Contents

INTRODUCTION

Letter from the Editors

GENERAL NEUROSCIENCE

Adult Neurogenesis: Then and Now  Stephen Bello  pages 3 - 9
Drugs and Toxicology  Chiara Di Censo  pages 10 - 12
Neuroinflammation: Friend, Foe, or Both?  Lorna Bo  pages 13 - 22

NEUROSCIENCE AND SOCIETY

The Right to Restfulness  Jacob Mesina  pages 23 - 27

DISEASE

Glioblastoma Brain Tumors  Lindsay Roberts  pages 28 - 30
Guillain-Barré Syndrome  Yasmeen Hmaidan  pages 31 - 33
Neurotoxic Vestibulopathy: A Review of Drug-Induced Toxicity  Christian Gonzalez  pages 34 - 36
Phantom Limb Pain: An Overview  Kazacham Dangata  pages 37 - 39
Urbach-Wiethe Disease- Fearless or Perilous?  Catherine Hobbs  pages 40 - 41

RESEARCH

A Molecular Approach to Addiction--ΔFosB  Deniz Kirca  pages 42 - 46
Why do clinical trials take so long?  Nigar Abdullayeva  pages 47 - 50

CONTRIBUTORS' PAGE

page 51
Readers,

Welcome to the second season of the IYNA Journal! We greatly appreciate your continued (or new) readership.

With the introduction of our second volume, we would like to highlight a change which has been made to the format of the IYNA Journal. In our first volume, we dedicated each issue to a specific topic in the field of neuroscience. We have decided to abandon this practice in favor of exploring an array of neuroscience topics in each issue. Here are brief summaries of just a few of the articles found in this issue:

In our neuroscience and society column, Jacob Mesina describes the right to restfulness and how sleep can affect our daily life.

In our disease section, Lindsay Roberts describes Glioblastomas, Yasmeen Hmaidan discusses Guillain-Barré Syndrome (GBS), Christian Gonzalez reviews Neurotoxic Vestibulopathy and Drug Induced Toxicity, Kazacham Dangata overviews Phantom Limb Pain, and Catherine Hobbs introduces the argument of whether the Urbach-Wiethe Disease is fearless or perilous.

In our section about research, Deniz Kirca describes the research of A Molecular Approach to Addiction, more specifically, AFosB, while Nigar Abdullayeva explains why clinical trials take so long.

As always, it is critical that we recognize all of our dedicated writers, editors, and assemblers for helping us make this issue the success that it is. You can see all of their names and positions on our Contributors page.

If you have any questions, comments, or suggestions for us, please feel free to contact us at info@youthneuro.org. We hope you enjoy reading our first issue of our second volume as much as we enjoyed writing it!

Best Regards,
The IYNA Journal Editing Team
Adult Neurogenesis: Then and Now

Stephen Bello

Abstract

Whether or not new neurons are born in the adult mammalian brain has been the topic of much debate in the early years of neuroscience. After the discovery that neurogenesis does indeed occur in the mammalian brain, it was hard for many to believe it was so. However, various studies with indisputable results supporting adult neurogenesis have been reported over the years. Much of adult neurogenesis occurs in the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus with different mechanisms of occurrence. Environmental factors and stress have been shown to influence adult neurogenesis. Neurogenesis in the adult brain occurs at a very low rate after maturity and the cells generated have limited inherent long-term restorative ability.

Various drugs have been shown to enhance as well as inhibit adult neurogenesis. In order to determine the existence of adult neurogenesis, various markers have been developed to reveal this process in species. Alterations in adult neurogenesis have also been shown to be implicated in various diseases.

History

There was a lot of controversy among early neuroscientists as to whether the adult mammalian brain undergoes neurogenesis, that is, whether new neurons are born in the adult mammalian brain. In fact, one of the leading early researchers in neuroscience, Ramon y Cajal, once stated that no new neurons are born in the mammalian brain. This statement was later accepted as a dogma in the early neuroscience community. Joseph Altman and Gopal Das published a research work in the 1960’s that challenged this belief by reporting evidence of adult neurogenesis in rodents. Even though their work was published in one of the leading journals of that time, they could not change the long-held scientific dogma that no new neurons are born in the adult brain due to the finding’s contradiction to Cajal’s interpretation of this matter. To further investigate whether new neurons are born in the adult mammalian brain and to validate or dispute the findings of Joseph Altman and Gopal Das, two other researchers in the 1970’s, Fernando Nottebohm [1] and Michael Kaplan [2], studied the brain of birds and rodents respectively. Nottenbohm’s studies with birds showed the existence of adult neurogenesis in their brains. Kaplan further proved the existence of adult neurogenesis in rodents. These research findings, especially Kaplan’s, received a lot of criticism. Although the neuroscience community could accept the existence of adult neurogenesis in birds, they found it rather difficult to accept the existence of adult neurogenesis in rodents. Most research investigations supported the existence of adult...
neurogenesis, but one in particular casted doubts on the existence of this phenomenon. In 1985, Pasko Rakic published a paper titled “Limits of Neurogenesis in Primates” and convinced many researchers that adult neurogenesis is restricted to evolutionarily lower order animals (rodents and birds), and that it is irrelevant for primates such as ourselves. The neuroscientific community went in the direction of Pasko Rakic until the 1990’s, when researchers such as Elizabeth Gould, Fred Gage, and Peter Eriksson published a series of papers that initiated an explosion of research on the existence, function, and implications of adult mammalian neurogenesis.

The loss of neurons in the adult human brain had long been thought to be irreversible and the inability to replace dead or disease neurons had been thought to be an important cause of neurological disease and impairment.

Where does it occur?

The generation of neurons is generally confined to a discrete developmental period. The hippocampus is one of only a few brain regions where production of neurons occurs throughout the lifetime of animals, including humans [3]. Two forebrain structures actively demonstrate adult neurogenesis, namely the subventricular zone of the lateral ventricles (SVZ) and the subgranular zone (SGZ) of the dentate gyrus. These structures actively demonstrate adult neurogenesis in several species and have been shown to generate new neurons well into the postnatal and adult period [4]. Granule neurons are generated throughout life from a population of continuously dividing progenitor cells residing in the subgranular zone of the dentate gyrus in the rodent brain. ‘Newborn’ neurons generated from these progenitor cells migrate into the granule cell layer, differentiate, extend axons and express neuronal marker proteins. The study of [5] has also shown that neurogenesis also occurs in the adult prefrontal cortex.

Mechanism of occurrence

The proliferating radial glia-like cells in the adult SVZ give rise to transient amplifying cells, which in turn generate neuroblasts. In the Rostral Migratory Stream (RMS), neuroblasts form a chain and migrate towards the olfactory bulb through a tube formed by astrocytes [6]. Once these neuroblasts reach the core of the olfactory bulb, immature neurons detach from the RMS and then migrate radially towards glomeruli where they differentiate into different subtypes of interneurons [7]. The majority of the differentiated neuroblasts become GABAergic granule neurons, which lack axons and form dendro-dendritic synapses with mitral and tufted cells. A minority become GABAergic periglomerular neurons, a small percentage of which are also dopaminergic. It has been suggested that a very small percentage of new neurons develop into glutamatergic juxtaglomerular neurons [8].
Adult neurogenesis in the subventricular zone of the lateral ventricle and olfactory bulb

Summary of five developmental stages during adult SVZ neurogenesis: (1) activation of radial glia-like cells in the subventricular zone in the lateral ventricle (LV); (2) proliferation of transient amplifying cells; (3) generation of neuroblasts; (4) chain migration of neuroblasts within the rostral migratory stream (RMS) and radial migration of immature neurons in the olfactory bulb (OB); (5) Synaptic integration and maturation of granule cells (GC) and periglomerular neurons (PG) in the olfactory bulb. Also shown are expression of stage-specific markers, sequential process of synaptic integration, and critical periods regulating survival and plasticity of newborn neurons. GFAP: glial fibrillary acidic protein; DCX: doublecortin; NeuN: neuronal nuclei; LTP: long-term potentiation. Source: [9]

On the other hand, in the adult SGZ, proliferating radial and non-radial precursors give rise to intermediate progenitors, which in turn generate neuroblasts (Figure 3). As the immature neurons migrate into the inner granule cell layer and differentiate into dentate granule cells in the hippocampus, newborn neurons begin to extend dendrites towards the molecular layer and project axons through the hilus toward the CA3. New neurons follow a stereotypic process for synaptic integration into the existing circuitry.
Adult neurogenesis in the dentate gyrus of the hippocampus
Summary of five developmental stages during adult hippocampal neurogenesis: (1) activation of quiescent radial glia-like cell in the subgranular zone (SGZ); (2) proliferation of non radial precursor and intermediate progenitors; (3) generation of neuroblasts; (4) integration of immature neurons; (5) maturation of adult-born dentate granule cells. Also shown are expression of stage-specific markers, sequential process of synaptic integration, and critical periods regulating survival and plasticity. ML: molecular layer; GCL: granule cell layer; SGZ: subgranular zone; GFAP: glial fibrillary acidic protein; BLBP: brain lipid-binding protein; DCX: doublecortin; NeuN: neuronal nuclei; LTP: long-term potentiation.
Source: [9]
Regulation

The regulation of neurogenesis can be targeted at several steps of the overall process. The morphological and genetic stages that characterize adult neurogenesis are taken advantage of in its regulation. Adult neurogenesis could be regulated by the local circuit factors [10], local signaling, and extrinsic factors such as learning, aging, and diet.

Factors influencing adult neurogenesis

The neurogenesis of the hippocampus can be influenced by various environmental factors and stimuli. Stressful experiences, including both physical and psychosocial stress, suppress the formation of hippocampal granule cells in a number of mammalian species. The down regulation of granule cell genesis induced by stress, as well as atrophy and death of CA3 pyramidal neurons, also contributes to the reduction in hippocampal volume [11]. A decrease in the proliferation of cells has also been reported in response to both acute and chronic stress paradigms.

