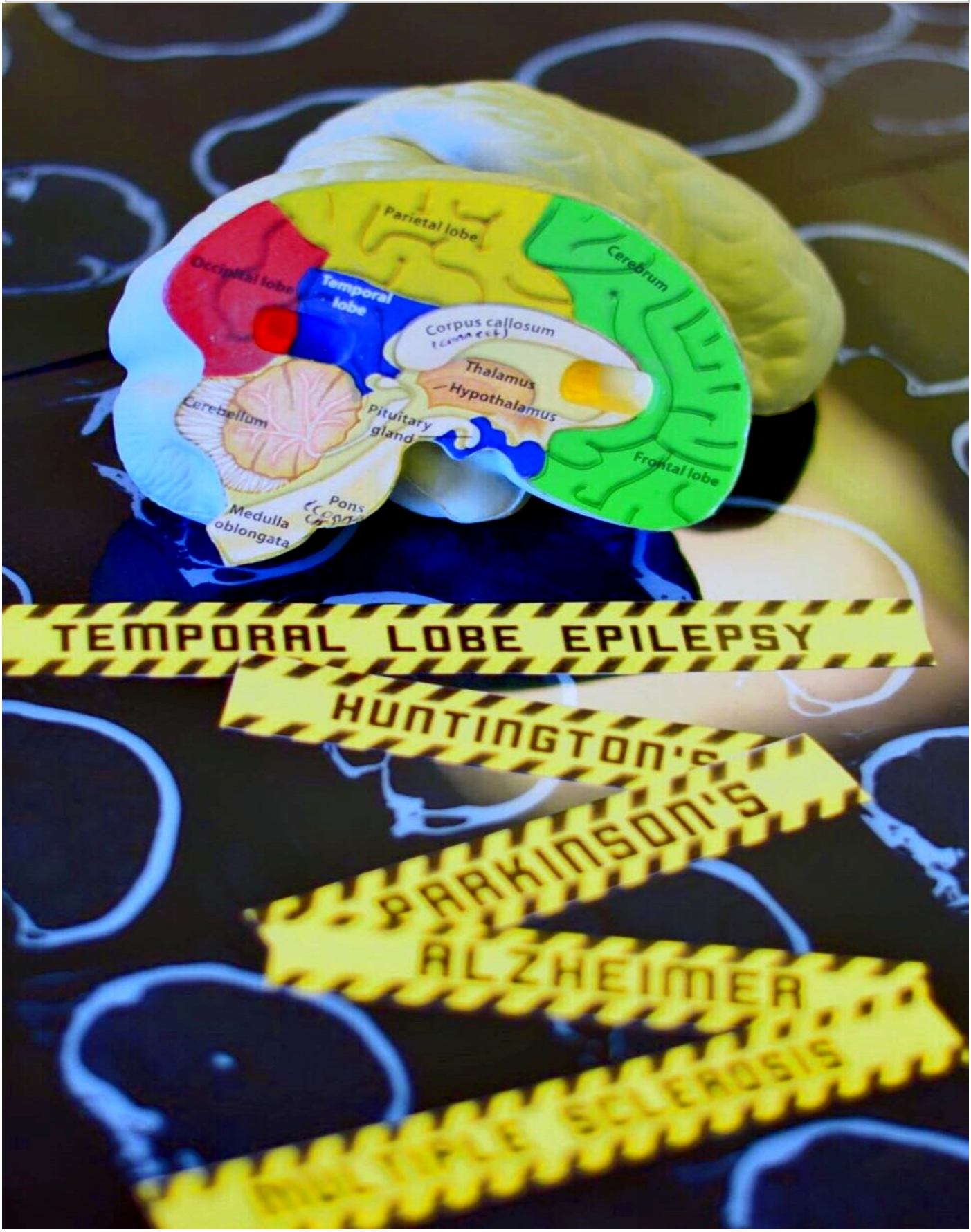
Kuwait Pharmacy Bulletin

DRUG INFORMATION FOR THE HEALTH PROFESSIONAL



Vol 21 No 4 Winter 2017 ISSN 1028-0480

Pharmacotherapy of neurodegenerative disorders

Neurodegeneration is the selective loss of particular subsets or elements of neurons in the brain[1] and result in a variety of neurodegenerative disorders (NDDs), the most common of which are Alzheimer's (AD), Parkinson's (PD), Huntington's (HD), multiple sclerosis (MS) and temporal lobe epilepsy (TLE).[1] The AD is caused by accumulation of the amyloid-β (Aβ) protein, while PD is caused by the buildup of α-synuclein. In addition, HD occurs because of huntingtin (Htt) protein accumulation.[2] Genetic and environmental factors also play an important role in their etiology.[3] Although NDDs reduce the life expectancy of the affected person, most are not directly fatal. Only those affecting neurons responsible for controlling vital functions such as respiration, heart rate or blood pressure can lead to fatality.[3] This review will examine aspects of NDDs in general with emphasis on MS and AD which are among the most well studied.

Overview

Alzheimer's disease is a gradual, progressive condition that impairs cognitive behaviour and functional status. Genetically, it can be caused by mutation in one of four genes; APP, PSEN1, PSEN2 and ApoE. This leads to accumulation of a toxic protein known as amyloid beta (Aβ) peptide in the brain. Additionally, neurofibrillary tangles (NFTs), which consist of tau proteins, are another marker of AD. NFTs are thought to be responsible for provoking AD. Consequently, affected neurons will die and the symptoms of this disease will appear.[4,5]

Multiple sclerosis is a chronic inflammatory and demyelinating disorder characterised by neurodegeneration. There are about 2.3 million people with MS worldwide.[6]

MS has two characteristic features. Firstly, the disease affects different areas of the brain and spinal cord, causing multiple neurological symptoms. Secondly, the presence of plaques or sclerosed areas in the brain, which are considered as neurological markers of this disease.

Parkinson's disease is a progressive neurological disorder that affects several regions of the brain, leading to movement imbalance and later cognitive impairment. Although not clear, the main cause of this disease is thought to be a result of interaction between aging and genetic and environmental factors. Two mutations have been described in PD: autosomal dominant e.g. PARK1/PARK4 and leucine rich repeat kinase2, or autosomal recessive e.g. PARK2[7]. Degeneration of the dopaminergic neurons in the substantia nigra in the nigrostriatal system is the main pathological feature of PD. Additionally, the presence of lewy bodies, which is the aggregation of the neuronal filament composed of presynaptic protein, α-synuclein, is another major hallmark feature of PD.[5] PD symptoms can be controlled by either surgical or pharmacological therapy but it remains incurable.[5]

Image taken from: https://cheba.unsw.edu.au/blog/whats-new-alzheimers-pacing-brain

Huntington's disease is a progressive NDD that is characterised by motor, cognitive and emotional disturbance. Genetic factors strongly underlie this disease which is associated with impairment in movement, cognitive and psychiatric functions. Unfortunately, there is no cure for HD and treatment only provides symptomatic relief without slowing disease progression.[8]

Temporal lobe epilepsy is a type of focal epilepsy that is characterised by seizures, which are initi-

In this issue

ated in the temporal lobe of the brain. It is considered as NDD due to neuronal death and gliosis in the amygdala, entorhinal cortex and hippocampus. This type of epilepsy is common in young children.[9] Reducing tau protein in the brain leads to reduction in seizure frequency and enhanced cognitive function.[10,11]

Causes of neurodegeneration

Exogenous Factors

Bacterial or viral infections

Infection of neurones leads to elevation of pro-inflammatory mediators, which triggers cell dysfunction and predisposes neurones to neurodegenerative insults. The most common bacteria that are associated with NDDs are chlamydia, borrelia, brucella and mycoplasma pecies.[12] Viruses causes neuronal dysfunction by direct cytolytic effects or by inflammatory reactions, resulting in cell death. Common neurotropic viruses are arboviruses, influenza viruses, herpes viruses, polyomaviruses and retroviruses. Viral infection activates toll-like receptors causing stimulation of intracellular cascade, and release of pro-inflammatory cytokines and chemokines leading to degeneration.[13,14]

