Treating Addictions:

A Genetic Approach

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Speaker Disclosure

Dr. Penny Kendall-Reed, N.D.

I am a paid medical advisor of Atrium Innovations. I have no other conflicts of interest to disclose.

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Addictions

- 41% increase in alcohol intake in the past 2 years. – *Harvard Health*
- 18% increase in overdoses since the beginning of the pandemic.– *AMA*
- 47% of adults admit to overeating with the inability to stop in the past 2 years. *Lancet Psychiatry 2021;8(2)*
- 63% increase in eating disorders– *Sick Kids Hospital*
- Stress levels have doubled since the onset of the pandemic. *CAMH*
- 59% of Canadians report worsening of their mental health and 44% report feeling anxious all the time. *Mental Health Canada*
- Clinical rates of anxiety and depression have risen 24.6% in the past 2 years. - *CDC*
- 20% of people will experience an addiction during their lifetime. *CAMH*
- Those who smoke cannabis daily are 50% more likely to develop another addiction. *CAMH*

New Years Resolutions or Addictions?

- 23% of people break their new resolution in the first week.
- 43% quit before the end of January *YouGovRealtime*
- Jan 17th is now knowns a "quitters day.
- Yet when they start, 87% of people say they are "very likely to keep it through the year." *Forbes 2023*.
- 5% of people who make a new year's resolution make it to 6 months and 1% make it to 1 yr. *Forbes Health.*

Addictions

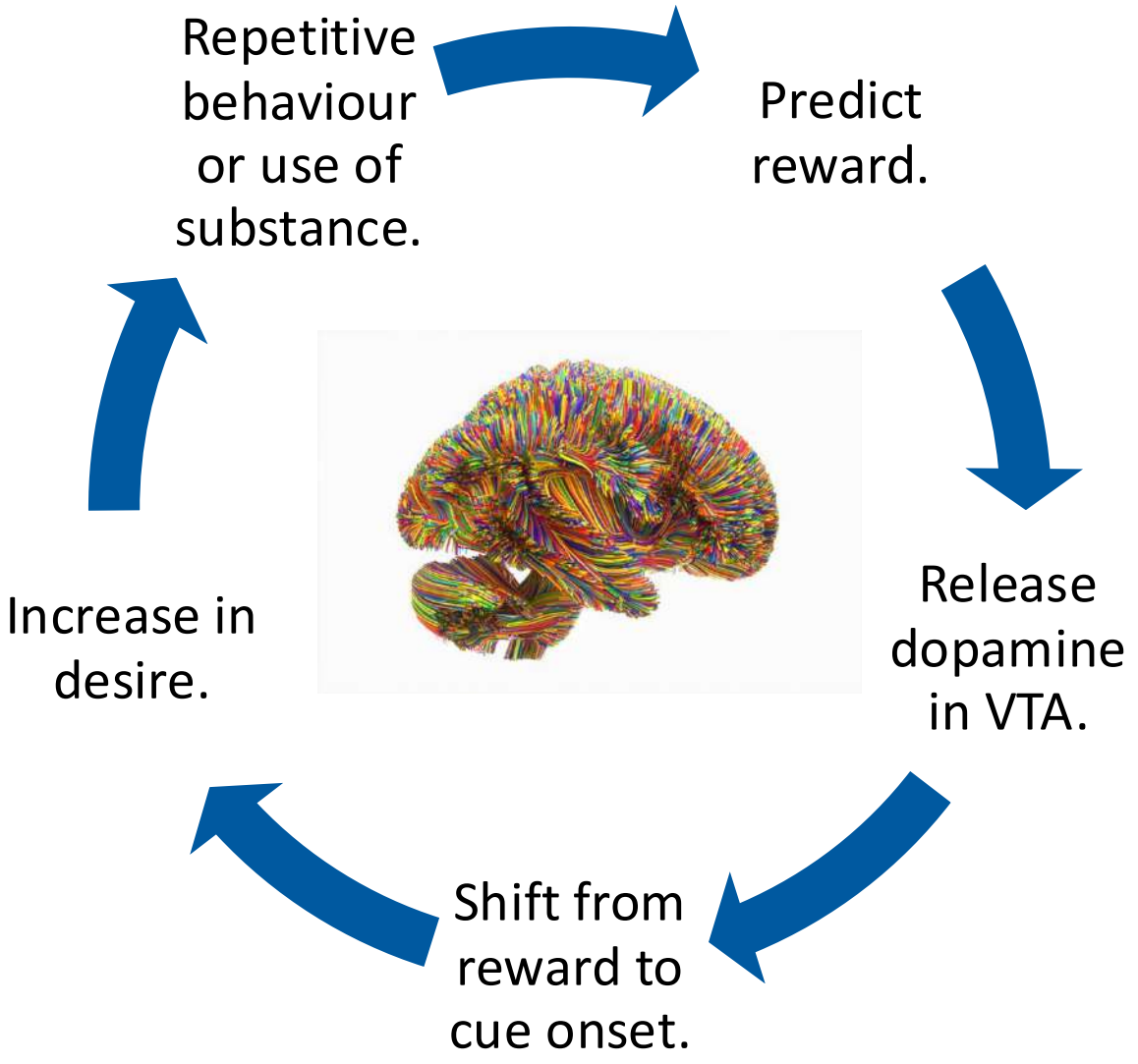
- It has long been recognized that addictions are a disorder of learning and memory.
- Repetitive drug/food/behaviour use strengthens the learned associations between the rewarding effects of the substance or behaviour and the various cues that predicts its availability or responses.
- The rewarding properties of the substance or behaviour arise from the release of dopamine (DA) in the VTA.