Rate of Occurrence

Neurogenesis in the adult brain occurs at a very low rate after maturity. Many of the newly generated neurons do not survive for long. Therefore, the new neurons born in the adult brain may support plasticity on an acute time scale because they have an increased excitability. However, these cells have limited inherent long-term restorative ability. The ultimate survival of these newly generated neurons increases with some interventions such as learning and enriching the environment [12]. Dormant stem cells may also exist throughout the brain. These cells could potentially be stimulated to mature in pathological situations or after pharmacological interventions.

Drugs enhancing adult neurogenesis

Antidepressants such as Tricyclic antidepressants and Selective serotonin reuptake inhibitors; Mood stabilizer such as Lithium and Valproic acid; Cognitive enhancers such as Galantamine and Memantine; Anesthetics such as Ketamine [13]; Steroids such as Estradiol and Dehydroepiandrosterone; and others include Rolipram, Statins and Sildenafil (Viagra).

Drugs inhibiting adult neurogenesis

Chronic morphine or heroin use inhibits hippocampal neurogenesis. Also, alcohol induces inhibition of dentate gyrus neurogenesis.
Markers of adult neurogenesis

Exogenous markers of adult neurogenesis

- The tritiated thymidine technique
  The earliest studies of adult neurogenesis were based on the quantification of the incorporation of tritiated thymidine into cells replicating their DNA in preparation of the last mitosis of stem cells before they become postmitotic. This technique proved to be a very useful approach and allowed great advances in the description and understanding of mechanisms that underlie the production, incorporation as well as survival of new neurons in the adult brain.

- Bromodeoxyuridine
  Much of what we know today about adult neurogenesis (and in fact neurogenesis in general) was obtained by this method that has consequently become a sort of “gold standard” in the field. The identification of a thymidine analog, 5-bromo-2′-deoxyuridine (BrdU) that could be injected into an animal, would be incorporated in its replicating DNA and could then be easily identified by a standard immunohistochemical procedure was a major technological improvement. And this has allowed neuroscientists over the last few decades to perform more easily a substantial number of studies in a variety of animal species and physiological conditions.

- Other non-radioactive thymidine analogs (EdU, IdU, CldU)
  In recent times, a number of alternative thymidine analogs that can be incorporated when cells replicate their DNA and later visualized in histological sections have become available. In the chemical structure of these compounds, the bromide atom of BrdU is replaced by iodine (IdU, 2′-deoxy-5-iodouridine), chloride (CldU, 2′-deoxy-5-chlorouridine) or a small organic molecule in 2′-deoxy-5-ethynyl-uridine (EdU). These compounds, especially EdU have gained popularity due to a number of obvious advantages including their easy detection in tissue. They can and have now been used as a substitute for BrdU.

Endogenous Markers of adult neurogenesis

- Markers of cell cycling that allow the identification of stem cells or progenitor cells that are cycling and replicating their DNA. Examples of these proteins include: Ki67, a nuclear protein associated with ribosomal transcription; the Proliferating Cell Nuclear Antigen or PCNA; the phospho-Histone H3 or pH3.
- Markers of neurons such as NeuN, Hu, or Tuj1 that allow one to distinguish these cells from other cell types such as glia that can additionally be identified by other more or less specific markers (GFAP, S-100)
- Markers of new cells that have become postmitotic and engaged into the neuronal fate. Hu and Tuj1 are to some extent part of this class but since they can also be expressed by much older neurons, at least in the case of Hu, they cannot really be used to label neurons that have relatively recently become post-mitotic.
Diseases associated with adult neurogenesis

Alterations in adult neurogenesis appear to be a common hallmark in different neurodegenerative diseases including Alzheimer’s disease (AD), Parkinson’s disease (PD), and Huntington’s disease (HD). This is remarkable because the distinct pathological proteins responsible for the different diseases induce the loss of different neural populations. Impaired adult neurogenesis has been shown in numerous animal models of neurodegenerative diseases; however, only few postmortem studies have been performed [14].

References


Drugs and Toxicology

Chiara Di Censo

Abstract

Drugs have always attracted human attention. Drugs have a central role in human evolution thanks to their therapeutic potential to help humans cope with illnesses and disease. However, drugs can also have very serious negative effects on health due to their capacities to influence human physiology. This article discusses the influences of several drugs on the fields of toxicology and medicine.

MPTP

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a molecule that can be produced through the synthesis of meperidine, more commonly known as MPPP. While MPPP is an opioid drug and shows the same properties as morphine, MPTP has no psychoactive effects despite being a potent neurotoxin. As a lipophilic drug, MPTP enters easily into the brain by passing through the Blood Brain Barrier, being later processed by MAO-B of glial cells into the cation MPP⁺. However, this compound is highly toxic to the dopaminergic neurons in the pars compacta of the Substantia Nigra.

As a major player in the progression of Parkinson’s disease research, MPTP and its toxicity have been heavily investigated since its accidental synthesis in 1976. Barry Kinston, a chemical graduate student of Maryland, synthesized MPTP for the first time in 1976. Kinston attempted to produce MPPP, but a contamination led to MPTP synthesis. Barry injected himself with the manufactured substance, and within three days, had developed early Parkinsonian symptoms. This sparked a strong interest in the scientific community, where MPTP later became crucial in major developments in understanding the mechanisms behind Parkinson’s disease.

Subsequently, MPTP’s Parkinsonian manifestations inspired further study into the mechanisms behind its neurotoxicity. In 1982, six young persons were diagnosed with Parkinson’s disease in Santa Clara County, California. The neurologist J. William Langston along with the NIH recognised the real cause of such common cases. All the patients had taken MPPP contaminated with MPTP, which generates Parkinsonian symptoms. The treatment with LevoDOPA helped mitigate the paralysis and tremors of PD. Despite the previous study on rats failing, Langstone wanted to test the substance on primates, in order to clarify the neurotoxic effects of MPTP. The neurologist found the relationship between the loss of dopaminergic neurons and the injection of MPTP, and subsequently published the results in the book The Case of Frozen Addicts.
Tetrodotoxin

Tetrodotoxin (TTX) is a strong neurotoxin produced by pufferfishes so that they are easily able to break shells. However, triggerfish, ocean sunfish, some species of octopus, and several bacteria like *Pseudoalteromonas* and *Pseudomonas* carry tetrodotoxin. The substance was isolated for the first time by the Japanese scientist Yoshizumi Tahara in 1909, while in 1964 Toshio Narahashi and John Moore described the action mechanism of tetrodotoxin, using a particular technique called sucrose gap of voltage clamp.

Tetrodotoxin is approximately 100 times more effective than Potassium cyanide. The median mice lethal dose is 334 µg per kg, whereas the lethal dose of box jellyfish venom reaches only 5 µg per kg. The toxic reaction occurs when tetrodotoxin is taken from ingestion, injection, or inhalation.

The molecule blocks the voltage-gated sodium channel; as a result, sodium ions cannot flow into the cell membrane, and the action potential is disrupted. Tetrodotoxin acts on both the peripheral and central nervous system. The muscles are unable to receive the neural impulses so the victim who has taken tetrodotoxin is totally paralyzed. Moreover, the substance affects respiratory and vasomotor nuclei in medulla oblongata causing respiratory failure and hypotension. Early symptoms arise within about 20 minutes of ingestion. Victims experience paraesthesia of tongue and extremities, hyper-salivation, sweating, headaches, incoordination, tremors, paralysis, cyanosis, aphonia, dysphagia, and even seizures. Nausea, vomiting, diarrhoea, and abdominal pain can often occur and death due to respiratory failure is possible. Victims are often conscious before death and sometimes may even fall into a coma.

Unfortunately, there is not an antidote capable of treating the toxic reaction from tetrodotoxin. Gastric lavage may be helpful for patients who have ingested a life-threatening dose of tetrodotoxin. In other cases, the patient needs controls of respiratory and cardiovascular system and glycaemia level.

Tetrodotoxin and Pop Culture

Tetrodotoxin is also considered to have a role behind the myth of zombies. Between 1982 and 1984, Dr. Wade Davis conducted a study on TTX’s potential for creating zombies in Haiti. The doctor was particularly interested in the case of Clairvius Narcisse, who had been seen in a Haitian village after he was declared death. It turns out that Narcisse was poisoned from TTX, and although totally paralyzed, he remained conscious while he was being pronounced dead.

After some research, Davis asserted that an obscure technique called *bokor* had the ability to create “zombies”. The *bokor* used a particular mixture of several substances such as natural toxins and tetrodotoxin. As a result, victims were paralyzed by TTX but remain conscious. Sometime they managed to survive to toxic reaction but appeared completely dead so doctors would declare them dead and proceed with burials. By then, presuming they had not been killed by the toxins, the toxic effects wore off, and the victim would resume normal activity. This would, naturally, scare other villagers as they had just seen the victim pronounced dead.

Tetraethylammonium

Tetraethylammonium (TEA) is a quaternary ammonium cation, commonly known for its blockage of voltage-gated K⁺ channels, the characteristic that determines its neurotoxicity. TEA inhibits
Tetraethylammonium has a crucial utility for research in neuroscience. The molecule blocks specifically voltage-gated potassium channel, allowing neurosciences to study the real response of other ion channels. Furthermore, TEA can relieve symptoms of Parkinson’s disease by improving motor learning and reducing the progression of the disease.

References


Neuroinflammation: Friend, Foe, or Both?

Lorna Bo

Introduction

Thanks to the blood-brain-barrier (BBB)—a structure made from specialised endothelial cells that prevents the passage of immune cells from the blood into the extracellular fluid of the brain and spinal cord (central nervous system)—the brain enjoys a special immunological privilege. However, research over the past few decades has now established that not only can this barrier be compromised and peripheral immune cells be let in, but the brain has its own immune environment consisting of resident immune cells such as microglia, which release inflammatory mediators such as cytokines and chemokines during an acute immune response. It is when this acute immune response is maintained that chronic neuroinflammation can occur—which has now been linked to several neurodegenerative brain diseases such as Alzheimer’s, Parkinson’s, and multiple sclerosis. This opens the possibility for a reorientation of the search for novel therapies in the direction of immunomodulatory drugs, and the possibility of saving those affected from diseases that can be debilitating, depersonalising, and often fatal.