The most common pathogen associated with MS is Chlamydia pneumoniae (C.pneumoniae). A study of 17 patients with relapsing-remitting MS and 20 patients with progressive MS strongly supported a relation between infection and MS disease, as C.pneumoniae was present in the CSF of 64% of MS patients versus 11% of patients with other neurological diseases.[12] Recently, brain infection triggering AD was recognised as an important issue. C.pnemoniae was found to be highly associated with this disease. However, not all studies support this hypothesis, as some of them were negative for this pathogen. A relationship was established between Herpes simplex virus infection and AD patients especially who has genetic risk factor ApoE e4 allele.[12]

The common neurotropic virus associated with MS is human herpes virus 6 (HHV6). A study reported that 57% of MS patients and 34% of other neurological diseases were positive for HHV6, while 37% of MS patients and 28% of control patients were positive for herpes simplex virus (HSV1 and HSV2).[13]

One pathogen was found to be associated with PD; Helicobacter pylori, which is usually found in the gastrointestinal region. It exacerbates PD indirectly by reducing L-dopa absorption and increasing the clinical disability. Treating this infection reduces late stage cachexia.[12]

Environmental toxins

A common example of experimental toxins is 1-methyl-4-phenyl-1,2,3,6-tetragydropyridine (MPTP), which is an accidental side product of 1-methyl-4-phenyl-4-propionoxypiperidine, an opioid analgesic drug. Accidental exposure to MPTP causes behavioral phenotype similar to PD. This observation led to the creation of one of the most important animal models for disease using MPTP, a gold standard for examining novel therapies or therapeutic agents. MPTP can cross the BBB and is metabolised in astrocytes to the active product, 1-methyl-4-phenylpridinium, (MPP+), which goes into catecholamine neurones via dopamine transporters, concentrates in mitochondria, leading to inhibition of complex 1. As a consequence, adenosine triphosphate (ATP) depletion and oxidative stress occur, causing catecholaminergic cell dysfunction and death.[14] Also, pesticides, herbicides and fungicides may be considered risk factors for PD.[5]

Heavy metals

The identification of environmental factors is very important in NDDs, as knowing them can reduce disease rate and progression. For AD, one of its risk factors is aluminum exposure, which may play a role in protein conformational changes and affect Aβ aggregation. Pre-clinical studies of transgenic mouse models of AD showed that exposure to aluminum potentiated Aβ deposition.[15] Systemic epidemiological reports found that 68% established a link between aluminum and AD, 23.5% were inconclusive and 8.5% did not find a relationship.[17]

Nutritional risk factors

Over-consumption of dietary iron can be a potential risk factor in NDDs such as PD. It may accumulate in the brain, resulting in transport and uptake disorders. Polymorphism in transferrin may determine progression of PD.[16] Vitamin D deficiency has a role in MS. One study was done on clinically isolated syndrome (CIS) patients, who suffered a single demyelinating attack. Vitamin D deficiency in these patients was a cofactor for developing definite MS.[18]

Head trauma

Sudden acceleration or deceleration forces on the brain may induce traumatic brain injuries (TBI), which are considered major causes of morbidity and mortality worldwide. There is good evidence supporting a relation between TBI and NDDs such as AD and PD. A meta- analysis of 15 case-control trials, strongly support a link between head trauma and AD. Head trauma may also accelerate PD.[19]

Stress

Physiological stress has a role in the progression of some NDDs such as MS. A prospective clinical study evaluated the link between stress and brain lesion development. Unfortunately, the findings of this study were inconclusive.[20]

Endogenous Factors

Genetic factors

Genetic risk factors play important roles in the pathogenesis of NDDs. An example of this genetic linking is AD, especially in younger population (<65 years).[21] Mutation in one of the genes that has a role in AD disease, such as presenilin 1, leads to conformational changes of the proteins and may alter their functions. HD is also a NDD that is totally due to genetic mutation. This disease is known as trinucleotide repeat disorder as it is caused by 36 or more repetition of CAG triplet nucleotide.[22]

Immune response

Over-activation of the immune response and ongoing inflammation may lead to destruction of the myelin sheath, as in MS and death.[5, 23]

Free radicals and oxidative stress

Over-production of reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, hydroxyl and nitric oxide, may produce undesirable oxidation, resulting in membrane destruction, protein changes, DNA damage, and cell death. This phenomenon may be involved in PD and AD.[24]

Molecular and cellular events of neurodegeneration

Commonalities in biological pathways across most NDDs

Degradation of the mis-folded proteins

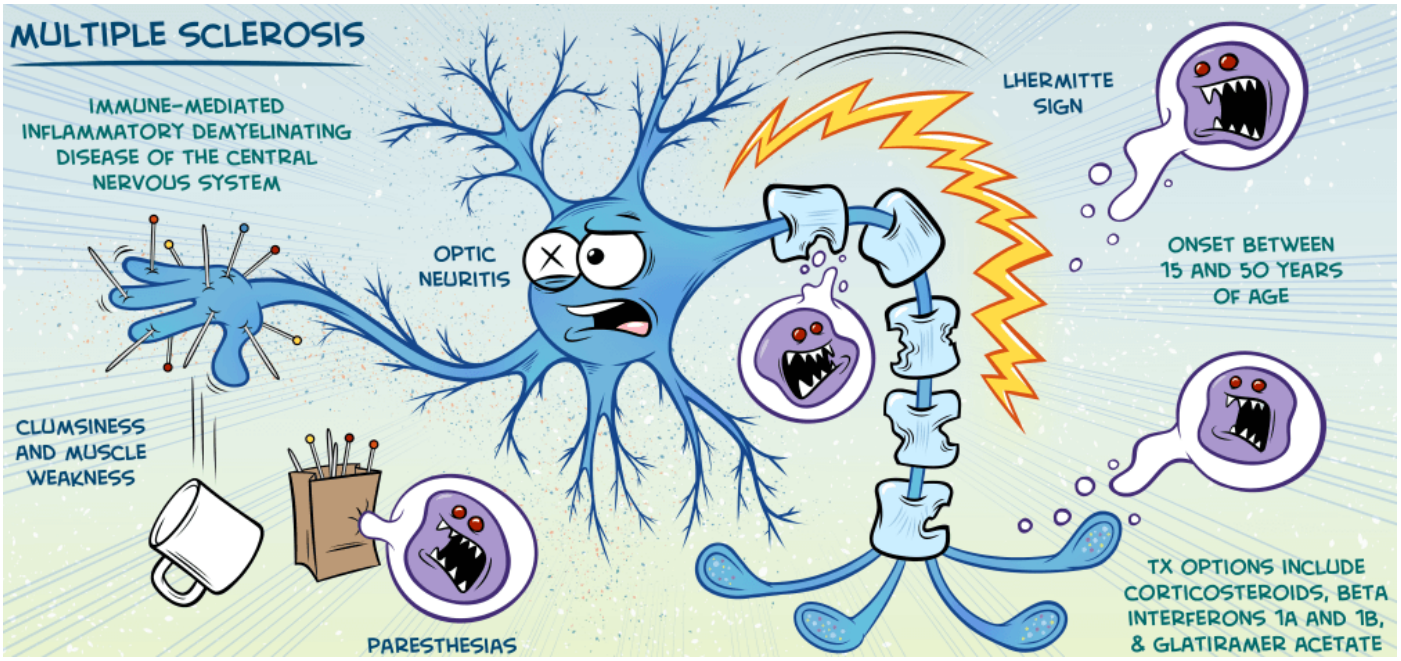
Diseases of protein mis-folding happen when there is inappropriate folding of the protein.[25,26] Generally, mis-folded proteins are removed by various proteolytic systems. There are two main systems, which are ubiquitin (Ub)-proteasome system (UPS) and autophagy-lysosome system.