Neurobiol Learn Mem. 2011; 96:609-62

Addictions

- Dopamine plays an integral role in learning and memory as well as reward, making it difficult to distinguish dopamine's effect on the experience as a hedonistic effect vs strengthening the behaviour through reinforcement learning.
- Once a cue becomes predictive of reward, dopamine neurons shift their firing from reward onset to cue onset.
- Overtime this incentive salience or motivation significance of substance or behaviour related cues becomes pathologically amplified.

Addiction 2001;96:103-114


Repetitive behaviour or use of substance.
Predict reward.
Release dopamine in VTA.
Shift from reward to cue onset.
Increase in desire.

Addictions

- Not really considered psychological disorder, more of a physiological disorder due to neurotransmitter dysregulation and receptor resistance which is why most psychological meds don't fully work.
- DRD2 – reward deficiency gene
- The gene gives you 74.4% risk of developing an addiction. Environment of epigenetic factors can reduce the risk of this gene expressing by 30-50%

https://www.fxmedicine.com.au/content/addiction-our-genes-elizma-lambert

Don’t swap out addictions

- Prisoners swapping crime for religion – a new fixation.
- DAT1 dopamine transporter gene amplifies addictive behaviour by increasing DA uptake.
- DRD2 genes “call to each other”. Frequently you see this in a husband and wife.

Dopamine- A Goldilocks Hormone

- Burst of dopamine when you do something new or incentive.
- With less sensitive or inflamed or fewer receptors, you need a bigger or more frequent boost of dopamine to get the same stimulation.
- Testing dopamine levels is accurate????
- Normal levels does not mean normal binding and normal dopaminergic activity.
- Need to look at the genetics.

Sugar Addictions

- 75% of Americans eat too much sugar and are classifies as "addicted to sugar".
- Separate basal ganglia circuitries are responsible for the hedonistic and nutritional actions of sugar.
- Sugar recruits a specific dopaminergic circuitry that acts to prioritize energy-seeking over taste quality by releasing DA in the dorsal striatum.
- Cell-specific ablation of dopamine-excitable cells in dorsal, but not ventral, striatum, inhibit sugar's ability to drive the desire and ingestion of sugary foods.

Nat Neurosci. 2016; 19:465-70. *Addictioncenter.com*

Dopamine and Ghrelin

- Addictive substances increase DA release but also alter DA transmission in response to appetite and consummatory behaviour motivated by food, drugs or alcohol.
- Ghrelin changes the frequency and patterns of the action potentials generated by DA cells of the VTA augmenting DA's addictive properties.
- Repeated exposure to high fat and sugar foods or drugs = compulsive food or drug consumption and higher stimulus conditioning.

European Journal of Pharmaceutical Sciences, 2014: vol. 57 (1);2-10

Systematic review and neuropsychological model," Progress in Neurobiology, 2014: (11); 4–101.

Dopamine and Early Substance Use

- Following the use of a substance or behaviour, DA is released in our reward centers: ventral tegmental area, nucleus accumbens and substantia nigra leading to a high or pleasure feeling.
- Biological purpose is to encourage life-sustaining behaviour (eating when hungry, sex for reproduction).
- Drugs, alcohol, sugary foods release more dopamine in general giving a bigger high.

J of Neurosci. 2002: 22(9)3306-3311

Hum Mutat 2014;23:540=545

Dopamine and Long-Term Substance Abuse

- Learning is tied to intense reward and creates stronger firing and wiring in the reward centers.
- Continued long-term use results in the brain reducing the number of dopamine receptors to adjust to the increased dopamine in the system.
- Reduction in dopamine receptors increases impulsive behaviour to get more "substance" and induces anhedonia.
- Toxic/inflammatory effects of long-term use erodes grey matter in the PFC, reducing the ability to consider consequences of actions and decreasing executive function.

Phil Trans of Royal Soc, 2008: 363;3125-3135. *Neurosci. 1996:18;319-340.* *Cell, 2015:162;712-725*

Serotonin and Addictions

- Certain drugs such as cocaine and foods high in sugar or fat increase the release of serotonin.
- Serotonin puts the break on over-excitement in the reward pathways caused by dopamine.
- Studies blocking the link between cocaine and serotonin transportation increases addiction by 60%.
- This is why serotonergic anti-depressants such as Imipramine or Tofranil, or Desipramine or Pertofran are also used to treat addictions.
- Work well in some individuals yet make things worse in other! *Science Daily 2021;373(6560)*

Opioids and Addictions

- Opioids such as heroine, oxycodone etc. bind into the mu opioid receptor and stimulate the release of DA in the VTA.
- Mu receptors are more sensitive than dopamine receptors.
- With continual stimulation mu receptors become less responsive (decrease DA) much more quickly creating withdrawal symptoms even with low substance use.
- Unlike other addictive substances, opioid withdrawal stimulates the locus ceruleus to hyper secrete noradrenaline (NA)- jittery, diarrhea, anxiety and muscle cramps.
- When opioids bind to the mu receptor it suppresses the release of NA.