Acute inflammation: characterising a typical neuroimmune response

It is important to establish that although the term ‘neuroinflammation’ is now associated with chronic and neurotoxic inflammation, this neurotoxicity arises from a prolongation of valuable acute, short-term inflammation that occurs during an immune response.

The cells with the largest role to play during this acute immune response are the microglia. These are the CNS analogue of peripheral innate immune cells, and constitute approximately 5-20% of glial cells (non-neuronal cells) in the CNS [1] (see Fig. 1. for a summary of glial cells in the CNS). They can be characterised as the sentinels of the neuroimmune system, being the first responders to infection or injury.

Interestingly, based on the signals from cytokines, microglia can be phenotypically ‘polarised’ according to the function they are to perform: one phenotype promotes ‘classical’ proinflammatory activation (this phenotype is named M1), while the other phenotype promotes ‘alternative’ anti-inflammatory and pro-healing activation (M2). Research has found, however, that the term ‘polarised’ is a little misleading, given that M1 and M2 are not in fact binary states; rather, the phenotype of any microglial cell will sit on a spectrum between the two (see Fig. 2.). [2]

In a typical neuroimmune response, microglia release cytokines such as interferon gamma (IFNγ), interleukin 1 beta (IL1β), tumour necrosis factor alpha (TNFα), and reactive oxygen species (ROS) (as seen in Fig. 2), which then cause microglia to become polarised to the M1 state—an instance of autocrine
signalling (acting on the cells that produced the signalling molecules) and paracrine signalling (acting on nearby cells). This M1 state allows microglia to perform functions such as antigen presentation and the destruction of intracellular pathogens. This also allows microglia and astrocytes (another type of glial cell, described in Fig. 1) to upregulate the pro-inflammatory cytokines that cause them to polarise in the first place, some of which can induce apoptotic cell death in neurons via complex intracellular signalling pathways. These cytokines will then go on to polarise more microglia - this self-propagating cyclicity characterises many cases of chronic neuroinflammation, which are detailed with reference to specific diseases below. This proinflammatory state therefore helps to kill pathogens and remove dead or damaged cells - ‘classical’ (M1) activation. Yet after this initial inflammatory response, the M1 state is shifted to the ‘alternative’ M2 state by the upregulation of cytokines such as interleukin 4 (IL-4), interleukin 10 (IL-10), interleukin 13 (IL-13) and transforming growth factor beta (TGF\(\beta\)) (as seen in Fig. 2). This state promotes anti-inflammatory functions by upregulating various enzymes and proteins that, promote the clearance of debris and the formation of new blood vessels. It is this M2 switch that brings the immune response to a resolution, and thereby characterises it as acute. [2]

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**Fig. 1.** Diagram of the supporting cells of the CNS. Microglia are the innate immune cells in the CNS. They perform many of the same functions as macrophages, such as performing phagocytosis, releasing cytokines, and presenting antigens, and play a key role in neuroinflammation. Astrocytes are more abundant, and are involved in a broader range of functions such as homeostasis, and respond to CNS injury through a process called reactive astrogliosis, which also contributes to neuroinflammation. The role of oligodendrocytes is covered below, with reference to MS. Taken from Algonquin College (2012).
Chronic inflammation: the link to neurodegeneration

Acute neuroinflammation serves the purpose it evolved to perform: protection, damage control, and repair that is immediate and short-lived.

Yet it is when these microglia do not get polarised to M2, and are instead constantly stimulated by inflammatory cytokines that a sustained, chronic inflammatory response occurs. This phenomenon has been found to play a causative role in many brain diseases. In many of these cases, however, it is difficult to separate cause from consequence and to establish a linear progression of events, since disease begets neuroinflammation which in turn begets disease, and so on – resulting in the vicious cycle that characterises all of the diseases described below.

Alzheimer’s disease (AD)

Alzheimer’s disease is a neurodegenerative disease and the most common form of dementia – a global loss of cognitive faculties, particularly memory – that affects 25% of those aged 85 or older [3]. It is characterised by two defining pathological features: amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) [4]. Aβ plaques are extracellular deposits of Aβ, which are derived from amyloid precursor protein (APP), while neurofibrillary tangles are intracellular conglomerations of abnormal tau protein.

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**Fig. 2.** Model of microglial polarisation. (A) Cytokines, as seen on the left, can ‘polarise’ microglia to a phenotype that is not necessarily either M1 or M2, but rather more M1-like or more M2-like. (B) Pro-inflammatory cytokines polarise microglia to a more M1-like state, causing the microglia to release more of these cytokines, resulting in a vicious cycle of inflammation. (C) After an acute response is over, anti-inflammatory cytokines polarise microglia to a more M2-like state. Taken from Cherry, et al. (2014). [2]
It is a multifactorial disease that has been shown to have both genetic and environmental risk factors that vary from high fat intake to head injuries [1]. While none of these risk factors act as the cause of AD, what has been found to be a common feature of all cases studies is chronic neuroinflammation. Thirty years ago, microglia were found to localise to Aβ plaques [5], and since then, much research has been done on the relationship between AD and neuroinflammation. It has been repeatedly found that microglia are polarised to an M1 phenotype when localised to plaques, performing all the cytokine-releasing functions of classical activation, while occurring fairly early in the disease [6].

Post-mortem AD brains show an abundance of these activated microglia, and an experiment in mice which were transgenic (containing artificially introduced DNA) for an AD mutation of APP found that astrocytes and microglia expressing the proinflammatory cytokines IL-1β, IL-6 and TNF were found to surround Aβ plaques [7]. Ironically, the presence of inflammatory cytokines reduces the ability of microglia to phagocytose Aβ, thus hindering the resolution of the disease [8]. It may even be the case that inflammatory cytokines such as IL-1β directly upregulate the expression of APP, thereby upregulating the production of Aβ [9] (this has been disputed, however, by studies in which IL-1β signalling was blocked in mice with AD, and Aβ deposits remained unaffected [10]). This means that neuroinflammation causes the accumulation of these plaques instead of their clearance, which continues to stimulate microglia and keep on releasing the proinflammatory cytokines that inhibit them from destroying the plaques. And so the cycle continues.

Knowledge of the role of neuroinflammation in AD has allowed for certain inflammatory mediators to be targeted for drug development. Cyclooxygenase 2 (COX2) is an inflammatory enzyme that is upregulated in an AD brain, and this strong upregulation is associated with neurotoxic mechanisms such as ischemia (inadequate blood supply) and excitotoxicity (excess glutamate over-stimulating NMDA receptors and causing neuron death). Non-steroidal anti-inflammatory drugs (NSAIDs) that target COX2 have therefore been shown to reduce the risk for AD by reducing microglial activation. NSAIDs may also have another mechanism of decreasing the proinflammatory response: acting as an agonist (or, an activator) for the nuclear transcription factor (protein that controls the rate of transcription from DNA to mRNA) peroxisome proliferator-activated receptor gamma (PPARγ), which, as can be seen in Fig. 2C, upregulates those cytokines that cause microglia to polarise to the M2 state, thereby also causing microglia to act in an anti-inflammatory manner. [11]

Whilst the longest epidemiological study to date has indeed found that long-term NSAID use (lasting over 5 years) is neuroprotective against AD [12], clinical trials of NSAIDs for those patients already with AD have found inconclusive and varied results [13, 14, 15], demonstrating the need for further research into curative, as opposed to prophylactic, treatment.

Neuroinflammation in AD is not all bad, however. Whilst IL-1β has been implicated in the upregulation of APP (perhaps falsely, as mentioned above), it also upregulates the expression of tumour necrosis factor-α converting enzyme (TACE), which decreases Aβ production [16]. C3, a key inflammatory protein that may be necessary for plaque clearance, is also activated during neuroinflammation [17, 18]. This ambiguity as to what is ‘good’ or ‘bad’ is emblematic of a greater need to sort through the complexity of interactions involved in neuroinflammation to identify specific protective pathways in the neuroimmune response, and exploit them for future therapies.
**Parkinson’s Disease (PD)**

Parkinson’s disease (PD) is the second most common neurodegenerative disease after AD. It involves the gradual loss of motor control involving tremor, rigidity, bradykinesia (slowness of movement), and sometimes dementia and depression [19]. Its pathology is characterised by the death of dopaminergic neurons in a region of the midbrain called the substantia nigra pars compacta (SNpc) due to the presence of Lewy bodies - accumulations of the protein α-synuclein. Much like AD, a complex smorgasbord of genetics and environment have been shown to be risk factors (including head injuries and exposure to certain pesticides [20]), whilst the cause of the disease itself is still unknown. Like with AD again, however, neuroinflammation has been found to be a common hallmark of the disease, with studies of postmortem PD brains showing the presence of inflammatory mediators in the SNpc [21].

The sequence of events in PD is a little easier to define than in AD. The inflammatory response is initiated by the activation of microglia against α-synuclein aggregates, which triggers the usual release of proinflammatory cytokines including TNF, inducing neuronal death. Yet this neuron death causes the accumulated α-synuclein to be released from within the cell body, again triggering the inflammatory response, leading to a feedback loop in which microglia are constantly polarised to M1 and astrocytes remain reactive (see Fig. 3) [22]. The involvement of the peripheral immune system exacerbates this, with T cells crossing a BBB compromised by these proinflammatory cytokines to release even more proinflammatory cytokines such as IFNγ and TNFα' (see Fig. 3) [23]. However, microglial cells are also able

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1 These T cells have recently been found to play a much larger role than previously thought. A recent study has shown that two fragments of α-synuclein can trigger T cells to attack. Blood samples from those with PD and from those without were introduced to fragments of α-synuclein. The T cells from non-PD blood did not react, whereas the T cells in PD blood reacted very strongly. This may be because certain variants of major histocompatibility
to phagocytose extracellular α-synuclein due to the presence of toll-like receptor 4 (TLR4) on their cell surface, the ablation of which was shown to ‘augment motor disability’ and resulted in increased TNF levels [24]. Like in AD, this is yet another example of the inflammatory response being a complex mixture of beneficial and detrimental pathways, and the need to isolate those which are useful and harness them for therapeutic use.