UPS in neurodegenerative diseases

The UPS is responsible for degradation of selective compounds by proteasomes, which is initiated by enzymatic cascade composed of 500 -1000 proteins leading to ubiquitination and de-ubiquitination. The pathogenesis of several NDDs such as PD and HD is associated with down-regulation of the UPS. Aging is considered one of the major risk factors underlying reduced UPS activity, which leads to decreased capacity to degrade mis-folded proteins e.g. tau protein in AD and α-synuclein in PD.[27]

Autophagy-lysosome system in neurodegenerative diseases

Autophagy is an intracellular degradation system that is responsible for delivering cytoplasmic constituents to the lysosome, and is able to remove the aggregated forms of pathologic proteins in specific neurodegenerative diseases such as tau in AD, α-synuclein in PD and polyQ-Htt in HD. Down -regulation of CMA and autophagic system may



Taken from: http://www.kevinmd.com/blog/2016/03/learn-multiple-sclerosis-with-the-power-of-comics.html

lead to reduction in the autophagic activities in aged neurones, which results in misfolded proteins accumulation. This event is related to pathological features in many NDDs.[27]

Oxidative stress

Mitochondrial (Mt) dysfunction and cytotoxicity due to oxidative stress have been reported as etiologies for aging and NDDs such as AD, PD and MS. Excessive production of ATP from oxygen makes neurones more sensitive to oxygen overload, leading to generation of free radicals and neurotoxicity.[28]

Specific pathophysiology of selected NDDs

Alzheimer's disease (AD)

The characteristic features of AD are deposition of Aβ and NFTs. Familial AD is characterised by over-production of Aβ peptide, commonly Aβ 42.[29] Another pathologic change in AD is a neurochemical one. Loss of cholinergic activity is linked to AD severity.

Multiple sclerosis (MS)

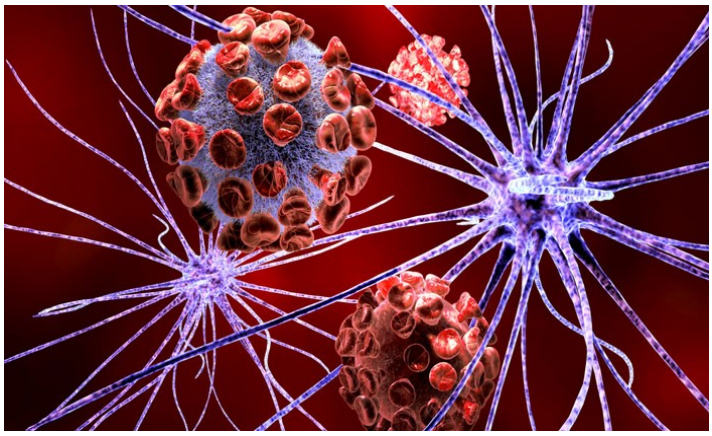
The main theory behind MS disease is an autoimmune theory. In this disease, the immunogenic cells have a tendency to be more myelin reactive. Upon activation of the immune system inside the CNS, T-cells produce pro-inflammatory cytokines such as interleukins (ILs) 1, 2, 12, 17 and 23, tumour necrosis factor –α (TNF-α) and interferon-γ. These cytokines will form holes in the BBB, which will allow B-cell, complement and antibodies to cross the BBB. Excess production of all these inflammatory species leads to destruction and damage directed against myelin and oligodendrocytes. Demyelination of the neurones is the hallmark feature of MS and it is responsible for the phenotypic features of this disease.[5,30]

Parkinson's disease (PD)

The major histopathalogic features of PD are loss of substantia nigra pars compacta (SNc) neurones and the presence of lewy bodies. Pathologically, a reduction in the activity of the two efferent pathways results in degeneration of the SNc neurones. The direct pathways responsible for activation of striatal dopamine (D1) that is linked to adenylyl cyclase and activate the inhibitory γ-amino-butyric acid (GABA)/substance P efferents to the globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr). These two regions are inhibitory to the thalamus. The reduction of D1 receptors activity in PD results in greater inhibition of the thalamus. On the other hand, the indirect pathway is responsible for activation of striatal dopamine D2 receptors that bind to guanosine triphosphate-binding protein to activate protein kinase G. Inhibition of GABA/enkephalin efferents to the globus pallidus externa occurs due to activation of striatal D2 receptors. The globus pallidus externa connects GABA neurons to the subthalamic neurons. Any reduction in D2 receptor activity results in inhibition of the thalamus as occurs in PD. Restoration of D2 receptors activity is more important than D1 receptors for mediating clinical improvement.[5,31]

Huntington disease (HD)

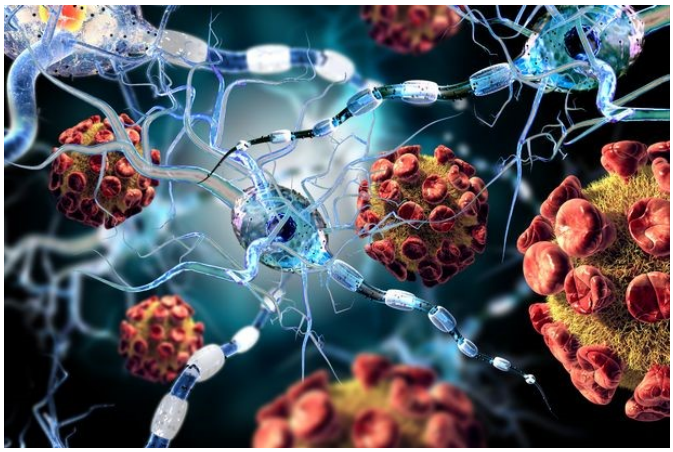
The pathology of HD involves the degeneration in the striatum. Genetic predisposition is also a relevant factor. The mutant gene is located on chromosome 4 and codes for proteins known as Htt, including more than 3000 residues. Asymptomatic carriers for this disease have less than 35 CAG repeats, while in clinically diagnosed HD, there are 36 repeats or more.[32] The mutation of Htt protein results in abnormal poly glutamine (polyQ) expansion, which results in the aggregation of Htt proteins. The overexpression of glutamine, leads to formation of hydrogen bonds within and between Htt proteins. As a result of this reaction, protein misfolding and aggregation occur.[33]



Taken from: https://www.drugtargetreview.com/news/22016/new-discovery-huntingtons-disease/

Temporal lobe epilepsy (TLE)

In TLE, there is loss of neurones in several regions of the hippocampus. Hippocampal sclerosis and atrophy lead to disruption of signaling and excitation enhancement that eventually leads to epilepsy.[34]



Taken from: http://www.cambridge-news.co.uk/news/health/cambridge-scientists-make-revolutionary-discovery-12463603

Drug therapy of MS and AD and their potential targets:

Multiple Sclerosis (MS)

The most common phenotype of MS is RRMS, which begins with a single mono/multi focal demyelinating episode, known as CIS, associated with partial or full recovery. Most patients with RRMS develop slowly progressive MS after some years.[35] As MS is an autoimmune disease characterised by inflammation and demyelination, therapy targets inflammation and immune cells/ mediators.

Disease modifying drugs (DMDs)

Interferon-β

Interferon-β (IFNβ) is a cytokine in the interferon family used to treat CIS and MS. There are three formulations of IFNβ, which are IFNβ-1a, IM injection (Avonex®), INFβ-1a, SC injection (Rebif®) and INFβ-1b, SC injection (Betaseron®). Recently, these formulations have become first line DMDs along with glatiramer acetate in the treatment of MS. It has been shown that INFβ reduces antigen presentation and modulates co-stimulatory molecules on dendritic cells. Additionally, it prevents proliferation, suppresses Th1 cells, increases IL-10 production, and shifts the cytokines function from proinflammatory to anti-inflammatory cytokines. INFβ also stimulates regulatory T-cells to prevent further progression of the disease. Common adverse drug reactions are injection-site reaction, flu like symptoms, elevated liver enzymes and hematological abnormalities.[36]

Pegylated interferon -β1a

Pegylated interferon -β1a (PEG-INF) is a conjugate product where a polyethylene glycol group is attached to N-terminus of INFβ1a. Pharmacokinetic and pharmacodynamic properties are improved by pegylation of this drug through reducing dosing frequency and enhancing the efficacy and safety of the drug. Its use is approved in some countries in the treatment of RRMS. It has lesser side effects compared to INF but some of them are similar to it.[37]

Glatiramer acetate (Copaxone®)