Sci Pract Perspect. 2002; 1(1): 13-20

Stress, Dopamine and Addictions

- Stress can increase or decrease the release of dopamine depending on the intensity, duration and avoidability of the stressor.
- Mild to moderate stressors that are *novel, short-lasting* and controllable moderately increase dopamine release.
- This promotes reward-related neural connecting with enhanced learning.
- Such event to not induce depressive behaviour.

Neurosci. Biobehav. Rev. 2012:36;79-89. *J. Neurosci 2020:40;4391-4400*

Stress, Dopamine and Addictions

- Intense, chronic and unpredictable stressors have an inhibitory effect on dopamine release due to the *uncontrollable and unavoidable* nature.

- Chronic stress results in depressive-like behaviour via the reduction in dopamine and serotonin.
- Chronic stress (12 consecutive days) begins to alter D1 receptors in the NAc, but not D2 receptors.
- 7-8 weeks of chronic stress reduces D2 receptors.

J Neural Transm. 2001:108;311-319 *Neurosci. Biobehav. Rev. 2012:36;79-89.* *Science 2016:311;864-868*

Stress, Dopamine and Addictions.

- Stress alters D1 vs D2 signaling in PFC. D1 receptor stimulation suppresses noise related neurons, creating too much "noise or activity" in the brain. As a result, signaling of neurons is adversely affected whereby information is "lost" and the PFC is unable to guide behavior.

- Stress pushes dopamine from the PFC to the AS decreasing focus and concentration, increasing emotion and increases addictive behaviour.

Nat Neuroscie. 2017 10, 376-384

Behavioural pharmacology 2018 Vol 29 (7):584-591

HPA Dysfunction and Addictions

- Dysfunctions of the hypothalamic-pituitary-adrenal axis and CRH are seen in the withdrawal phase of the addictive cycle.
- Withdrawal is accompanied by increased CRH expression and heightened electrophysiological responsiveness from palatable foods or drugs.
- 67 cortisol genes related to increased addictions, FKBP5 and NR3C2 are the most clinically and statistically significant.

Neuropsychopharmacology, 2017; 42(12):2446-2455.

Cortisol, Addictions and Drugs

- Cortisol has a stimulatory effect on DA transmission in the nucleus accumbens, similar manor to drugs. Conversely, drug induced DA release increases cortisol.

- Cortisol is positively associated with amphetamine-induced DA release in the ventral striatum.
- Glucocorticoid receptor antagonists inhibit drug-induced DA release.

ProcNatl. Acad Sci, 1998;98:7742-7747. *Neuropsychopharm. 2005; 30:821-832*

Receptor Inflammation

- IL6, TNFa and to a lesser degree IL1B cross the BBB.
- Cytokines alter synaptic plasticity by reducing neurotransmission and dendritic branching and directly stimulate HPA axis.
- Studies show that prolonged inflammation alters functional connectivity and cortical thickness in specific areas of the brain altering memory and focus.
- Cytokines reversibly mutate neurotransmitter receptors.

Front. Pediatr. 2020 doi.org/10.3389. Brain *Behav Immun 2011, 25:181-213.* *Int J Obes 2020. 44:1487-96*

Pharmacological Treatment

- Drug Withdrawal and Detox
  - Benzodiazepines to reduce anxiety and irritable – cocaine and opioids.
  - Antidepressants- Block on DA release and increase happiness.
  - Clonidine– reduces sweats, muscle cramps and aches, tremors and seizures.

- Addiction medications
  - Naltrexone – blocks neural receptors, reduces cravings.
  - Acamprosate- reduces anxiety and depression.
  - Disulfiram – for alcoholics, induces nausea and vomiting if they drink.

Pharmacological Treatment

- Lorcaserin is a 5HT2C receptor agonist administered for the treatment of obesity but is now also used in patients with drug dependence, obsessive-compulsive disorder, and gambling disorder.
- Selective serotonin reuptake inhibitors are partially efficient for treatment of binge eating disorder.
- Tricyclic antidepressants (desipramine, imipramine) as well as serotonin and norepinephrine reuptake inhibitors (duloxetine) are also be used to treat addictive behaviour with limited success. *Ther Clin Risk Manag 2012:8;219-41*

Pharmacological Treatment

- Bupropion (Wellbutrin), dopamine-based antidepressant, is used in food, addictions, particularly binge-eating disorder as well as drug and alcohol addictions.
- Anticonvulsants (Topiramate, Lamotrigine) have been proven efficient in binge eating disorder.
- Naloxone (Narcan) an opioid antagonist used to restore normal breathing and reverse the effects of of an opioid OD. *Ther Clin Risk Manag 2012:8;219-41*

Addictions and Genetics

- Who is more susceptible?
  - Who produces more dopamine, has more receptors, clears it out slowly????
- Can a boost of serotonin have an adverse effect on addictions?
  - Who doesn't transport serotonin well leading to serotonin syndrome?
- Who is more susceptible to the adverse effects of stress?
  - Who blocks the negative feedback in the HPA axis?
- Who blocks more neurotransmitter binding?
  - Who has increased inflammation and decreased neural repair?

