neuroglia (which are closely involved in guiding the growth of neurones in early development) with resultant abnormalities in neuronal

pathways leading to the development of schizophrenia in the adult. Furthermore, evidence is accumulating that inflammatory responses in the periphery may have consequences on brain function, e.g. peripheral release of cytokines at sites of inflammation can stimulate CNS neuroglia by (a) stimulation of peripheral nerves which can then activate neuroglia surrounding the nerve's terminal regions in the CNS, and (b) peripheral cytokines circulating in the blood can elicit the secretion of PGE_2 by endothelial cells lining brain ventricles – this can then stimulate release of cytokines in the brain with resultant glial activation. Specific cytokines appear to have specific effects on neurotransmitter systems within the brain – for example, IL-1 stimulates release of 5-HT from serotonergic neurones originating in the raphe nuclei. Other cytokines promote release of corticotropin-releasing hormone from the hypothalamus. Both of these mediators are known to be involved in depression – this, together with the observation that major depression is accompanied by the activation of an 'acute phase' peripheral inflammatory response (resulting in increase of cytokines), has been proposed to indicate that causes of inflammation (e.g. viral infection) may contribute to the aetiology of depression.

Specifically, Schizophrenia is a psychotic disorder that affects over 50 million people worldwide. It is described as the fragmentation of a single, often dysfunctional personality that is triggered by a psychotic break and often has a post-pubertal onset displaying great heterogeneity. 10% of patients will eventually commit suicide.

The symptoms presented in schizophrenia may be divided into positive and negative symptoms. The positive symptoms include grossly disorganized behavior, delusions, hallucinations and disorganized speech/thinking, also known as thought disorder. These patients are often the ones who construe paranoid or erroneous beliefs based on distortions and exaggerations due to misconceptions of perceptions of experiences. They have difficulty in carrying out goal-oriented behavior, unpredictable agitation and bizarre behavior often hearing voices and having distorted senses. The negative symptoms on the other hand resemble those of apathy and depression. They are: anhedonia, alogia, affective flattening and avolition. Negative sufferers have no interest in being involved in social activities and are reluctant to initiate goal-oriented behavior. They often have poverty of speech; their

sentences don’t fit together and they have a massive reduction in the range and intensity of emotional expression.

Based on presentation of these symptoms, there are five distinct types of schizophrenia. These are: the paranoid subtype, which shows a high degree of positive symptoms. These patients respond best to antipsychotic medication. In contrast, catatonic schizophrenia displays more negative symptomology to the point of immobility and respond less to medication. The residual subtype patients experience more positive symptoms at a young age but more negative symptoms after ages 40-50. The disorganized subtype is the one found mostly in street hobos demonstrated by a German-lead study. Thought is disorganized and illogical and sentences don’t fit together. Finally the undifferentiated subtype caters for those who clearly have psychotic symptoms but do not fit into any other category.

The causes of schizophrenia can be attributed to three theories which involve the neurotransmitters dopamine, serotonin and glutamate.

The dopamine theory was proposed by Carlsson, who observed that administration of adrenaline and dopamine agonists such as bromocriptine into both mice and patients, seem to induce psychotic symptoms. The positive symptoms reflect too much dopamine activity in the prefrontal regions of the brain. All successful therapies for schizophrenia seemed to antagonize dopamine D2 receptors or modify the amount released. Typical drugs such as chlorpromazine and haloperidol are used. There seemed to be an excess of dopamine unlike in PD which showed a lack of dopamine. Side effects of the typical drugs included PD like symptoms. D1 are found more in the prefrontal cortex than D2 and this is the next focus.

The serotonin hypothesis best explains the negative symptoms. Atypical drugs, that is, 5HT2 antagonists such as clozapine and quetapine seem to have antipsychotic effects on negative symptoms. Their side effects include neuroleptic malignant syndrome (high fever and fluctuating consciousness), tardive dyskineasias and dystonias. Schizophrenics have been found to have elevated levels of platelet or whole blood 5HT and decreased levels of 5-hydroxyindoleacetic acid in the CSF have been correlated with cortical atrophy and ventricle enlargement.

The recent glutamate theory explains that insufficient glutamate transmission may be occur in these brains. PCP and ketamine are antagonist to the NMDA receptor and seem to exacerbate schizophrenic symptoms. So maybe more glutamate is needed! This has been shown in mice with reduced glutamate levels and show social outcast behaviors. NAAG and kynurenic acid also counter the effects of NMDA and are found elevated in postmortem brains.

Genetic causes are also under investigation and there are currently several loci on several chromosomes that are candidates. Disc-1 on chromosome 1q24 is a gene thought to be important in brain development and neurite growth whose mutant truncation is associated with major psychiatric illness. Microdeletions on 22q11, fragile areas on 19q13 and the MTHFR gene on 1q36 are only a few propositions. In first degree relatives, the chance of getting schizophrenia is 10%, with monozygotic twins, its 50%.

Rasmussen's syndrome

In Rasmussen's syndrome, marked infiltration by T lymphocytes occurs in parallel to astroglial and microglial activation. Interestingly, a subset of RS cases showed evidence of cortical dysgenesis, a finding that suggests that cytoarchitectonical abnormalities and neuronal disorganization may trigger autoimmune reactions responsible for the inflammatory changes seen in this disorder. These findings strongly suggest that neuroglial and neuroinflammatory responses are involved in the pathogenic mechanisms of epilepsy. Our main focus of research is to identify immune mechanisms and inflammatory pathways involved in neuroglial responses and their effect on neuronal dysfunction by using novel proteomic techniques in brain tissues of well characterized pediatric epilepsy disorders. The ultimate goal of these studies is the development of new therapeutic strategies for the treatment of seizures disorders and their effect on CNS function.