Glatiramer acetate (GA) is a synthetic AA polymer, one of the first line agents for MS. GA increases the affinity of MHC binding in the periphery and regulates T-cells by shifting from Th1 to Th2 and Th3 types. It also has a neuroprotective function through over-expression of brain-derived neurotrophic factor (BDNF) by GA-specific T-cells. It was found that GA reduced relapse rates by 76% in initial phase II trial in RRMS patients. Furthermore, GA decreases the frequency of new lesions compared to baseline at diagnosis. GA is well tolerated with lesser side effects.[36]

Mitoxantrone (Novantrone®)

Mitoxantrone, a member of anthracyclines, is a second line DMD. Immunosuppressive and immunomodulatory properties are clearly identified as the main mechanism of action of mitoxantrone. Early immunomodulatory properties include reduction in secretion of interferon-γ, TNF-α and IL-2. Its efficacy is confirmed in RRMS and early SPMS, especially rapidly progressive disease. Side effects include cardiac toxicity and acute myelogenous leukemia.[36]

Natalizumab (Tysabri®)

Natalizumab is the first partially humanised monoclonal antibody (mAb) used in treatment of RRMS. It is directed at the cell surface adhesion molecule α4β-integrin of all leukocytes, which is known as very late activating antigen-4 (VLA-4). Natalizumab antagonises VLA-4 and prevents the binding of leukocytes to vascular cell adhesion molecules (VCAM) -1 and fibronectin to prevent infiltration into target tissues. It is used to delay the physical disability and reduce the relapse rate in patients who cannot tolerate other MS therapies. Most common side effects are headache, fatigue, respiratory infection and arthralgia.[36]

Alemtuzumab

Alemtuzumab was recently approved for use in RRMS. It is a humanised monoclonal antibody that works against CD52 on monocytes and lymphocytes. Rapid and prolonged lymphocyte depletion occurs

due to its action. Additionally, it increases regulatory T cells and autoreactive T cells. In some trials, it efficacy appears superior to IFNβ-1a. Common side effects include thrombocytopenic purpura and autoimmune thyroid disease.[37]

Fingolimod

Fingolimod was the first oral DMD approved in 2010 for the treatment of MS, especially RRMS. This drug antagonises sphingosine1 phosphate receptors, which are a class of G-protein couple receptors. It has an immunosuppressant effect via sequestering lymphocytes into secondary lymphoid organs. Also, it decreases the penetration of T-lymphocytes and macrophages into the CNS. Side effects include first dose bradycardia, infections, macular edema and elevation of liver enzymes.[5]

Dimethyl fumarate (Tecfidera®)

It is a derivative of fumaric acid approved for the treatment of RRMS. It is a nicotinic receptor agonist and in vivo activator of nuclear factor-like 2 pathway that involves oxidative stress mechanism. According to CONFIRM study, DMF reduced the annual relapse rate by approximately 44% and 51% with multiple daily dose. Common side effects are lymphocytopenia, elevated liver function, and flushing.[5,38]

Teriflunomide (Aubagio®)

Teriflunomide has shown efficacy and safety in the treatment of relapsing MS. It is the active form of the parent drug, leflunomide. It inhibits dihydro-orotate-dehydrogenase which takes part in the *de novo* synthesis of pyrimidines in T and B lymphocytes, thus reducing inflammation and demyelination. Additionally, it has an immunomodulatory effect by which it inhibits protein tyrosine kinases and cyclo-oxygenase-2. A multicenter randomized, placebo-control trial showed that teriflunomide, as an add-on to INFβ, caused decrease in MRI activity compared with IFN-β alone.[39] Teriflunomide can cause elevated liver function, alopecia, nausea, diarrhea, headache and paresthesias. It has a black box warning for risk of hepatotoxicity and teratogenicity.[5]

Daclizumab

Daclizumab is an approved monoclonal antibody that is an interleukin-2 receptor blocker used to treat RRMS. This drug should only be used in case of failure of other drug therapies due to its serious side effects such as severe hepatotoxicity and immune diseases. Common side effects of this drug are upper respiratory tract infection and elevated liver function.[40]

Ocrelizumab

Ocrelizumab is a humanised monoclonal antibody, and the only DMD approved, in March 2017 by FDA, for the treatment of both RRMS and PPMS. It is designed and directed against CD20 that depletes B-lymphocytes and believed to be a mediator of myelin and axonal nerve damage. Several clinical trials demonstrate its efficacy in reducing relapse rate and clinical disability in MS. Ocrelizumab may cause infusion related reaction, low blood pressure, fever and nausea.[41]

Acute flare up drugs: corticosteroids

Corticosteroids are used mainly in the treatment of MS exacerbation. Corticosteroids, such as methylprednisolone, are used for a short duration due to systemic side effects such as osteoporosis, GI intolerance, hyperglycemia and infections.[42]

Alzheimer's disease (AD)

Two classes of drugs are used to manage cognitive symptoms of AD: cholinesterase inhibitors and glutamate antagonists. Several trials showed modest benefits of early treatment with cholinesterase inhibitors such as donepezil, rivastigmine or galantamine. Memantine is added in cases of moderate to severe disease.[5]

Acetyl cholinesterase inhibitors

Acetyl cholinesterase inhibitors (AChEIs) are a group of drugs that are indicated in the treatment of mild stages of AD. They increase ACh levels thus, reducing disease symptoms associated with progressive reduction in cholinergic function. Although these medications appear to be equally effective, they differ in terms of target protein specificity. Side effects include GI intolerance, dizziness, syncope, bradycardia and atrial arrhythmia.[43]

Anti-glutamatergic therapy

Memantine is used in the treatment of mild to severe AD. Several trials demonstrated the efficacy of this drug in delaying clinical worsening, and therefore may be considered as a DMD. Common side effects of memantine include headache, confusion, dizziness and hallucination.[43]

Conclusions

NDDs are generally incurable and debilitating, which are characterized by degeneration of neurons and neuronal structures in the brain. These diseases share similarities in terms of endogenous and

exogenous triggers such as infection and oxidative stress. Different therapeutic modalities have been used in the treatment of NDDs. However, there are more options (drugs) to treat MS than for AD. More investigations need be done to discover therapeutic agents that target amyloid β or tau protein to reduce the morbidity and mortality rate in AD.