DRD2 rs6277

- Normal Allele is A Variant Allele is G
- Dopamine receptor D2 is a crucial dopamine receptor that stimulates dopaminergic pathways involved in reward, addiction, learning, motivation, pleasure and addiction.
- DRD2 receptor is a known target for antipsychotic drugs used to treat neuropsychiatric disorders such as schizophrenia.
- Several dopamine receptors on the kidneys, and abnormal coding for this gene alters the Renin Angiotensin System (RAS), increasing bloating, edema and blood pressure.

DRD2 rs6277

- Characteristics of the G Allele:
  - Reduced DRD2 receptors.
  - Less pleasure derived from everyday events.
  - Frequent excitement seeking behavior.
  - Increased addictions.
  - Increased interaction with FTO and MC4R.
  - Increased food cravings for chips, cheese, nuts and wine.
  - Increased ADD and ADHD.

DRD2/ANKK1 rs1800497

- Normal Allele is G Variant Allele is A
- Second most important dopamine receptor that stimulates dopaminergic pathways.
- This gene, along with DRD2 is involved in demyelination.

DRD2/ANKK1 rs1800497

- Characteristics of the A Allele:
  - Reduced DRD2/ANKK1 receptors.
  - Less pleasure derived from everyday events.
  - Frequent excitement seeking behavior.
  - Increased addictions.
  - Increased interaction with FTO and MC4R.
  - Increased food cravings for chips, cheese, nuts and wine.
  - Increased ADD and ADHD.

DAT1 rs463379 (SLC6A3)

- Normal Allele is C Variant Allele is G
- Dopamine transporter plasma membrane protein.
- Increases dopamine reuptake into presynaptic terminals, thus decreasing DA concentration in extracellular space.

- Expressed in the CNS, high levels in anterior striatum, nucleus accumbens and VTA.
- Associated with increased Bipolar, ADHD, alcohol, cocaine and food dependence or addictions, and susceptibility to Parkinson's.

GeneID:6531 National Library of Medicine *Int J Neuropsychopharmacol 1999:2(4):305-320*

DAT1 rs463379

- Characteristics of the G Allele:
  - Less dopamine reuptake.
  - Less dopamine transportation.
  - Decreased dopaminergic activity.
  - Increased ADD, ADHD.
  - Increased addictions – drugs, food, alcohol and nicotine.
  - Increased Bipolar disease, anxiety and depression.
  - Increased Parkinson’s risk.

COMT rs4680

- Normal Allele is G Variant Allele is A
- Catechol-O-methyltransferase is the enzyme produced by the COMT gene.
- Metabolizes several catecholamines including *dopamine*, adrenaline and noradrenaline along with estrogens and certain drugs.
- COMT is very active in the prefrontal cortex.

COMT rs4680

- Characteristics of the G allele:
  - Increased COMT production and activity.
  - Decreased dopamine leading to increased addictive behaviors of all forms.
  - Decreased pleasure response from smaller stimuli.
  - Increased addictions.
  - Decreased anxiety, OCD and PTSD – watch other stress genes for interactions.

Dopamine Support

- L-Tyrosine (333 mg) , Mucuna pruriens seed extract (66 mg) , Rhodiola, camelia sinesis (33 mg) , methyl folate (167 mcg) combo– 1-2 caps BID empty stomach for 8 weeks for variants and 4 weeks for heterozygotes. Check methylation genes.
- L-Tyrosine - 1 cap (1000 mg) BID empty stomach.
- Can reduce doses in half (after 4 or 8 weeks) depending on lifestyle.
- Tryptic Milk Decapeptide (175 mg) and L-theanine (50mg) 1 BID (look to stress genes to see when to reduce) to push dopamine back to PFC. – 2 BID empty stomach and reduce to

Dopamine Lifestyle Hacks

- Do something new!
- Aged cheddar cheese, walnuts.
- Regular Exercise.
- Nonfood treats!!!
- 8 hours of sleep, every night.

TPH2 rs4570625

- Normal Allele is G Variant Allele is T

- Tryptophan hydroxylase is the enzyme made by the TPH2 gene that converts tryptophan into 5-HTP, the precursor to serotonin.
- TPH2 is most active in the brain.
- Serotonin is converted into melatonin, affecting sleep.

TPH2 rs4570625

- Characteristics of the Variant Allele:
  - Low TPH production.
  - Increased depression.
  - Increased addictions, especially alcohol and food.
  - Increased anxiety.
  - Difficulties sleeping, especially waking at 5 am.
  - Increased muscle myalgia and fatigue.

5-HTTLPR rs11867581

- Normal Allele is G Variant Allele is A
- 5-HTTLPR is a serotonin transporter gene that is responsible for the re-uptake of serotonin.
- The normal G allele is called the "long version" or "L" and is associated with normal transportation and production of serotonin from the bowel.
- The variant A allele, the "short version" or "S", is associated with far less serotonin production and transportation from the bowel.

5-HTTLPR rs11867581

- Characteristics of the A Allele:
  - Decreased serotonin production and transportation out of the intestines.
  - Decreased serotonin uptake.
  - Increased depression.
  - Difficulty letting go of past events, PTSD.
  - Increase alcohol intake, craving and binging.
  - Increased sugar cravings, especially chocolate.

Biol Psychiatry 2009: 66(2): 102-9

MAOA rs77905

- Normal Allele is G Variant Allele is A
- MAOA gene produces the enzyme monoamine oxidase A.
- Monoamine oxidase A is involved in the breakdown of the neurotransmitters serotonin, epinephrine, norepinephrine, and dopamine.