**Multiple Sclerosis (MS)**

MS is known as the “neurological disease of young people,” being most commonly diagnosed in people in their 20s and 30s [26]. It is a neurodegenerative disease characterised by the destruction of the myelin sheath surrounding the axons of neurons (demyelination), which then causes inflammation and disseminating lesions that are visible on MRI scans. This is most likely due to a protein associated with myelin becoming an autoimmunogen (a target of the immune system that is not foreign, but ‘self’) [27]. The symptoms expressed as a result of this depend on the regions of the brain in which these lesions form, and can include problems with vision, movement, and balance [26].

Historically, MS has always been perceived as an autoimmune disease, initiated by T cells crossing a compromised BBB from the peripheral immune system into the CNS, and, alongside macrophages and B cells, targeting and destroying myelin, causing degeneration that further fuels the immune response. However, this ‘outside-in’ theory as to the primary stimulus for MS has been challenged with its antithesis: the ‘inside-out’ theory (see Fig. 4.). This proposes that the initial stimulus comes from a yet unknown cytodegeneration within the CNS itself, perhaps one that targets the oligodendrocytes that form the myelin sheath (see Fig. 1.), leading to the release of antigenic debris, which the immune system then reacts to, causing further degeneration, and so on. This paints a picture of the pathology of MS that is much like that of AD and PD, in that it is not the immune system that is defective, but a fault within the CNS itself complex (MHC) associated with PD treat these fragments as foreign, and so display them on the cell surface for recognition by T cells, thereby driving helper and cytotoxic T cell responses. [25]

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**Fig. 4.** Diagram showing the two competing hypotheses as to the initial stimulus of MS. The traditional view is that of the ‘outside-in’ model, which presents MS as an autoimmune disease in which autoreactive T cells cross into the CNS and destroy myelin. However, recent studies show that this order of events may in fact be reversed: primary cytodegeneration may in fact be the initiator, which causes a secondary inflammatory response due to releasing antigenic proteins. This, then, further drives degeneration through neurotoxic cytokines. Taken from Kamm, et al. (2014) [33]
(in AD, this comes in the form of Aβ plaques, and in PD, this comes in the form of α-synuclein aggregates). [28]

In any case, the immune system becomes activated, and T cells such as Th1 and Th17 cells become potent exacerbators of pathology due to the IFNγ cytokine they release. As mentioned above, this polarises microglia to the M1 state (see Fig. 2.), and the consequential neuroinflammation produces cytokines that are neurotoxic to the oligodendrocyte-myelin complex, and inhibit oligodendrocyte precursor cell (cells that differentiate into oligodendrocytes) proliferation and maturation [29]. This exposes neurons to damage by, reactive oxygen species (ROS) [30], leading to further degeneration.

Yet again, there have been found to be beneficial sides to neuroinflammation in MS. For example, astrocytes can infiltrate T cells clusters to induce apoptosis, and are also responsible for producing neurotrophic factors, which reduce degeneration and stimulate regeneration [31]. Counter-intuitively, remyelination (a process involving the differentiation of oligodendrocyte precursor cells into oligodendrocytes, which then synthesise new myelin) is also impaired after the depletion of TNFα and IL-1β (two proinflammatory cytokines) acting on oligodendrocyte precursor cells [32]. This may indicate that the proinflammatory cytokines released by microglia actually stimulate regeneration, although not enough regeneration to overcome the extent of neuroinflammation and neurodegeneration. Isolating these pathways will prove to be vital when considering a cure.

Harnessing neuroinflammation

What all three of the above neurodegenerative diseases have in common is chronic inflammation and stimulation of microglia, so that they remain in the classically activated M1 state. Research into M2-inducing factors may therefore provide therapies that could potentially be applied to all three, and perhaps even more neuroinflammation-associated neurodegenerative diseases.

The anti-inflammatory cytokine IL-4, for example, has been tested in animal models of MS, with overall success. A group using an MS animal model called experimental autoimmune encephalitis (EAE) found that transduction (transfer of genetic material) with a viral vector expressing IL-4 reduced the symptoms of EAE [34, 35], most likely due to the induction of M2 microglia, which produce neurotrophic mediators such as activin-A [36] that support oligodendrocyte differentiation, remyelination and regeneration.

In AD, the induction of M2 microglia is also significant, because while M1 microglia cannot clear Aβ, M2 microglia can. Treatment with IL-4 can block inhibition of Aβ phagocytosis [37], lowering the pH of the phagosome (the vacuole into which the Aβ is engulfed) to allow for better degradation of Aβ. Injections of only 100 ng of IL-4 decreased Aβ levels in a few days, correlating with an increase in pro-phagocytic and degradative enzymes [38]. Another group showed the longer-term results of sustained IL-4 expression using a viral vector, which yielded a reduction in gliosis, decreased Aβ, and improved spatial memory [39].

IL-4 treatment could be administered indirectly in the form of an already FDA-approved drug for relapsing-remitting MS called glatiramer acetate (GA), which works by shifting the Th1 state of T cells to
Th2, and inducing production of IL-4. The latter is probably essential to its function, since the phenotype of microglia after treatment with GA was similar to the phenotype of microglia after treatment with IL-4 [40].

To the knowledge of the author, IL-4 studies have not been performed in PD patients, but may perhaps yield similar positive results. An M2 inducer that has been tested in PD is the PPARγ agonist (also the mechanism by which NSAIDs may work, as detailed above), a type of drug which was found to be neuroprotective in animal PD models, and works by upregulating anti-inflammatory cytokines that induce an M2 microglial state [41]. In MS, PPARγ activation has also been demonstrated to decrease T cell proliferation and increase T cell apoptosis [42], thereby generally decreasing the autoimmune response. Larger scale trials are currently underway to assess the therapeutic potential of PPARγ agonists in the treatment of MS.

**Always beneficial?**

Examples were provided for AD, PD, and MS as to the ways in which classical M1 activation is not always deleterious, and, in fact, may involve pathways that are essential for neuroprotection or regeneration, or mediators that bring about both negative and positive consequences. In the same way, M2 microglia are not always beneficial – one study involving IL-4 injections into AD mouse models found that amyloid pathology was in fact exacerbated [43]. Indeed, while the usual functions of M2 microglia are associated with wound repair and regeneration, some studies have shown that they can trigger inflammation [44] and recruit macrophages [45]. Much like how M1 and M2 states are not as binary as they seem, the effects of the M1 and M2 states are similarly complex and non-polarisable.

**Conclusion**

Fundamental similarities have been drawn between many different diseases beyond those described here. Neuroinflammation can play a primary or secondary role in Huntington’s, ALS, stroke, traumatic brain injury, and spinal cord injury; this role can be characterised by shifts between a reparative, acute inflammatory response to one that is chronic, exacerbating the vicious cycle of inflammation and degeneration. The three examples simply put these principles into context, using some of the most recent research to demonstrate how these seemingly isolated diseases share a universal milieu. It is this universality that allows one treatment – whether that be a type of drug such as PPARγ agonists or a specific cytokine such as IL-4 – to target the fundamental problem: the inability of microglia to switch to the anti-inflammatory M2 state.

Nevertheless, this issue becomes so much more complex when one realises that the labels M1 and M2 are simply labels. These are labels which are purely abstract, and generate the misconception that microglia can either be one way or another, good or bad, when they really describe complex, intertwined processes that can sometimes go against our expectations. Attempts to characterise, while they generally apply, ultimately fail. Neuroinflammation and its mediators are neither friend nor foe – rather, they are completely indifferent. It is only by closely examining the specific pathways that are productive or
counterproductive that researchers can isolate them and begin to bring them together, in what could one day be a one-pill-solves-all for degenerative disease.

References


The Right to Restfulness

Jacob Mesina

Abstract
How people get their rest at night and stay awake in the morning is constantly changing. Good sleep has always been a necessity; however its true purpose has largely been misunderstood. In recent years, the number of people who have reported difficulty in sleeping and being alert has increased rapidly. This has caused medications alleviating conditions such as insomnia and drowsiness to gain immense popularity in society [1,2]. These medications, however, have the potential to harm as they have to heal. Medications such as benzodiazepines and antidepressants have been shown to be effective in helping people fall and stay asleep, but they also have adverse side effects and various levels of success that suggest further exploration. Likewise, the use of amphetamines to stay awake has caused controversy in the medical community. Therefore, it is clear that the concept of sleep is a highly beneficial and necessary natural process that needs to be understood in greater depth.

Treatments to Stay Asleep

The necessity of sleep and restfulness is universally recognized. Humans cannot function properly without an adequate amount of sleep, which is known to have various functions in maintaining the body, such as boosting wakeful cognition and promoting physical well-being [3]. Thus, not having enough sleep has the possibility of being detrimental to one’s health. Insomnia, or the condition of having difficulty sleeping, affects many people around the world. In fact, about 30% of adults from various countries have reported suffering from some form of insomnia [4]. Advancements in technology have led to new treatments for insomnia. From sedatives to hypnotics, the world of sleep medication has grown tremendously [5]. However, these medicines come with their own risks.

One of the earliest and safest solutions developed for insomniac patients was benzodiazepines. Prior to the development of these drugs, sedative drugs known as barbiturates were used to help people rest. Unfortunately, these drugs were very addictive and susceptible
to overdosage, making them unfit for the general population to use [5]. With benzodiazepines, which act upon GABA neuroreceptors, REM-sleep is reduced. Since REM is associated with memory processing, using benzodiazepines may inadvertently affect REM-related memory consolidation [5]. Benzodiazepines have been found to have particularly strong sleep inducing effects. These substances also have considerably long half-lives, with medication remaining in the system for upwards of 11 days [5]. Common benzodiazepine medications include temazepam and estazolam [5], which have been found have been found to reduce the length of sleep stages 1, 3, and 4 in patients [6]. Non-benzodiazepines can also influence benzodiazepine receptors. However, these substances do not significantly shorten the sleep stages like temazepam and estazolam do. If benzodiazepines are suddenly discontinued, then withdrawal symptoms tend to occur. These symptoms arise in various stages, starting from day one and leading all the way to day fourteen and beyond, depending on the medication's half-life. Some of these withdrawal symptoms include weight loss, nausea, anxiety, and restlessness [7]. Hence, the use of benzodiazepines to prevent insomnia is cautioned.