References

1. Choonara YE, et al. (2009). International Journal of Molecular Sciences, 10(6), 2510–2557.
2. Ramanan VK & Saykin AJ (2013). American Journal of Neurodegenerative Disease, 2(3), 145–175.
3. Przedborski S, et al. (2003). Journal of Clinical Investigation, 111(1), 3–10.
4. Alzheimer disease - Genetics Home Reference. (n.d.). https://ghr.nlm.nih.gov/condition/alzheimer-disease
5. DiPiro, JT (2014). Pharmacotherapy: a pathophysiologic approach. McGraw-Hill Education.
6. Epidemiology of MS. https://www.msif.org/research/epidemiology-of-ms/
7. Wider C, et al. (2010). Current Opinion in Neurology, 23(4), 388–393.
8. Ross C, et al. (1997). Huntington Disease. https://www.acnp.org/asset.axd?id=8c04590f-3411-4db5-8bd4-688e7cb795e4
9. Diehl B & Duncan J (2015). Temporal lobe epilepsy (1st ed.). UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen.
10. David YK (2014). Temporal Lobe Epilepsy. http://emedicine.medscape.com/article/1184509-overview#a4
11. Bernasconi N (2016). Brain139 9):2336-2337.
12. Nicolson GL (2008). Laboratory Medicine, 39(5), 291-299.
13. Deleidi M & Isacson O (2012). Science translational medicine, 4(121), 121ps3-121ps3.
14. De Chiara, G. (2012). Molecular neurobiology, 46 (3), 614-638.
15. Praticò D et al. (2002). The FASEB Journal, 16(9), 1138-1140.
16. Cannon JR & Greenamyre JT (2011). Toxicological Sciences, kfr239.
17. Ferreira PC, Piai KD (2008). Rev. lat-Am. Enfermagem, 16(1), 151-157.
18. Alharbi FM (2015). Neurosciences, 20(4), 329.
19. Sundman, MH et al. (2014). Journal of Alzheimer's disease & Parkinsonism, 4.
20. Weygandt M (2016). Proceedings of the National Academy of Sciences of the United States of America 113(47), 13444–13449.
21. Checkoway H et al. (2011). Neurodegenerative diseases. IARC scientific publications, p407-419.
22. Myers RH. (2004). Huntington's disease genetics. NeuroRx, 1(2), 255-262.
23. Cappellano G et al. (2013). Am J Neurodegener Dis, 2(2), 89-107.
24. Singh RP et al. (2004). J Indian Acad Clin Med, 5(3), 218-225.
25. Shaffer C (2017). Protein Production: Initiation, Elongation and Termination. http://www.news-medical.net/life-sciences/Protein-Production-Initiation-Elongation-and-Termination.aspx
26. Mitchnick M (2009). Protein Structure. Particle Sciences (8) 610-861.
27. Ciechanover A, & Kwon YT (2015). Experimental & molecular medicine, 47(3), e147.
28. Uttara B, et al. (2009). Current neuropharmacology, 7(1), 65-74.
29. Crankshaw CL (2011). Alzheimer's Disease. Neurodegenerative Diseases. BioFiles 7(2), 4-8.
30. Wingerchuk DM, et al. (2001). Laboratory investigation, 81(3), 263-281.
31. Rodriguez-Oroz MC, et al. (2009). The Lancet Neurology, 8(12), 1128-1139.
32. Rubinsztein DC (2003). Current Medicinal Chemistry-Immunology, Endocrine & Metabolic Agents, 3 (4), 329-340.
33. Liou S (2011). Huntingtin Protein and Protein Aggregation. http://web.stanford.edu/group/hopes/cgi-bin/hopes_test/huntingtin-protein-and-protein-aggregation/
34. Brandt C, et al. (2003). Epilepsy Currents, 3(5).
35. Jones JL, & Coles AJ (2010). Experimental neurology, 225(1), 34-39.
36. Vosoughi R, & Freedman MS (2010). Therapy of MS. Clinical neurology and neurosurgery, 112(5), 365-385.
37. Oh J, & O'Connor PW (2015). Current opinion in neurology, 28(3), 230-236.
38. Bomprezzi R (2015). Therapeutic advances in neurological disorders, 8(1), 20-30.
39. Oh J, & O'connor PW (2013, February). Teriflunomide for the treatment of multiple sclerosis. In Seminars in neurology (Vol. 33, No. 01, pp. 045-055). Thieme Medical Publishers.
40. Tuma RS (2016). FDA Approves Daclizumab (Zinbryta) for Multiple Sclerosis. http://www.medscape.com/viewarticle/863970
41. Mayo clinic staff (n.d). Personalized therapy for multiple sclerosis (MS). http://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/in-depth/personalized-therapy-for-multiple-sclerosis/art-20095758
42. Ontaneda D & Rae-Grant AD (2009). Annals of Indian Academy of Neurology, 12(4), 264.
43. Parsons CG, Danysz W, Dekundy A & Pulte I (2013). Neurotoxicity research, 24(3), 358-369.

Google images

Arwa Khalifa Al-Fraij
Final Year student
Faculty of Pharmacy,
Kuwait University

TEST YOUR KNOWLEDGE

Answers on back page

1. ***Which of the following cholinesterase inhibitors showed modest benefit in the early treatment of Alzheimer disease?***

   A. Teriflunomide
   B. Daclizumab
   C. Donepezil
   D. Fingolimod

2. ***The first partially humanised monoclonal antibody used in the treatment of RRMS is***

   A. Dimethyl fumarate
   B. Ocrelizumab
   C. Natalizumab
   D. Methyl prednisolone

3. ***Which of the following drugs is used to treat multiple sclerosis?***

   A. Rivastigmine
   B. Galantamine
   C. Interferon-beta
   D. Donepezil

Is there a problem?

A child with respiratory infection, which is not severe, was prescribed an antibiotic. Is there any major error with the prescription?

MDB HOSPITAL

Patient Name: Naseem Iqbal Age: 4 years Weight: 16kg
Address: Street No:.33

Rx

Azithromycin 200 mg/5ml oral suspension
7.5 ml once daily for 3 days
Send one bottle

Dr. Ahmad
Signature Date: 26/11/17

Answer (Prescription Exercise)

The dose of 7.5ml (300mg) is wrong. For a child of 15-25 kg, the dose is 200mg once daily for 3 days.

Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Obesogens

Obesogens are environmental chemical factors causing hormonal imbalances and making the body susceptible to obesity when exposed to them. In the past decade, researchers have identified dozens of chemicals that can cause obesity in animals or metabolic disruption at the cellular level. Observational studies in humans have suggested a link between environmental chemical exposures and greater body mass index (BMI) without minimising the role of diet and physical activity.

Obesogens, such as the fungicide tributyltin (TBT), can act in a variety of ways to promote fat storage and adipose tissue production, often by disrupting hormonal signaling. Such effects have been well documented in animal models and in human cell culture, but the impact of these compounds on people is still unclear.

In the early 2000s, the Blumberg group found that TBT activated a fatty acid receptor called PPARγ,[1] the master regulator of fat-cell development. Mice exposed to TBT end up with fat deposits in the liver and testis and greater fat mass throughout the body. These effects can perpetuate through generations, presumably via epigenetic mechanisms. In mice exposed to endocrine-disrupting TBT *in utero*, bone marrow and adipose tissue–derived mesenchymal stem cells become fat cells (as opposed to bone, cartilage or muscle) in far greater numbers than do the corresponding cells in untreated mice.

Potential Obesogens

NAME	USE	EVIDENCE OF HARM	MECHANISM
Tributyltin (TBT)	Fungicide / disinfectant; added to marine paints to discourage growth of barnacles and other organisms; also found as non-intentionally added substance in some plastics	Lipid accumulation in preadipocytes in culture; mice exposed in utero develop larger fat deposits, and effects perpetuate for multiple generations	Activates PPARγ/RXR transcription factors, among other effects
Organo-bromines	Flame retardants and other uses	Male rats gain weight and fat mass; exposed human infants have low birth weight	Not yet detailed; human cord blood and rodents show low thyroid hormone levels
Organo-chlorines DDT,PCBs ,tolyfluanid	Pesticides; electronics manufacture	Weight gain, increased fat mass, and metabolic dysfunction in rodents; associated with higher BMI in humans	Glucocorticoid receptor and PPARγ activation; antiandrogenic activity
Organo-phosphates	Insecticides	Weight gain and metabolic dysfunction in exposed rats	Unknown
Bisphenol A (BPA)	Plastics production	Lipid accumulation in preadipocytes in culture; rodents exposed in utero or postnatally have greater fat mass and weight as adults; linked to obesity and type 2 diabetes in humans	Activates estrogen and glucocorticoid receptors and PPARs, among other actions
Phthalates (diethyl hexyl phthalate)	Plastics production	Lipid accumulation in pre-adipocytes in culture; progeny of exposed mice have increased fat mass and higher body weight; linked to type 2 diabetes and increased fat mass in women	Activate PPARs and glucocorticoid receptors, among other actions
Heavy metals cadmium, arsenic, lead	Mining, fertilizer, plastics production, wood preservatives	Associated with increased risk of type 2 diabetes in humans; female mice exposed to arsenic in utero become obese	Mimic estrogen; disrupt glucose metabolism
Perfluoro-octanoic acid (PFOA)	Nonstick coatings and other uses	Increased body weight among exposed female mice; linked to higher BMI in humans	Unknown

In 2005, the Skinner research group at Washington State University published a disturbing observation: pregnant rats exposed to high levels of a commonly used fungicide had sons with low sperm counts as adults. When the males did succeed in impregnating a female, they bore sons who also had fewer sperm, and the gametes were less viable. The problem perpetuated through multiple generations, as they observed the rats over several years.[2] They found that altered DNA methylation patterns in the germ line were to blame. To see if other environmental chemicals could have the same effect, they screened a host of potentially toxic chemicals: jet fuel, plastics ingredients, and more pesticides. Again, exposed animals had offspring with reproductive problems, which were passed down for generations. The researchers also saw another phenotype pop up again and again: obesity. Skinner first saw fat rats in his experiments after he'd injected females with a mixture of bisphenol A (BPA) and phthalates, substances used to make plastic products and, like the fungicide TBT the researchers originally tested, known to be endocrine disruptors. Animals that had direct exposure to the chemicals were of normal weight. However, roughly 10% of third-generation (F3) rats descended from exposed females became obese[3]

Skinner and his team tested DDT. Again, rats whose mothers or grandmothers had been exposed to the chemical had normal body size. But by F3, 50% of the population, both male and female, had obesity.[4] Skinner's thoughts turned to the dramatic rise in obesity rates among US adults over the past few decades.