MAOA rs77905

- Characteristics of the ”G” Allele:
  - Note, the normal allele is the one that carries the risk.
  - Increased MAOA production.
  - Increased clearance of serotonin.
  - Increased binge eating and drinking.
  - Increased addictions.
  - Increased depression and decreased motivation.
  - Decreased anxiety.

Serotonin Support

- 5 HTP – 100-150 mg BID with food for 8 weeks for variants and 4 weeks for heterozygotes.
- 5HTP (50 mg), inositol 250 mg), taurine (100 mg) , B6 (3.4 mg), methyl folate (250 mcg) combo– 2 caps BID with food- timing as above. Check methylation genes.
- Either precursor can be reduced at 8 weeks depending on lifestyle.
- Melatonin time released – 6 to 9 mg at 8:30 pm for those who can’t transport serotonin well and need extra serotonin.

Serotonin Lifestyle hacks

- Boost foods high in tryptophan – turkey, cottage cheese, lean red meat, chicken, EFA's, soy or tofu, nuts and seeds.
- Check your carbohydrate genes, some do better with a higher complex carb diet.
- Exercise regularly.
- 8 hours of sleep every night.
- Spend time in the sun!!!!

BDNF rs6265

- *Master Molecule of the brain*.

- Neurotrophic involved in the growth of new neurons and the proliferation and expansion of existing neurons and the maintenance of synapses.
- Increases firing of neuronal pathways to consolidate memory, plays key role in the prevention of age-related memory loss.
- Increases repair of mildly damaged areas of the brain and apoptosis and cellular death of significantly damaged areas.

BDNF rs6265

- An important neurotropic factor involved in the extinction of circuits involved in addictive behaviour.
- 2 forms of treatment:
  - Erase the pathological memory (apoptosis)
  - Create a new inhibitory memory that opposes the pathological one (dendritic growth).
- BDNF plays a role in both.

Neurosci 2014;34:2242-2431

BDNF rs6265

- Normal Allele is C Variant Allele is T
- Decreased BDNF production.
- Decreased neuronal and synaptic repair.
- Decreased dendritic growth.
- Decreased memory and increased risk of dementia and Alzheimer's.
- Increased depression and anxiety.
- Increased addictions.
- Increased rate of aging.

Front Cell. Neurosci. Aug 2019

Am J of Med Genetics 2018;177B:143-167

Support for BDNF rs6265 T Allele

- Resveratrol (100 mg) - *Neurochem Res. 2011 36(5):761-5*
- Astaxanthin(4 mg)- *Nutr Neurosci 2020;23(6):422-431*
- Curcumin (400 mg) (if CYP1A2 is normal)- *Prog Neuropsychopharmacol Biol Psychiatry 2010 1;34(1):147-53*
- 5HTP(100 mg)– (if serotonin genes are hetero or variant)- *Science Daily News, Feb 2010*
- Theanine- (100 mg) *Clin Neuropharmacol 2011;34(4):155-60*
- Prebiotics, especially resistant starch – *Neurochem Int 2013 63;(8):756-764*
- Exercise – especially HIIT if genetics allow for it)- *Front Neurosci. 2018*

SIRT6 rs352493

- *Known as the Longevity Gene*.
- One of the main genes responsible for DNA repair.
- Belongs to the NAD+ dependent deacetylases.
- Prolongs lifespan, regulates genomic stability and telomere integrity.
- Regulates oxidative stress, neurodegeneration, glucose and fat homeostasis.
- Regulates autophagy and slows senescence.

Front. Cell Dev. Biol March 2021

ScienceDaily April 2019

SIRT6 rs352493

- Normal Allele is T Variant Allele is C
- Increased ROS production.
- Decreased NRF2.
- Increased rate of telomere shortening.
- Decreased autophagy.
- Decreased DNA repair.
- Increased CV dz., dyslipidemia and heart failure.
- Increased rate of aging.
- Increased addictions.

Support for SIRT6 rs352493 C Allele

- Flavonoids: especially **Resveratrol-** (100 mg) (2-fold activation)
- Quercetin (20 mg)
- Catechins (500 mg)
- Anthocyanidins (300-350 mg)

Sci Reps 8, 4163(2018)

IL6 rs1800795

- Inflammatory cytokine that is stimulated during infections, fevers, injury, exercise, stress, obesity and toxicity.
- Recruits neutrophils and thus B cells to increase inflammation to attack a pathogen.
- Increases inflammation in blood vessels and stimulates TNFa and CRP.
- Crosses BBB to increase PG's to increase body temperature.
- Inflames receptors.
- Stimulates HPA axis and alters BDNF.

IL6 rs1800795

- Normal Allele is C Variant Allele is G
- Increased IL6.
- Increased inflammation and reduced glutathione.
- Crosses the BBB inflaming neural receptors.
- Increased insomnia, sleep disturbances, anxiety, depression and addictions.

Bashati M, et al, Cytokine 2017 Nov;99:132-138

TNFa rs1800629

- Cell-signaling cytokine expressed in T and B cells, NK cells, macrophages, fibroblasts and dendritic cells.
- Modulates processes such as cellular differentiation, remodeling, tissue adhesion and the acute phase of immune reactions.
- Induces apoptosis, and stimulates inflammation via increasing production of IL6, IL-1B and MMP3's.
- Also crosses the BBB and inflames neural receptors and stimulates HPA axis.