Other hypnotic medications such as zolpidem and zaleplon have seen a rise in popularity [5]. Having fewer known side effects and less abuse potential than benzodiazepines [5], zolpidem (Ambien or Edluar) and zaleplon (Sonata) are both designed to help users fall asleep. Some rare side effects of zolpidem include hallucinations, amnesic symptoms, and somnambulism (sleepwalking) [9]. Therefore, doctors are advised to take in various factors such as the gender of the patient and dosage when prescribing this medication [9]. Eszopiclone (Lunesta) is another popular medication prescribed for sufferers of insomnia [8]. This drug is considered special for its selectivity on certain GABA receptors. It has decent tolerance and has been shown to lengthen total sleep time and sleep quality for patients of all ages. In conjunction with fluoxetine, eszopiclone has been found to be more effective in helping patients get rest [10]. However, there is still the possibility of eszopiclone leading to dependence [8]. Ramelteon (Rozerem) helps its users fall asleep and is intended to be non-dependent [8]. It is unique in that it is a melatonin receptor agonist and does not have an active sedative effect. Rather, it operates through mechanisms in the suprachiasmatic nucleus, the part of the hypothalamus that helps to control our sleeping patterns. Ramelteon has a relatively low potential for abuse [11]. Antidepressants including the tricyclic family have helped to alleviate insomnia in patients, but their side effects and overdose potential render them relatively unfit for prescription in these cases [5]. Selective serotonin reuptake inhibitors (SSRI), a type of antidepressant, have been found to paradoxically cause insomnia and daytime drowsiness [12]. Ethanol, an alcohol, is also used to help insomniacs find rest; this helps to explain the phenomenon of drowsiness experienced by heavy drinkers [5].

Patients who are considering taking sleeping medication are advised to be well researched on the medication that they consume. For example, people 65 and older are advised to not use diphenhydramine and doxylamine. In one study, however, 52% of the medications used by older participants contained these two substances, and 59% of participants reported taking these medications with these potentially
harmful substances [13]. Diphenhydramine can be found in common medicines like benadryl and can lead to daytime drowsiness and dry mouth, while doxylamine can be found in unisom sleeptabs and has similar side effects [14]. Drugs like zolpidem have been linked to an increased risk of fainting (4 times greater occurrence in one study) and can impair people’s driving skills, both of which could result in serious injury and even death [15]. Next-day drowsiness is common in sleeping-pill users and should be taken seriously.

Overall, sleep medications have various strengths and weaknesses which should be explored by potential users. The potentially detrimental effects of sleep medications have led scientists and doctors to start suggesting more cognitive ways of inducing tiredness, such as hypnosis and relaxation training [5]. Research continues in the field of sleep medication to further understand why certain drugs perform the way they do.

Treatments to Stay Awake

While the best course of staying awake during the day would be to have a good night’s rest the night before, this is not an option for everyone for various reasons. Insomniacs who struggle to sleep at night may experience daytime drowsiness, and as a result, may need to take substances to stay alert. This daytime sleepiness has been recorded in nearly 15% of the population of the U.S. [5].

In addition to substances found in everyday items, such as caffeine, various medications are used to stay awake including amphetamines and pemoline. In one study in Brazil, 456 truck drivers provided urine samples when stopped by police officers, and 9.2% tested positive for drugs in their system. Over 60% of these drugs were amphetamines, which the drivers were using to stay awake on their long trips [16]. In another study, 4% of surveyed students on a college campus recorded that they had taken stimulants in recent memory, with 34% of those students recording that they had taken stimulants to stay awake [17]. Amphetamines, which work by increasing extracellular dopamine levels [18], can be easily abused and are known to cause physical changes in the brain such as lower cortical grey matter and white matter abnormalities, such as gliosis.

Another drug known as modafinil has been explored in achieving wakefulness. It has been found to have less adverse side-effects than amphetamines and the potential for use by patients in high pressure situations, such as soldiers in the middle of a battle. Consequently, modafinil has been eyed by the US government. Modafinil still has the potential to become addictive, meaning patients should be cautious when consuming it [19].

Remaining awake continues to be an ongoing struggle for many people, but the medications used to reach this state can hurt as well as harm.

Conclusion

While restfulness has the potential of being achieved by everyone, this achievement unfortunately is not realized by many. Sleep medications are still being used to promote rest. Some medications, such as ramelteon, show the potential of using the body’s natural sleep cycles to induce sleep. Other medications take advantage of different biochemical pathways to invoke rest, or rather, they
try to promote wakefulness during the day. Most medical options come with side effects, compelling scientists and physicians to promote a more natural, pill-free approach to obtaining rest. Knowing the effects of medications is essential for every potential medicine consumer, regardless of what symptoms they exhibit, be it insomnia or daytime sleepiness.

References


Glioblastoma Brain Tumors

By: Lindsay Roberts

Abstract

Glioblastomas (GBMs) are one of the deadliest and most common brain tumors. GBMs are included in the class of glioma tumors, since they arise from the glial tissues of the brain. The purpose of this glue-like glial tissue is to keep the brain’s neurons in place, as well as to maintain the proper functioning of the neurons. Although various types of glia are capable of producing tumors, GBMs arise primarily from the star-shaped glial cells known as astrocytes, which support nerve cells. The tumors usually also include cystic minerals, blood vessels, and/or calcium deposits. Generally, these astrocytic GBMs can develop throughout the central nervous system. These aggressive tumors are typically found in the cerebral hemispheres. Contained within the hemispheres are both the centres for speech production and motor control, so the presence of a tumor poses great concern. A vast quantity of malignant tumor cells reproduce continuously, thriving off of an easily accessible bloody supply. There are two types of glioblastomas: primary and secondary. Primary GBMs are extremely aggressive and proliferate rapidly. Although secondary GBMs have a slower growth period and only represent 10% of all glioblastomas, they are still relatively aggressive. Symptoms resulting from glioblastomas can vary between patients. The most common indications are headaches caused by an increase in intracranial pressure from the GBMs' rapid growth. Seizures, loss of balance, and alterations in speech and cognition may also be present [6].

Diagnosis and Treatment

Different scans are taken using MRIs, CAT scans, and CTs. If a brain tumor is discovered in a scan, a neurosurgeon then gathers tumor tissue through a biopsy. Next, a neuropathologist analyzes the specifics to classify the tumor. Surgery is often the first option following a diagnosis of glioblastoma, although not all GBMs are operable. Due to the tumor’s invasiveness, it is impossible to fully remove a glioblastoma without risking damage to surrounding tissue. However, if surgeons are able to remove a large portion of the tumor, the patient’s life expectancy is usually prolonged. Following surgery, the goal of radiation or chemotherapy is to attack the remaining tumor cells and slow malignant cell growth.
Figure 1: Above is a photo of a preserved brain affected by a highly invasive glioblastoma.

**Risk Factors**

Although there is not one particular cause of GBMs, there are certain factors which could increase the likelihood of this abnormal cell reproduction in the brain. For instance, age as well as exposure to ionizing radiation may increase the risk of developing a brain tumor. Genetics may also be an important factor; in fact, a family history of gliomas doubles one’s risk of developing a tumor. Gliomas generally occur in adults between 60 and 80 years old. Specifically regarding glioblastomas, only 3% develop during childhood, while approximately 15.4% develop during adulthood. As one of the most fatal brain tumors, glioblastomas are classified as grade IV tumors. This classification of tumors is characterized as being both aggressive and malignant. Currently, researchers have discovered four separate “subtypes” of glioblastomas, which all respond differently to advanced treatments. Generally, treatment must use multiple approaches, since not all cells in a GBM can be targeted at once. Due to the wide variety of cells within a GBM, some cells may respond well to certain therapies, while others may not be affected at all. Therefore, patients diagnosed with glioblastomas are given a prognosis known as a “median survival” [2]. The median rate of survival is approximately 15 months for patients with aggressive GBMs, while patients with less severe cases can live up to three years with proper treatment. Unfortunately, up to this point, no treatment has been discovered that can completely cure this aggressive type of cancer. However, scientists continue to search for treatments that can slow the progress of glioblastomas and extend both years and quality of life.
References


Guillain-Barré Syndrome
Yasmeen Hmaidan

Introduction

Guillain-Barré Syndrome (GBS) is an autoimmune inflammatory disorder of the peripheral nervous system. According to the National Institute of Neurological Disorders and Stroke, 1 in 100,000 Americans are diagnosed with GBS annually [1]. This rare disorder causes your body’s immune system to attack your nerves, leading to myelin breakdown and axonal degeneration. Because the affected nerves cannot transmit signals efficiently, those who are affected by GBS suffer from motor weakness. Eventually this leads to a subacute ascending paralysis. Guillain-Barré Syndrome occurs in several forms, the most common being Acute Inflammatory Demyelinating Polyneuropathy [2]. This will be discussed in detail further in the article. Whilst the exact cause of Guillain-Barré Syndrome is unknown, the disorder is usually preceded by a bacterial or viral infection such as gastroenteritis (stomach flu) or pneumonia two to four weeks beforehand. Notably, there have been increased worldwide reports of GBS after the zika virus epidemic in 2016. Unfortunately, there is no cure for Guillain-Barré Syndrome, but most people make a full recovery after treatment.

Symptoms

Whilst GBS’s symptoms are similar to other paralytic disorders such as poliomyelitis, an infectious disease of the spinal cord, several unique symptoms such as symmetrical leg and arm weakness help distinguish GBS from these other disorders [4]. In the preliminary stages of GBS, symptoms begin with lower limb tingling, weakness, and numbness. This is because the signals that transmit from and to the legs have the longest distance in the nerve network, making them the most susceptible to interruption. The initial emergence of lower limb weakness is a common sign of a form of GBS known as Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP). After the initial phase of symptoms, the muscle weakness progresses to the upper body, arms, and face, eventually leading to paralysis [5]. During the progression to the upper limbs, the autonomic nervous system dysfunctions. Subsequently, the affected individual develops Autonomic Dysreflexia (AD) and cardiac arrhythmia.