Some researchers have found a relationship between BPA and obesity. Among children in China, pre-teen girls (not boys) with higher BPA levels in their urine were more likely to be in the heaviest category.[5] Generally, there is a correlation. But BPA is metabolised quickly, so a one-time urine sample doesn't reveal a person's lifetime exposure. It's also impossible from these studies to determine which came first, the exposure or the condition.

Could environmental endocrine disruptors (obesogens) cause obesity and metabolic problems through glucocorticoid signaling? BPA, dicyclohexyl phthalate (a plasticizer) and two pesticides, endrin and tolylfluanid activate the glucocorticoid receptor and promoted fat-cell differentiation and lipid accumulation.[6] Tolylfluanid jammed normal insulin signaling by down-regulating a member of the insulin signaling cascade. This caused the cells to become insulin resistant.[7]

Endocrine disruptors that act as estrogen mimics can also predispose animals to obesity. Take BPA, for instance, which binds to estrogen receptors. Just as with exposure to other obesogens, BPA given to mice during pregnancy can lead to fatter offspring. A metabolite of BPA, called BPA-G, causes lipid accumulation and expression of fat-cell differentiation markers in cultures of both mouse and human adipocyte precursors.

In addition to disrupting cell signaling, some obesogens appear to leave specific, long-lasting epigenetic marks on cells' DNA. For example, the methylation profile of a rat exposed to DDT is different from that of one exposed to plastics compounds.

In conclusion, scientists can face the challenge of environmental toxins as an opportunity to understand the health damage they can wreak and put a stop to it- and maybe even learn some new biology along the way. But certain chemicals may be difficult to avoid, either because of their ubiquity or their persistence in the environment or because the damage was done generations ago.

† Adapted from A.S. Janesick et al., "Environmental Chemicals and Obesity," in *Handbook of Obesity*, Vol. 1, 3rd ed., G.A. Bray, C. Bouchard, eds. (Boca Raton, FL: CRC Press, 2014), 471-88.

References

1. F. Grün, B. Blumberg, "Environmental obesogens: Organotins and endocrine disruption via nuclear receptor signaling," *Endocrinology*, 147:S50-S55, 2006.

2. M.D. Anway et al., "Epigenetic transgenerational actions of endocrine disruptors and male fertility,"*Science*, 308:1466-69, 2005.

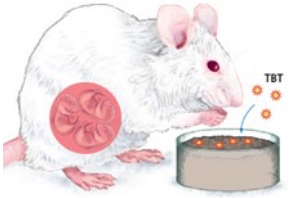
3. M. Manikkam et al., "Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations," *PLOS ONE*, doi:10.1371/journal.pone.0055387, 2013.

4. M.K. Skinner et al., "Ancestral dichlorodiphenyltrichloroethane (DDT) exposure promotes epigenetic transgenerational inheritance of obesity," *BMC Medicine*, 11:228, 2013.

5. D.-K. Li et al., "Urine bisphenol-A level in relation to obesity and overweight in school-age children,"*PLOS ONE*, 8:e65399, 2013.

6. R.M. Sargis et al., "Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation," *Obesity*, 18:1283-88, 2010.

7. R.M. Sargis et al., "The novel endocrine disruptor tolylfluanid impairs insulin signaling in primary rodent and human adipocytes through a reduction in insulin receptor substrate-1 levels," *Biochim Biophys Acta*, 1822:952-60, 2012.



IN THE NEWS

A new drug to reverse the effects of aging?

A newly-developed anti-Alzheimer's drug may have a more expansive impact in helping reverse one of the disease's greatest underlying risk factors: aging. A report in the journal *Aging* showed that the synthetically developed compound, J147, has both anti-Alzheimer's and anti-aging effects. In rapidly aging mouse models, it restored vascular health, improved synaptic function, and reduced brain inflammation and other degenerative symptoms shared between aging and dementia. The problem in treating Alzheimer's is that most drugs have been developed based on an assumption that amyloid plaque formation on the brain is the main cause of Alzheimer's to be targeted. But these drugs have all failed. A different approach was trying to identify the age-related causes of late onset Alzheimer's disease, which would account for 99% of cases.

A research team at the Salk Institute used a multi-omics approach to chart the gene expression and age-associated molecular changes in the brains and blood of three groups of rapidly aging mice. They then treated one group of older mice with J147 for seven months and compared their behavior and molecular data with young control mice and untreated older mice. The J147-fed group showed significantly improved locomotor activity and better performance on memory and cognition tests. The treated mice also displayed genetic and metabolic data profiles resembling the younger mice, rather than the control group of similarly aged mice. These positive anti-aging effects on the blood/brain vasculature, as well as reduced brain inflammation, and improved oxidative stress and energy metabolism encourage the team to conduct lifespan studies since J147 has shown beneficial effects to overall health.

While J147 must undergo more preliminary tests before human testing, another anti-aging drug, metformin becomes the first of its kind to enter human clinical trials starting 2016. These studies could help raise consciousness of other age-related aspects that could be the deeper cause of Alzheimer's and other diseases.

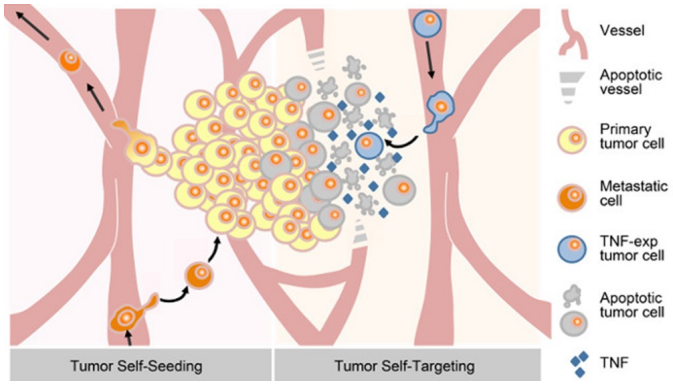
Reference

Currais A et al. Aging. 2015 (11):937-955.
www.biotechniques.com/news

Turning tumour cells against cancer

A research team at University of New Mexico engineered murine tumour cells, derived from melanoma, lung and mammary adenocarcinoma, to express and release TNF-α, a cytokine shown to damage tumor vasculature, among other anti-cancer activities. It's extremely potent as an anti-cancer agent but also extremely toxic, which makes it a perfect payload to use as a targeted agent. When given only locally, the efficacy is increased and the toxicity decreases.

When any of the three types of TNF-α–expressing CTCs were injected into immunocompetent mice with implanted mammary adenocarcinoma, the tumours' growth rates were reduced. Challenging the mice that had the TNF-α–expressing tumour cells in circulation with additional cancer-initiating tumour cells appeared to prevent the formation of tumours, suggesting that the GM CTCs helped protect mice from new tumours. The researchers also observed that the TNF-α–expressing CTCs did not propagate *in vivo*.



When injected into mice with the corresponding primary tumours, each of the three TNF-α–expressing CTC lines resulted in inhibition of tumour growth by 50-60%, the researchers reported. They also noted that injecting the GM CTCs into the bloodstream appeared more effective than subcutaneous administration.

To test whether the GM CTCs might impact metastasis, the researchers first injected standard tumour cells into mice with growing primary tumours. Normal CTCs formed lung metastases, but when the mice with metastatic tumours were

injected with the GM CTCs, the researchers observed fewer metastatic colonies formed than in control animals.