Greco L, et al, Am J Hum Gen 1998 62, 669-675

Saif K, et al, Sci Rep 2016;6:32677

TNFa rs1800629

- Normal Allele is G Variant Allele is A
- Increased TNFa production.
- Increased inflammation.
- Crosses the BBB inflaming neural tissues.
- Increased risk of CV disease, IBS, allergies, asthma, psoriasis, arthritis and autoimmune disorders.
- Increased HPA activity and sleep disturbances.
- Increased addictions.
- Decreased memory.

Support for IL6 and TNFa

- Liposomal Glutathione (343 mg)– *Antioxidants 2020;9(7):62*
- N-Acetyl Cysteine (900 mg)- *Curr Neurovasc Res 2016;13(2):107-14*
- Low sugar diet - *Evid based Complement Alternat Med 2012:639469*
- Sleep – *Neuropsychiatr Dis Treat 2019;15:1695-1700*

FKBP5 rs3800373

- Normal Allele is C Variant Allele is A
- FK binding protein – member of the immunophilin protein family.
- Regulates glucocorticoid binding and sensitivity.
- Binding of FKBP5 into the GC receptor reduces cortisol-binding capacity leading to impaired negative feedback regulation.

FKBP5 rs3800373

- Characteristics of A allele:
  - Increased FKBP5 expression blocking receptors.
  - Increased loss of negative feedback in the HPA axis.
  - Increased anxiety, depression.
  - Increased addictions of all forms.
  - Prolonged short-term stress response, easier to get “stuck” in a stress loop.
  - Increased PTSD- especially from childhood memories.

NR3C2 rs5522

- Normal Allele is T (A) Variant Allele is C (G)
- Nuclear receptor subfamily C member is a mineralocorticoid receptor (MR).
- Cortisol binds into the MR initiating negative feedback in the HPA axis.
- The greater the number of MR's, the greater the feedback and thus ability to return to the parasympathetic NS.

NR3C2 rs5522

- Characteristics of the C Allele:
  - Fewer mineralocorticoid receptors.
  - Decreased negative feedback in the HPA axis.
  - Increased plasma ACTH.
  - Increased addictions of all forms.
  - Increased anxiety, depression and hyperactivity.
  - Increased ADD/ADHD.

CRHR1 rs242939

- Normal Allele is T Variant Allele is C
- Corticotropin releasing hormone receptor 1 is the receptor that binds CRH, stimulating the HPA axis into the sympathetic stress side.
- Increased number of CRH receptors allows for a great stimulation of the HPA axis.

CRHR1 rs242939

- Characteristics of the C Allele:
  - Increased CRH receptors.
  - Increased binding of CRH.
  - Significant increase in addictions of all forms.
  - Increased stimulation of the HPA axis.
  - Increased anxiety, depression and panic disorders.

COMT rs4680

- Normal Allele is G Variant Allele is A
- Catechol-O-methyltransferase is the enzyme produced by the COMT gene.
- It degrades or metabolizes several catecholamines including dopamine, *adrenaline and noradrenaline* along with estrogens and certain drugs.
- COMT is very active in the prefrontal cortex.

COMT rs4680

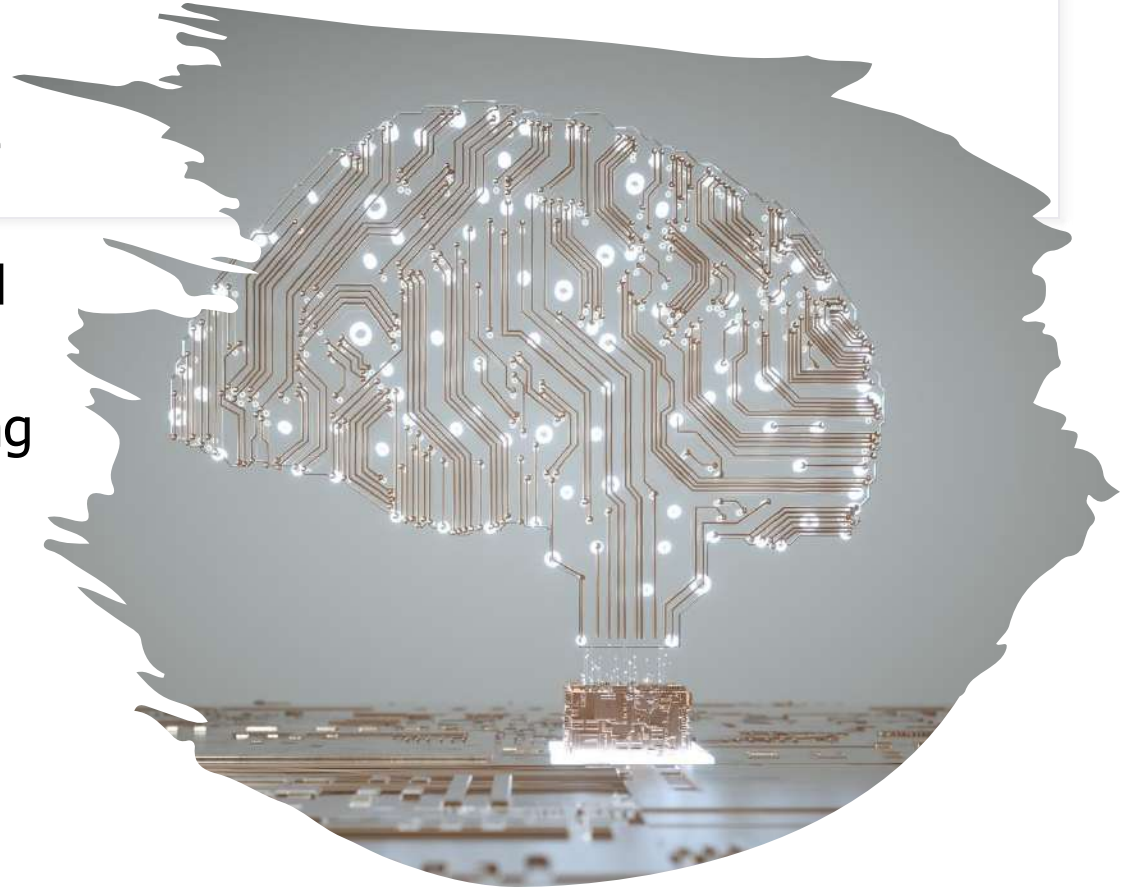
- Characteristics of the A allele:
  - Decreased COMT production and activity.
  - Increased catecholamine levels.
  - Increased anxiety (Worrier).
  - Increased fear response associated with PTSD
  - Increased dopamine levels.