Additional symptoms include palsy (facial drooping/paralysis), difficulty breathing, and loss of tactile ability [6]. For Guillain-Barré Syndrome, the most significant symptoms occur during the three to
four weeks following the initial manifestation of the disorder. After that stage, the syndrome’s severity typically plateaus and the symptoms begin to stabilize.

**Diagnosis**

It is quite difficult to diagnose Guillain-Barré Syndrome in its early stages because its condition is characterized by a set of associated symptoms that correspond with multiple neurological disorders. However, there are numerous tests that can verify unique patterns and symptoms that distinguish GBS from other disorders. These tests include electromyography (EMG), nerve conduction studies (NCS), and lumbar punctures (spinal taps) [7]. If positive, the EMG will indicate that the muscle weakness is caused by nerve damage. Through the damaged nerves, the NCS will measure the speed of conduction of stimulated electrical impulses and conclude with *polyneuropathy*. The lumbar puncture would detect infection or abnormally high levels of protein in cerebrospinal fluid [8]. These test results would diagnose an individual with Guillain-Barré Syndrome.

**Treatment**

Whilst there is no cure for Guillain-Barré Syndrome, there are several treatments which decrease the severity of the illness and catalyse recovery amongst most individuals. GBS treatments include plasmapheresis (plasma exchange), which is effective in removing antibodies that attack the nerves through a blood-filtering machine. Injecting high doses of Intravenous immunoglobulin (IVIG) is the most common treatment for GBS. The immunoglobulin provided by blood donors contains healthy antibodies which impede the harmful antibodies [9]. Other treatments used to relieve pain and limit blood clot formation include physiotherapy, ventilator use, and medication. In most cases, the recovery period for Guillain-Barré Syndrome lasts three months to up to three years depending on each individual’s case [10]. In addition to these effective treatments, new research conducted by the Guillain-Barré Syndrome/CIDP Foundation International has shown potential for a cure for GBS. In essence, the ongoing collaborative efforts among research facilities, neurologists, and immunologists provide hope in discovering the *etiology* and pathology of Guillain-Barré syndrome.
Key Terms (In order of their mention)

**Autonomic Nervous System:** Nerves that control involuntary functions of the body such as blood pressure and heart rate.

**Autonomic dysreflexia (AD):** A condition in which the Autonomic Nervous System overreacts to external or bodily stimuli.

**Cardiac arrhythmia:** An irregular heartbeat which is either too slow or too fast.

**Polyneuropathy:** The plural form of neuropathy, meaning that many nerves in different sections of the body are damaged.

**Etiology:** The causes of a disease’s manifestation.

References


Neurotoxic Vestibulopathy: A Review of Drug-Induced Toxicity

Christian Gonzalez

Abstract

Since the beginning of the 1980s, soldiers working in malaria-ridden areas have received drugs for the prevention and treatment of malaria, resulting in serious neurological side effects. Specifically, the anti-malarial drug Mefloquine, and other widely-used treatments in malaria prophylaxis known as quinolines, leads to the poisoning of neurons that are responsible for regulating balance. The neuronal damage sustained when this occurs is permanent, and as a result, so is the loss of balance. Broadly speaking, the loss of balance and its accompanying symptoms, such as dizziness and fatigue, are referred to as neurotoxic vestibulopathy. Neurotoxic vestibulopathy is a disorder of the central nervous system that causes a disruption of the proper communication between sense organs, particularly between the inner ear and the brain, which leads to the inability to experience regular vestibular function. The disease is chronic, resulting in irreversible neurological damage, and there is no cure available [1].

Overview and Symptoms

The majority of patients with neurotoxic vestibulopathy are soldiers and other military personnel who were exposed to malaria while residing in a region where the condition is prevalent. The symptoms experienced in neurotoxic vestibulopathy are not due to malaria itself, but rather are the result of the pharmacological treatments used to treat the disease. The most common symptoms in neurotoxic vestibulopathy are difficulty with balance, disequilibrium, dizziness, and vertigo. Alongside these balance-related symptoms, many patients also experience fatigue and difficulty with changing focus between tasks, a problem known as accommodative dysfunction. Although less common, oscillopsia is also experienced by some patients as well. These symptoms are also experienced in patients with central vestibulopathy, a similar neurological disorder, but vary highly based on the degree of neuronal damage. If a patient’s pharmacological treatment does not cause widespread neuronal damage, the symptoms are significantly less severe than those exhibited by patients who have suffered pharmacologically induced symptoms [1, 2].
Causes

Neurotoxic vestibulopathy is the result of toxin-induced neuronal damage in the brain. The antimalarial drug class known as quinolines can be quite useful in the treatment of malaria, but in a great deal of patients, these drugs have neurotoxic effects on cells in the central nervous system. Depending on which drug is used, certain patients may show greater neurotoxic side-effects. Although thorough studies have not yet been conducted to establish a relationship between approximate dose ranges and corresponding neurotoxic damage, it is known that the most frequent causal drugs are Mefloquine (Lariam), Clioquinol, and Pamaquine [1].

Pathophysiology

When quinolines are used to treat malaria, they can directly impact the functions of the central nervous system through causing neurotoxicity in a number of brain regions. Areas of the brain that are involved in communication with sense organs, mainly the inner ear, are most noticeably affected. These areas include the vestibular nuclei, brainstem, hindbrain, midbrain, and limbic system. In addition to vestibular difficulties caused by damage to these regions, neurotoxicity can occur in places that are involved in the control of vision, such as the tracts of the visual reflex, as well as in the extrapyramidal system [1].

Diagnosis

There is no single test that can reliably diagnose the disorder on its own. As neurotoxic vestibulopathy is the result of microscopic damage to neurons in the central nervous system, there are no neuroimaging techniques that can accurately identify the disorder as well. Only when an autopsy is performed on a patient can neurotoxic vestibulopathy be confirmed with entire certainty through histopathological examination of damaged brain tissue [1].

Treatment

Since neurotoxic vestibulopathy involves the irreversible damage of neurons, treatments for this disorder are quite limited. There are no specific treatments such as drugs or procedures that can mitigate the effects of the neurotoxicity. However, therapies that aim to placate symptoms by regaining certain vestibular functions may be helpful. Current research focuses on improving the outcome of patients with the disorder through development of novel therapies. Moreover, another primary goal is to gain a better understanding of the relationship between the physical and mental symptoms of neurotoxic vestibulopathy and other disorders, such as PTSD, that are commonly brought about after being in military settings [3].
Advocacy and Awareness

If you would like to find out more information on how to get involved in helping patients with Neurotoxic Vestibulopathy, please contact the following organizations listed below.

Vestibular Disorders Association
https://vestibular.org/

Academy of Neurologic Physical Therapy
http://www.neuropt.org/

Key Terms

Mefloquine (Lariam)- Anti-parasitic drug used to treat and prevent malaria
Malaria Prophylaxis- Preventative treatment of malaria
Quinolines- Aromatic class of drugs made from organic compounds that is used to treat malaria
Disequilibrium- Loss of equilibrium and balance experienced in neurotoxic vestibulopathy
Accommodative Dysfunction- Difficulty or inability to change focus between two or more tasks
Oscillopsia- Optical illusion in which objects appear to be oscillating
Clioquinol- Antifungal drug of the hydroxyquinolines that is a neurotoxin in large doses
Pamaquine- Drug that is used to treat malaria
Vestibular Nuclei- Cranial nuclei of the vestibular nerve in the brainstem
Limbic System- Group of brain structures involved in memory, emotion, motivation, and learning

References


Phantom Limb Pain: An Overview

Kazacham Dangata

Abstract

In 1866, American neurologist S. Weir Mitchell published a short story in the Atlantic Monthly about a man who had undergone an amputation for both of his legs during the Civil War. Mitchell reported that despite receiving this operation, the man remained unaware that his legs were absent in the hospital and complained of cramping pains in his left leg. Mitchell named this phenomenon by coining the term “Phantom Limb Pain”, descriptions of this phenomena date as far back as the 16th century[1]. Phantom Limb Pain (PLP) is described as the false sensation of a limb that has been amputated. In the United States, it is estimated that there are around 1.9 million amputees above the age of 20 and various studies have shown the onset incidence of PLP among amputees to be between 42.2 to 78.8%[2][3]. Immediately after loss of a limb between 90 to 98% of amputees experience PLP[4]. Despite the obvious need for pharmacological treatments for PLP, this has proven difficult due to an incomplete understanding of its underlying cause.

Etiology

While PLP was previously believed to be a psychiatric illness, the accumulation of evidence from more recent patient studies suggest that the pathological source of PLP is located in multiple levels of the neural axis, most crucially in the cortex. There are two predominant hypotheses as to the cause of PLP: peripheral mechanisms and central neural mechanisms. Peripheral mechanisms can be thought of as a precursor to central mechanisms.

Peripheral Mechanisms

Inceptive hypothesis of PLP’s pathology is that nerve endings at the stump of the amputated limb grow into nodules called neuromas through a process called deafferentation. The accumulation of molecules which enhance the expression of sodium channels in these newly formed neuromas cause hyperexcitability of the neurons which leads to uncontrolled discharges. These impulses travel to the somatosensory areas of the cerebral cortex via the spinal cord and thalamus. These abnormal impulses are transmitted to the brain which interprets these signals as pain. This theory is supported by several studies. They show that drugs that inhibit the sodium channels lead to the transmission of impulses from neuromas and can reduce PLP.