The researchers suggest that using TNF-α as a "warhead" was a good first choice, where TNF-α is probably working principally as an anti-vascular agent.

The challenge now will be to make sure the GM CTCs don't contribute to metastasis. Going forward, their attempt will be to target an endogenous tumor in mice with modified CTCs derived from the same tumour.

Source:
www.the-scientist.com/?articles.view/articleNo/45268/title/Turning-Tumor-Cells-Against-Cancer/&utm_campaign=NEWSLETTER_TS_The-Scientist-Daily

Anti-inflammatory drugs as anti-venom?

Compounds typically used to calm the immune system can prevent death from scorpion venom in mice, researchers report.

Researchers in Brazil have found that they could keep mice stung by scorpions from succumbing to the toxic effects of the venom by administering the anti-inflammatory drugs indomethacin or celecoxib. The team, led by investigators at the University of São Paulo, published its results in *Nature Communications*.

The team administered either indomethacin or celecoxib to mice dosed with scorpion venom, finding that both anti-inflammatory drugs protected against death. If the drugs have the same effects in humans, they could become regular fixtures of first-aid kits, obviating the need for expensive, more-volatile, and less-widely applicable antibody-based anti-venoms. It seems that the possibility for a generic treatment does exist.

The anti-inflammatory drugs apparently blocked prostaglandin E2, a lipid signaling molecule that causes lung edema and inflammation in animals stung by scorpions. This saved the mice from the deadly effects of the toxin. The next plan of the team is to test the drugs in human blood *in vitro*

Source:
www.the-scientist.com/?articles.view/articleNo/45438

Clarithromycin tied to higher short-term risk of cardiovascular events

Clarithromycin is associated with an increased short-term risk of cardiovascular morbidity, especially in older patients and those with hypertension or diabetes, according to a new population-based study. Based on the findings, the antibiotic should be used with caution in higher-risk individuals. While avoidance of use among patients at high risk (patients with older age, hypertension, and/or diabetes mellitus) could be a possible way to reduce the excess cardiovascular risk associated with clarithromycin, it will also be useful to monitor the potential adverse cardiac outcomes in the high-risk patients if clarithromycin is needed.

Current use was also associated with increased risk of all-cause, cardiac, and non-cardiac mortality, as well as arrhythmia. The adjusted absolute risk of myocardial infarction associated with clarithromycin versus amoxicillin was 1.90 excess events per 1,000 patients. However, the risk of myocardial infection is not increased over the long term.

Absolute risk differences were highest in patients over 75, as well as patients with hypertension and patients with diabetes. For example, subgroup analysis found that there were 2.63 excess cardiac deaths and 5.77 excess myocardial infarctions in patients 75 or older treated with clarithromycin.

Case reports have suggested that clarithromycin is proarrhythmic which could be due to blockade of the potassium channel. Another recent case report suggested that clarithromycin could rupture coronary plaque by triggering an allergic response.

In conclusion, there is a clear demonstration that a significant association between current exposure of clarithromycin and the risk of myocardial infarction, arrhythmia and cardiac mortality does exist.

Source:
www.medscape.com/viewarticle/857572?nlid=98083_1842&src=wnl_edit_medp_wir&uac=118197BN&spon=17&impID=970260&faf=1

First triple combination inhaler launched for COPD

Trimbow is a 3-in-1 treatment for chronic obstructive pulmonary disease (COPD), which combines the inhaled corticosteroid beclometasone, the long-acting beta$_2$-agonist formoterol and the long-acting muscarinic antagonist (LAMA) glycopyrronium. It is approved for use as maintenance treatment in adults with moderate to severe COPD, who are not adequately controlled by the combination of an inhaled corticosteroid and a long-acting beta$_2$-agonist. Treatment of patients with COPD often needs to be progressively increased, as they tend to deteriorate with time. Patients may require several drugs that have to be taken through two or three inhalers.

By allowing patients to take three drugs via a single inhaler, Trimbow could simplify treatment regimens, decreasing the burden on patients and improving adherence. Trimbow is supplied as a pressurised metered dose inhaler, which may be used with the AeroChamber Plus spacer device. The active components of Trimbow are formulated as extrafine particles. For beclometasone, this results in a more potent effect than non-extrafine formulations.

Each delivered dose of Trimbow (the dose leaving the mouthpiece) contains 87 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate and 9 micrograms of glycopyrronium. Each metered dose (the dose leaving the valve) contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate and 10 micrograms of glycopyrronium. The recommended dose is two inhalations of Trimbow twice daily.

Clinical trials

The phase III clinical development programme for the triple combination inhaler, that showed benefit in patients with COPD, included two 52-week active-controlled studies.

1) TRILOGY was a randomised, double-blind, two-arm, parallel-group, 52-week study in 1368 patients with COPD, which compared beclometasone/formoterol/glycopyrronium to beclometasone/formoterol (Fostair). Patients with COPD, who were eligible, had post-bronchodilator forced expiratory volume in 1 s (FEV_1) of lower than 50%, one or more moderate-to-severe COPD exacerbation in the previous 12 months, COPD Assessment Test total score of 10 or more, and a Baseline Dyspnea Index focal score of 10 or less. The patients, who met the selection criteria, entered a 2-week open-label run-in period where they received beclometasone dipropionate (100 µg) and formoterol fumarate (6 µg) in two actuations twice daily. Patients were then randomly assigned with an interactive response technology system to either continue BDP (100 µg) and FF (6 µg) or step-up to BDP (100 µg), FF (6 µg), and GB (12·5 µg) in two actuations twice daily for 52 weeks through pressurised metered-dose inhaler. The three co-primary endpoints were pre-dose FEV_1, 2-h post-dose FEV_1, and Transition Dyspnea Index (TDI) focal score, which were all measured at week 26 in the intention-to-treat population. At week 26, the triple combination significantly improved pre-dose FEV_1 by 0.081L (95% CI 0.052–0.109, p<0.001) and 2-hour post-dose FEV_1 by 0.117L (95% CI 0.086–0.147, p<0.001) compared with beclometasone/formoterol. Adverse events were reported by 368 (54%) patients with BDP/FF/GB combination and 379 (56%) with BDP/FF. Atrial fibrillation occurred in one patient in the BDP/FF/GB group.

2) TRINITY was a randomised, double-blind, double-dummy, three-arm parallel-group, 52-week study in 2691 patients with COPD, which evaluated the superiority of beclometasone / formoterol / glycopyrronium to tiotropium (Spiriva Handihaler) in terms of effect on COPD exacerbations. The triple combination reduced the incidence of moderate and severe exacerbations (the primary endpoint) by 20% (95% CI 8–31, p=0.0025) and significantly improved pre-dose FEV_1 by 0.061L (95% CI 0.037–0.086, p<0.0001), demonstrating superiority to tiotropium. Pneumonia was reported in a small number of patients, with similar incidence in the three treatment groups. The most frequently reported adverse reactions with the triple combination were oral candidiasis (affecting 0.5% of the exposed individuals), which is normally associated with inhaled corticosteroids, and muscle spasms (0.5%), which is due to the long-acting beta$_2$-agonist.

References

1) www.mims.co.uk/first-triple - combination-inhaler-launched-copd/ respiratory-system/article/1441106

2) Singh D et al. The Lancet. 2016; 388 (10048), 963-973

3) Vestbo J et al. The Lancet. 2017;389 (10082), 1919-1929

Herbal Products in focus

Ylang Ylang oil

Plants have been used for medical ailments throughout recorded history, and such traditional remedies are still widely practiced today.

The *Cananga odorata* is an aromatic tree which produces flowers that are considered to have medicinal properties. Located in the tropical rainforests of Indonesia, Philippines and Java, they are commonly referred to as the "Ylang ylang" flowers, earning their name from their distinctive odour and rich yellow colour. The flowers contain esters, such as geranyl acetate, methyl benzoate, benzyl acetate and benzyl benzoate, all of which contribute to its odour. In some countries, they are used in traditional festivals as well as everyday life; for example the flowers are hidden in the hair of Malaysian and Indonesian women for their fragrance, as well as being used as a primary ingredient in hair pomade in the Molucca islands. They are often spread out on the nuptial bed in Indonesia.