Support for all Stress Genes

- Lactium (150 mg) - *LFASEB Journal June 2001*
- Theanine (100 mg) – *Nutrients 2019;11(10):2362*
- Hemi-Synch – www.hemi-synch.com
- Meditation
- Exercise
- Be careful with Rhodiola???

Leptin

- Leptin regulates satiety (opposing ghrelin) in the hypothalamus.
- Too low or too high leptin increases cravings and decreases satiety via aMSH and dopamine.
- Increase in leptin creating leptin resistance during withdrawal of an addictive substance reduces dopaminergic activity in the mesolimbic system.
- Increases cravings and the maintenance of addictive behaviour, especially with tobacco, alcohol and food.
- Leptin levels are significantly higher, leading to leptin resistance in alcoholics and foodaholics vs non addictive individuals.



J Clin Med Res. 2013;5(3):164-167

Leptin Receptor rs1137101 and rs113100

- Normal Allele = A Variant Allele = G
- Produces the proteins that form the leptin receptor and stimulates leptinergic activity.
- LEPR gene greatly interacts with the DRD2 gene.
- Highly expressed in the hypothalamus and binds free circulating leptin released from adipose tissue.

Leptin Receptor rs1137101 and rs113100

- Characteristics of the G allele:
  - Lower leptin production
  - Fewer leptin receptors.
  - Increased food cravings, appetite and weight gain.
  - Increased alcohol and tobacco abuse.
  - Increased binding.
  - Altered dopamineric activity in the VTA.

Mol Neurobio 2011;44(2):160-165

Hum Genet 1997;1000:491-496

Ghrelin

- Increased ghrelin stimulates reward-driven feeding that can override satiation.
- Ghrelin receptor is also expressed in the VTA and mesolimbic areas.
- Ghrelin stimulates all dopaminergic pathways in the VTA.
- All worsened by increased CRH and stress.

Addiction Biology 2010;15(3): 304-311

Rev Endocr Metab Disord. 2011; 12(3):141-51

FTO rs9939609

- Normal Allele = T Variant Allele = A
- Regulates ghrelin, leptin and adiponectin.
- Can stimulate dopaminergic activity in the Ventral Tegmental Area.
- Increased synaptic firing and wiring for Feeding Seeking Behaviours.

Abisaid et al 2006 and 201, Addict Biol 2001 Jan;16(1):82-91, Citri and Malenka, 2008:, Nicoll, 2017

FTO rs9939609

- Characteristics of the A allele.
  - Lowered metabolic rate.
  - Increased food addictions.
  - Increased risk of obesity by 1.7%
  - Increased adipogenesis – IRX3 and IRX5
  - Gene expression turned on with saturated fats, simple carbohydrates and/or increased caloric intake.

MC4R rs17782313

- Normal Allele =T Variant Allele = C
- Melanocortin 4 receptor on the hypothalamus.
- Regulates satiety vs hunger.
- Ghrelin>>increases NPY and AgRP= hunger.
- Leptin>> increases a-MSH and inhibits NPY= satiety.

Prog Mol Biol Transl Sci. 2013;114:14791

Nature Genetics 2008;40 (6):716–8

MC4R rs17782313

- Characteristics of the C Allele.
  - Heterozygote increases obesity and BMI by 8% independent of diet and exercise.
  - Homozygote variant increases obesity and BMI by 43%.
  - Increased food addictions.
  - Increased insulin resistance by14% especially with sugars and saturated fats.
  - Variants have significant increase in weight with antidepressants and antipsychotics.

Hinley et al, Prog Mol Biol Transl Sci. 2013;114:147-91

Chambers JC, P et al, (Jun 2008). Nature Genetics 40 (6): 716–8.)