Central Neural Mechanisms

-Spinal Cord: Axonal sprouts at the site of amputation form connections with neurons in the receptive field of the spinal cord. This process of sensitisation includes an increase in neuronal activity,
expansion of the neuronal receptive field, and hyperexcitability of other regions. There is also a simultaneous increase in the activity of NMDA receptors, which are controlled by two types of neurotransmitters called tachykinins and neurokinins in sensory neurons contained in the spinal cord. Subsequently, what is known as the ‘windup phenomenon’ occurs and the number of receptors in this area (Dorsal Horn of the spinal cord) are increased. This causes a change in the firing pattern of sensory neurons (called central nociceptive neurons) that in turn can cause the loss of target neurons at the spinal cord level, which lowers the inhibitions of transmission from cortical centres. An increase in nociceptive inputs to the supraspinal centres can also be caused by a decrease in local intersegmental inhibitory mechanisms. These changes at spinal cord level which remove working inputs are thought to be the cause of PLP.

-Brain: Cortical Reorganisation - a function of neuroplasticity - has received increased support in the past few years as the cause of PLP. This occurs after deafferentation when changes to the somatosensory and motor areas of the cortex associated with the amputated limb occurs. Areas representing the missing limb are taken over by surrounding representational areas. This is thought to be a result of dormant synapses becoming activated when these neighbouring areas increase their reception field, which infringes onto the representational areas of the amputated limb. For example in the case of an amputated hand, the sensory area for the hand is located next to the sensory area for the face. In studies have shown that stimulation of sensory neurons in the face can cause simultaneous sensations to be felt in the phantom limb. This explains why stimulation of neurons in areas surround a phantom limb can cause sensation in the missing limb. Further imaging studies have linked the size of the distinct somatosensory region to the intensity of PLP experienced.

An additional mechanism which is believed to be responsible for PLP is body schema. Body Schema is the representation of the positions of various body parts in space. This is usually registered autonomously and updated based on the movement of body parts. This congenital template to how body parts should be arranged means that alterations to the body, such as amputation of a limb, is perceived as a phantom limb.

**Treatment**

There are both pharmacological and nonpharmacological treatments available for PLP. There are several pharmacological treatment such of the use of analgesics and anesthetics to prevent agitation of the new amputations site causing central neural sensitization. Nonsteroidal Anti-inflammatory drugs can be used to inhibit the action of enzymes essential for the synthesis of prostaglandin and decrease nociception in peripheral and central mechanisms.
Antidepressants are also a treatment for PLP. They work by inhibiting the serotonin-norepinephrine uptake blockade; NMDA receptors and sodium channel blockade.

Nonpharmacological treatments includes both invasive and noninvasive treatments. Perhaps the least invasive treatment for PLP is mirror therapy. The treatment involves the amputee patient watching the reflection of their intact limb in a mirror. This matches their proprioception with visual sensory feedback of the amputated limb tricking the brain into perceiving movement of the amputated limb to be painless.

Transcutaneous electrical nerve stimulation (TENS) is another non-invasive treatment involving the stimulation of nerves at the skin surface near the area of pain using a weak electrical current. This interrupts impulses from the neuromas which are perceived as pain preventing them from reaching the brain. TENS machines a relatively portable and this treatment has little to no side effects. Spinal cord stimulation is a slightly more invasive treatment which works in the same way as TENS. In this treatment small electrodes are inserted along the spinal cord to allow for the weak electrical current to be delivered directly to the spinal cord. If the prior treatments are unsuccessful then deep brain stimulation can be used as a treatment where electrodes are inserted directly into the brain through MRI guided surgery. Then electrical current can now be delivered within the brain.

Key Terms

**Analgesics** - A drug which relieves pain

**Deafferentation** - Interruption in sensory fibres usually resulting in the loss of sensory input from a portion of the body

**Sodium Channels** - Channels which cause the initiation of nervous impulses by conducting sodium ions through a cell’s membrane

**Nociception** - Response by sensory nervous system to harmful stimuli

**Opioids** - Substances that bind to opioid receptors which results in reduced sensitisation to pain

**Proprioception** - The sense of the relative positions of the different body parts of one’s body

References


Urbach-Wiethe Disease- Fearless or Perilous?
Catherine Hobbs

Abstract
Urbach-Wiethe disease (UW) is a condition that is characterised by the biological inability to feel fear - an emotion so ingrained in our evolution that its absence is undoubtedly dangerous. Scientists have identified around 400 people with this condition. The most well-known case is that of ‘SM’, whose real name remains unpublished. The Urbach-Wiethe disease has 3 main physical symptoms: an extremely hoarse voice, small bumps around the eyes, and calcium deposits in the brain [1]. Other symptoms include thickening of the skin and mucous membranes as well as dry, wrinkled skin which does not heal easily when wounded. This article will discuss the symptoms of UW and their dangers, as well

Mechanisms Underlying the Urbach-Wiethe Disease
A distinguishing feature of UW is the presence of calcium deposits within the amygdala. The amygdalae are two almond-shaped structures deep within the temporal lobes of the brain, critical for the processing of fear. Those with the disease can experience complete calcification of the amygdala. Once the amygdala becomes completely calcified, it fails to process any information or deliver any response. The amygdala is thus unable to initiate appropriate physiological and psychological reactions to fearful stimuli, such as sweaty palms or increased alertness.

The fight or flight response, controlled by the amygdala and sympathetic nervous system, is an involuntary product of evolution which in the past helped our ancestors avoid predators; in the modern world, its activation allows us to respond to stressors which might pose a danger. In most individuals, stress activates the amygdala, triggering a response from the sympathetic nervous system so that all of the individual’s energy can be focused on the threat they are facing [3]. Urbach-Wiethe disease and the calcified amygdalae that it entails mean that a fight or flight response is physically impossible to achieve, therefore stripping the sufferer of thousands of years of evolutionary experience and leaving them unfazed in the face of threat.
The case of SM - a closer look

SM is a woman who suffers from UW, despite having an otherwise normal emotional and intellectual presentation. Her spectrum of feelings is consistent with the majority of the world except for the subtraction of fear - she feels happiness, sadness, joy, and most other emotions, just like everyone else.

The significance of SM's anonymity is to protect her and her family from plausible threats - a major vulnerability upon such a diagnosis in modern-day society.

Picture a middle-aged woman, totally normal in appearance and demeanour, walking to the shops with her 3 young children when a man on a park bench, a total stranger, calls her over to him. SM, who imagines nobody in the world would have bad intentions or dangerous motives, goes over to him. The man pulls out a knife, holds it to her throat and threatens to cut her. SM, who is emotionally blind to the experience of fear, says “go ahead and cut me, I'll be coming back and I'll hunt your a** [2].” When asked how this situation in retrospect made her feel, her only explanation was “I wasn’t afraid.”

The impact of the disease on SM’s brain means that she cannot be frightened, despite having had the ability to experience fear before calcification. For example, when she was a young girl, she was too afraid to pick up a catfish when she went fishing [1].

Urbach-Wieth; fearless or perilous?

Whilst it is true that being fearless in usually nerve-wracking situations may seem desirable, the reality is that a life without fear in the modern world is hazardous and only makes you more susceptible to life-threatening situations.

Crossing a road without any fear of being hit by a car or walking up to a man with a knife without any worry of being harmed goes against human nature. The history of evolution has put these neuroscientific adaptations in place, such as the fight or flight response, to protect us from danger and so to go without them is potentially the biggest risk one could ever face.

References


Introduction

Ravaging communities, tearing apart families, and ruining livelihoods, addiction is undoubtedly one of the most costly afflictions—both societally and financially—in the United States today. In 2013, the U.S. Substance Abuse and Mental Health Services Administration estimated that 24.6 million Americans aged 12 or older were illicit drug users at the time of the survey [1]. For reference, that is more than the populations of New York, Los Angeles, and Chicago combined.

As more information is amassed, the possible solution to this national epidemic becomes all the more elusive. While addiction is ultimately a complex social, political, and economic issue, the focus of this article is one aspect of the biological component of the problem: the impact of the molecule ΔFosB on the molecules that ultimately translate into the expression of an addictive phenotype.

The purpose of this article is to provide a brief summary of current research regarding the ΔFosB molecule, its mechanism of action, impact on behavior, and further research directions.

The Molecule--What is ΔFosB?

ΔFosB is a member of the FOS family of proteins, which are a group of proteins that can dimerize, or form, bonds, with another group of proteins via leucine zippers—JUN family proteins. The complex formed is called an AP1 Transcription Complex [2]. A diagram of the components of AP1 can be found in Figure 1 below:

![Figure 1: Interactions between AP1 proteins and other transcription factors, adapted [3].](image-url)
ΔFosB is a truncated splice variant of FosB, meaning that after mRNA translation, the protein is cut after its 237th amino acid. (the full length FosB protein in most species is 338 amino acids long) This is important because after truncation, the protein lacks two c-terminal degron domains, which are areas in the protein that signal protein destruction and degradation when activated by kinases and other cellular mechanisms [4]. This leads to ΔFosB having a half-life of up to 7 days, making it a prime candidate for molecular studies relating to transcriptional changes associated with addiction [5] [6] [7]. One more factor that contributes to this increased stability has been found to be a phosphorylation of the amino acid serine 27 by CAMKII (a kinase in the cell) in ΔFosB [7][8].

The Molecule- What does ΔFosB do?

ΔFosB, being a splice variant of an Immediate Early Gene (IEG), or a gene that is found to be expressed rapidly in response to various cellular stimuli including drug abuse, has the capability to act on other such genes when in the AP1 transcription factor complex, which is proposed to lead to the various morphological and cellular changes associated with addiction [9] [10] [11].

As described in a subsequent section, more research is warranted in order to determine the exact biological mechanisms and gene targets through which ΔFosB acts.

The Molecule-- How is ΔFosB expressed?