More recently the plant has become more widely popular through appearance in advertisements of perfumes such as Chanel No 5, food flavourings and beverages. Medical uses of the tree were discovered during the beginning of the 20th century. The dried Ylang ylang flower has been used to treat malaria in Java, and pastes of the fresh petals used to alleviate asthmatic conditions. The seeds of the tree are rubbed externally to treat intermittent fever. The oil is extracted by steam distillation of fresh flowers collected from the tree and used in aromatherapy, as an antiseptic and anti-seborrheic.

Aromatherapy is a combination of art and science, utilising plant extracts and essential oils, and claimed to provide both psychological and physical benefits. Ylang ylang oil is an essential oil extract that has many uses in aromatherapy. The oil is used in hot baths or in massage; it has a sedative effect probably due to a constituent called Linalool, a compound that has two enantiomers, each one having its own scent. The (S)-coriandrol enantiomer has a more floral scent (found in the Ylang ylang oil) than the (R)- licareol enantiomer. This compound acts by slowing down the heartbeat and decreasing blood pressure, both of which would lead to a relaxing effect on the body.

Ylang ylang oil is used by people who are experiencing insomnia, due to its strong scent that leads to drowsiness. It is claimed to have hypotensive properties by decreasing adrenaline, which in turn makes it easier to have a good night's sleep. Linalool is also an anti-depressant, as it can increase serotonin, a neurotransmitter that has a positive psychological effect related to mood. Serotonin increases libido and appetite.

The emergence of drug resistant bacteria has become a global concern with increasingly uncontrolled use of antibiotics and antiseptics. This has driven researchers back to nature to discover new chemicals with medicinal actions, even going through plants that have already been analysed.

Ylang ylang oil contains recently discovered compounds that allow it to act as a natural antiseptic against some bacteria when rubbed on wounds or cuts. One of the active constituents is Liriodenine, a cytotoxic oxoaporphine alkaloid that is a potent inhibitor of topoisomerase II, an enzyme essential for DNA replication. This compound has also proved to be active against Gram positive bacteria (*Staphylococcus aureus, Staphylococcus epidermis, Streptococcus pyogenes, Streptococcus faecalis, Bacillus subtilis*), by inhibiting the formation of peptidoglycan, an important constituent of the bacterial cell wall. Another type of alkaloid found in the oil is Sampangine, which exhibits anti-fungal, anti-microbial and anti-malarial activities.

Seborrheic dermatitis is an unpleasant condition caused by malfunctioning of the sebaceous glands promoted by the Malassezia species, a type of fungus. This disorder results in irregular sebum production, leading to a dry scalp, thin and brittle hair and consequent infection of the epidermal cells. It can occur anywhere that hair follicles are present, but principally on the scalp, cheeks and eyebrows. Ylang ylang oil has anti-seborrheic effects due to Sampangine and other components such as geranyl acetate, which contain anti-fungal properties, and act by inhibiting Malassezia activity, leading to renewed sebum production, with consequent reduction of skin irritation and redness caused by the disorder.

As with most herbal remedies, caution should be exercised in their usage, with reference to a medical practitioner, as many claims are clinically unsubstantiated and these substances are not authorised by drug regulatory bodies such as the FDA.

Sources:

1. *www.ncbi.nlm.nih.gov/pmc/articles/PMC3836517/*
2. *www.ncbi.nlm.nih.gov/pmc/articles/PMC4534619/*
3. *www.scielo.br/scielo.php?script=sci_arttext&pid =S0080-62342014000300492*

Article contributed by Ajwan Behbehani

STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from June to September 2017

Adrenaline Aguettant Solution for Injection in PFS; Adrenaline (as tartrate) -0.1mg/ml; Laboratoire Aguettant /France

Aloxi Soft Capsules; Palonsetron (as HCl) -500 µg; Helsinn Birex Pharmaceuticals Ltd./Ireland

Alprolix Powder and Solvent for Solution for Injection (200, 250, 500, 1000, 2000 and 3000 IU); Eftrenon acog alfa (rDNA) -200, 250, 500, 1000, 2000 and 3000 IU; Swedish Orphan Biovitrum AB/Sweden

Andaran Plus Film Coated Tablets 150mg/12.5mg; Irbesartan -150mg Hydrochlorothiazide -12.5mg; Hexal AG/Germany

Andaran Plus Film Coated Tablets 300mg/12.5mg; Irbesartan -300mg Hydrochlorothiazide -12.5mg, Hexal AG/Germany

Andaran Plus Film Coated Tablets 300mg/25mg; Irbesartan -300mg Hydrochlorothiazide -25mg; Hexal AG/Germany

Archifar Powder for Solution for Injection or Infusion 500 and 1000mg; Meropenem trihydrate (equivalent to Meropenem -500 and 1000mg); Medo Chemie Ltd./Cyprus

Clopidogrel Azevedos Film Coated Tablets; Clopidogrel (as bisulphate) -75mg; Laboratorios Azevedos-Industria Farmaceutical S.A./Portugal

Diva Film Coated Tablets; Ethinylestradiol -0.03mg Drospirenone -3mg; Exeltis Healthcare S.L./Spain

Drospera Film Coated Tablets; Ethinylestradiol -0.02mg Drospirenone -3mg; Exeltis Healthcare S.L./Spain

Ephedrine Agettant Solution for Injection in PFS of 10ml; Ephedrine hydrochloride -3g/ml; Laboratoire Agettant/France

EpiPen Injection Syringe Auto-Injector; Adrenaline (epinephrine) - 0.15 and 0.3mg; Alphapharm Pty Ltd./ Australia

Infasurf Sterile Intra-tracheal Suspension 35mg/3ml; CLSE (Calfactant) -35mg/ml (3ml); ONY, Inc./USA

Matador Film Coated Tablets; Levofloxacin hemihydrate -500mg; Dar Al Dawa & Inv. Co. Ltd./Jordan

Muxava Film Coated Tablets; Moxifloxacin HCl -400mg; A-Taqqaddom Pharmaceutical Man. Co./Jordan

Nurofen Double Strength Tablets 400mg; Ibuprofen -400mg; Reckitt Benckiser Healthcare Int Ltd./UK

Nurofen Express Film Coated Caplets 342 and 684mg; Ibuprofen Lysine -342mg and 684 (equivalent to Ibuprofen 200 and 400mg); Reckitt Benckiser Healthcare (UK) Ltd./UK

Nurofen for children Strawberry Oral Suspension; Ibuprofen -100mg/5ml; Reckitt Benckiser Healthcare (UK) Limited/UK

Olumiant Film Coated Tablets 2 and 4mg; Baricitinib -2 and 4mg; Eli Lilly Nederland B.V./Netherlands

Ridon Film Coated Tablets 1 and 2mg; Risperidone -1 and 2mg; Tabuk Pharmaceutical Manufacturing Co./Saudi Arabia

Roztor Film Coated Tablets 10 and 20mg; Rosuvastatin (as calcium) -10 and 20mg; KSPICO

Saizen Solution for Injection 6, 12 and 20mg; Somatropin (rDNA) 6mg/1.03ml, 12mg/1.5ml and 20mg/2.5ml; Merck Serono Ltd./UK

Answers to: Test your knowledge

Correct answers:
1-C; 2-C; 3-C

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs as received from the MoH. It aims to provide instructive reviews and topical news items on a range of drug and medically related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

The information in this bulletin does not necessarily reflect the views of the editorship, nor should it be taken as an endorsement of any product that is mentioned herein. Articles are generally adapted from literature sources and re-written or occasionally reproduced with permission from the appropriate sources.

Readers wishing their own copy may ask to be added to the mailing list by contacting the Executive Editor.

***Executive Editor*: Yunus Luqmani.** ***Assistant Editors*: Leyla Hasan Sharaf, Samuel Koshy**
Cover design by Ajwan Behbehani and Fatma Al Faraj

Editorial Office: Faculty of Pharmacy, Health Sciences Centre, Kuwait University, PO Box 24923 Safat, 13110 Kuwait, Fax:25342087; email: yunus@hsc.edu.kw