There are many separate mechanisms of induction for ΔFosB and other similar transcription factors, many of which involve activation of receptors on the cell membrane as a switch for induction. The diagram below depicts four key mechanisms of this nature:

![Diagram](image-url)

Figure 2: Common signaling cascades leading to activity-dependent TF activation [12].
A: GPCR-mediated pathway          C: VGCC-mediated pathway
B: NMDAR-mediated pathway         D: RTK-mediated pathway
As is visible in the diagram, all four of the listed mechanisms involve one key modality: a stimulus signals the opening of a receptor, which leads to a phosphorylation cascade of different kinases. This in turn leads to the activation of certain transcription factors which alter DNA directly inside of the nucleus. This is the basic mechanism through which the production of ΔFosB, as well as of a plethora of other transcription factors, can be increased or decreased. However, it is important to note that this mechanism is not necessarily specific to ΔFosB, and the mechanism of ΔFosB induction still remains unknown in the hippocampus. Whereas in the Nucleus Accumbens the aforementioned systems (CREB/SRF) have been shown to directly increase fosb gene expression [14].

Current research has shown that antidepressants [14], ischemia [15], stress [14][16], maternal separation [17], spatial learning [18] and nearly all drugs of abuse [19] can cause ΔFosB induction in the hippocampus. Additionally, drugs of abuse cause robust ΔFosB expression in Medium Spiny Neurons (MSNs) that feature Type-1 Dopamine receptors in the Nucleus Accumbens and dorsal striatum [20].

The Impacts of ΔFosB

Perhaps one of the most relevant impacts of ΔFosB for the purposes of this article is the well documented increase in locomotor sensitivity and **Conditioned Place Preference** -- hallmarks of addictive behavior-- that Cocaine induces in ΔFosB overexpressed mice [21][22]. This means that when mice are exposed to unnaturally elevated levels of ΔFosB, they have enhanced receptiveness to cocaine coupled with an increased preference for stimuli that they have learned to associate with the cocaine.

Tying into this, a 2009 article chronicles a similar response in positive sexual reward as a stimulus in hamsters, with increased Conditioned Place Preference (cPP) for sexual activity in sexually mature female hamsters [23]. Conversely, the overexpression of ΔJunD, which has a similar effect as the silencing of ΔFosB, has been documented in a separate study to have nearly the opposite effect on hamsters [24].

Additionally, ΔFosB overexpression has been shown to significantly increase patterns of behavior associated with anxiety in mice, as well as to increase immature dendritic spine formation in the hippocampus in mice. The same study also showed that this overexpression impaired learning and memory, in a pattern similar to the effects observed in ΔFosB silencing or inhibition [18].

Studies conducted postmortem on humans revealed that individuals with a history of depression coupled with antidepressant treatment had decreases in ΔFosB as well as other FosB isoforms in the hippocampus, whereas patients who suffered from depression without antidepressant medication did not express this finding, suggesting that antidepressant medication impacts FosB expression not only on an acute level as described earlier, but on a long-term level as well [25].

Further Research

Currently, there is much ground to be made with regards to discovering both novel ΔFosB gene targets and its exact molecular mechanism of induction, particularly in certain brain regions such as the hippocampus, through comparative mRNA sequencing before and after stimulus or other tests [26].
Advancement in bioinformatics technology in order to actually analyze the data from these tests is also necessary for further research. Finding these gene targets or mechanisms may ultimately allow researchers to identify sites for therapeutic or pharmacological treatment of depression and addiction [27]. However, in order to achieve the aforementioned goal, more research must also be done regarding the other factors that dictate how and why a particular transcription factor binds to its target gene [27].

Ultimately, the burgeoning field of ΔFosB and addiction research is one that has the potential to become extremely influential in our understanding of addiction and mental illness as a whole. By being able to understand the exact molecular mechanisms that underlie the pathology of addiction and mental illness—in other words, what happens when things go wrong—we will be able to take one step closer to understanding what goes on when things go right, including the processes, substances, and molecules that collectively make us who we are.

References


Why do clinical trials take so long?

Nigar Abdullayeva

Introduction

Why is it that it takes about 12 years for a drug to go from lab to bedside, especially with the present-day funding for research and clear urgency for cures? What makes research take so long? And how can it be sped up? This article walks you through just that, in an effort to understand the challenges that drug development companies face, and what steps are taken to expedite this process.

Preclinical research is lengthy and multifaceted

Before a potential drug can even begin clinical trials, it needs to be thoroughly researched in the preclinical trial phase; this is a strenuous series of steps using animal models that need to be taken to submit the Investigational New Drug application (IND) to the Food and Drug Administration (FDA) in order to begin testing on human patients.

So what makes preclinical research take so long? First, researchers identify the "best" or the most chemically active version of the pharmacological compound (this is known as the drug candidate), followed by the tracking of absorption, distribution, metabolism, and excretion of the drug after it is ingested [1]. Then, everything from delivery of the drug to its dosage and timing needs to be determined, and this is done through further animal testing. The next steps include the formulation of ingredients in the delivered drug, extensive research on toxicology which takes a minimum of 12 weeks, and establishing a manufacturing process after the potential drug candidate successfully passes all the previous tests. The most critical step at this point is to design the next phase of research, clinical trials; this must be thoroughly revised since planning is where most mistakes can be avoided. The entirety of the preclinical research findings is finally compiled into the IND, the standard review of which takes 10 months according to the FDA [2].
Understandably, preclinical research takes on average 12 years and approximately 1.8 billion dollars to finance [1]. To do this, a myriad of trained investigators and clinicians need to be recruited. On top of that, animal research may not always reflect human processes; for example, while the SOD1 mouse research for ALS (Amyotrophic Lateral Sclerosis) gave insight into treatment of the rarer genetic version of the disease, it did not shed any light on treatment of the more common sporadic form which constitutes 95% of cases [3].

**Not enough patients participate in clinical trials**

Clinical trials are broken up into three phases of research on humans; the first phase involves healthy volunteers while the last two have actual patients participate. According to the New York Times, 1 in 5 cancer trials close because of insufficient enrollment [4]; by reducing the number of teams working towards a cure, the entire research movement is undermined, making all of the time and money spent thus far go to waste. The statistical disparity between the number of Americans who say they are willing to enroll in a clinical trial (72%) and the actual percentage that does (2%) is gravely astounding. In addition to that, only 6% of the critically sick enroll, causing only 6% of trials finish on time. Researchers experiencing an average 4.6-month delay are more fortunate still than those conducting 20% of clinical trials, who never enroll a single participant. Of those participants who do make it past these obstacles, only 70 to 75% of them actually complete a trial; the main reason of this is the lack of compliance with the prescription [5].

Right from the start, it can be said that recruitment for research on rarer diseases is difficult and often requires the collaboration of several countries. However, for the more general diseases, there exist other reasons for a lack of volunteers. Real patients face the gamble of being placed in the placebo control group, where their time and hopes will be invested in a "sugar pill". In addition to this, there is a lack of awareness of what a clinical trial is — to the stunning degree that only a quarter of Americans can describe one. It is not made clear that participation is free and the placebo is not a "sugar pill" but a functioning standard of care. Sadly, little can be done but to motivate those who consider it too much effort to sign the detailed consent form. On the other hand, patients often do not want to give up alternative treatments for a research trial as is required in the conditions of the agreement, this makes them ineligible for the trial by default [5]. Moreover, the form itself creates trouble for illiterate participants from third world countries and has a lack of culturally specific explanations for consent for ethnic participants.

**It takes a significant amount of work to conduct thorough clinical trials.**

Presently, there is insufficient support from doctors. Whether it be from the fear of losing the patient or even lack of time and information to be up to date on new treatments and investigational drugs, doctors do not refer enough patients to clinical trials [5]. Thus, investigators are pushed to use smaller and smaller populations for research; however, statistical analysis of such results is unreliable. This gives rise to a disjointed effort to develop cures.
Should the nature of the delivery of the drug be complex, this extends the time required to set up and carry out research at the site. Non-standard delivery methods, such as those that require special equipment or trained staff, reduce the number of hospitals that are able to participate. Ideally, drugs in the form of a pill or drip are best. Also, delivery length should either be a single dose or a short course, not several years [6].

At the end of clinical trials, there is a follow-up period, this can take anywhere from a few months to 10 years and is important for clinicians to pick up on the long-term effects of the drug [6]. Should anything troubling arise, the drug needs to be immediately revised, recommencing clinical research.

**How can we speed it up?**

Since there are no contesters to the FDA in terms of the thoroughness of research required before release of a new drug, a standard 12-week long study cannot be made to take any less time. Nevertheless, there exist many solutions to smoothen out the transitions from one step of research to another. Some of these were already touched upon, such as international recruitment of patients, and more committed involvement of doctors. In like manner, clinicians are implementing the advice of experts on areas ranging from conducting the correct studies to using the correct drug candidates [1]. These seasoned individuals assist in providing solutions to inevitable problems and set milestones to keep developers on track.

Assistance also comes in the form of supplementary organizations such as Fastercures, which speeds up drug discovery during the preclinical phase, and the Muscular Dystrophy Association (MDA) Venture program which provides funding to stop sites from being shut down once they run out of money [1]. To organize the research process, there is the DLTA (drug lifecycle tracking application) that manages drug lifecycle and regulatory review processes, sets milestones and priorities, and reports progress of all drug approval tasks [7].

For the research itself, new biotechnology in the form of biomarkers is able to indicate how a patient will respond to a particular drug, thus allowing to select patients most likely to do well with it [3][8]. With this tool, fewer patients will be needed for trials and they can be completed in shorter time spans. Additionally, IT is being implemented more and more to speed up data collection and analysis [9].

Development companies are encouraging more communication and accessibility. This has been achieved by the following methods: investing to create mobile stations in sites located in third world countries, storefront laboratories to draw blood, allowing clinicians to visit patients’ homes or having trials conducted over skype [10]. A big step forward was boosting recruitment through social media and connecting with local medical science officials to publicize and give tours of the sites, promoting awareness. Terri Robertson, senior director of clinical program development at AbbVie conducted a recent global experiment where she opened 40 clinical sites in 40 days. She attributed the success of her projects to the following points: a mass outreach effort for investigators, conducting assessments by
phone, issuing non-negotiable contracts, qualifying each site in one visit, and having a 24/7 hotline [10]. Unsurprisingly, this allowed for 100% faster enrollment than existing trial sites and plants hope for faster, more efficient and ultimately more successful efforts in finding a cure.

References


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