Leptin and Ghrelin Support

- L-Carnosine (166.7 mg) , Berberine (166.7 mg) and Resveratrol (66.7 mg) combo: 2 caps twice a day empty stomach 30 mins or more before lunch and dinner for 8 weeks for heterozygotes and 12 weeks for variants.
- Rotate 1 week out of every 4-6 weeks thereafter.
- Boosts adiponectin, reduces ghrelin and regulate leptin production.

Lossa Set al. J Nutr.2002 Apr;132(4):636-42

Giancaterini A, et al. (June 2000). Metabolism: Clinical and Experimental 49 (6): 704-8.

Case Study #1

- Dale is 24-year-old graduate student who struggles with sleep.
- He started using cannabis to sleep each night but soon started using it during the day to relax as well.
- In his final year at school, he was so exhausted he started using amphetamines during the day and sleeping pills at night.
- He lost all interest in food, social activities and sports, things he had always enjoyed in the past.
- Focus and concentration became such a problem he almost failed out of his last year.
- His GP put him on Wellbutrin but this only decreased his focus further and did not change his drug use.

Dale's Genotyping

- DRD2- AG: less dopamine production and receptors.
- DAT1-GG: little dopamine reuptake and transportation.
- COMT- AA: slow clearance of dopamine and stress hormones.
- FKBP5-AA: significant increased loss of negative feedback in HPA axis.
- NR3C2- TC: fewer receptors and increased loss of negative feedback in HPA axis.
- BDNF – TT: decreased neural repair, increased neural inflammation.
- SIRT6- TC: decreased neural repair, increased neural inflammation.

Dale's Interpretation.

- Dale had less dopaminergic activity, but the bigger issue was the lack of DA transportation. Taking Wellbutrin will not work, and will force the DA to the AS vs the PFC.
- His stress genes not only inhibited sleep, but also stimulated inflammation and his BDNF and SIRT6 genes, all of which blocked DA binding, stimulated the HPA axis and decreased neural repair and synaptic firing.
- Soon he was oscillating between "uppers" and "downers" with very little neural balance creating an increased dependence on all drugs and cravings.

Dale's Program

- Lactium 150 mg, L-theanine 57 mg combo– 2 BID empty stomach for 12 weeks and then reduce to 1 BID.
- Resveratrol 200 mg– 1 BID empty stomach for 8 weeks and then reduce to 1 per day.
- Astaxanthin 4 mg- 1 BID empty stomach for 8 weeks and then reduce to 1 per day.
- Melatonin PR – 9 mg at 8:30 pm
- Immovane – prn until able to switch to a passionflower combo.
- Slow withdrawal of Wellbutrin with his psychiatrist.
- Daily exercise, HIIT every other day (genes indicated it) and a stretch or yoga class the other days.

Dale's Outcome

- In the first 2 weeks Dale felt worse from being off the cannabis and amphetamines.
- At the end of the 2nd week, we increased his lactium combo to TID and within 4 days his body began relaxing into the program.
- By the end of the first month, his sleep was 70% better. He could fall asleep more easily and if he woke up in the middle of the night, he was able to fall back asleep most times.
- By the end of the 2nd month, he was off Immovane, sleeping well, calmer, with significantly less desire to use cannabis. Focus still remained an issue.
- At the 6-month mark, Dale reported feeling like he did at the start of grad school.

Case Study #2

- David called himself an adrenaline junkie. Rather than using athletic highs to fill this, he indulged in "less safe" behaviour (frequent sex with strangers, experimenting with heroine and opioids).
- He often had headaches that he would "control" with T3's (from the street).
- His mom put him into rehab where he was put on Wellbutrin and 2 different SSRI's. He felt less cravings but more anger and anxiety.
- They increased his doses and things got worse.
- David left rehab, took himself off all meds and went back to street drugs.

David's Genotyping

- DRD2- GG: less dopamine production and receptors.
- DAT1-CC: normal dopamine reuptake and transportation.
- COMT- GA: moderate clearance of dopamine and stress hormones.
- TPH2- GG: normal serotonin
- 5-HTTLPR- AA: low serotonin transportation.
- BDNF – TT: decreased neural repair, increased neural inflammation.
- SIRT6- CC: decreased neural repair, increased neural inflammation.

David’s Interpretation

- David has low dopamine production and a moderate clearance.
- During times of stress and inflammation the DA will move to the AS augmenting cravings and addictions.
- His transportation of DA is normal allowing for easy and effective DA boosting without side effects.
- His serotonin is normal and his transportation low, causing serotonin boosting to push him into serotonin syndrome.
- His neural firing, wiring and repair is quite low through his BDNF and SIRT6, further inhibiting neurotransmitter function and augmenting addictive behaviour.

David's Program

- Get him back on Wellbutrin with a psychiatrist.
- Lactium 150 mg, l-theanine 57 ,g– 1 BID empty stomach (normal stress genes, but constant stress) for 8 weeks and then reduce to 1 per day for 4 weeks and then 1 prn
- Resveratrol 200mg- 1 BID empty stomach for 12 weeks and then reduce to 1 per day.
- Astaxanthin 4 mg- 1 BID empty stomach for 12 weeks and then reduce to 1 per day.
- At the 3-month mark, a slow transition off Wellbutrin onto L-tyrosine, macuna combo– 2 BID empty stomach.

David's Outcome

- David struggled for the first 3.5 weeks as the Wellbutrin built up in his system.
- His headaches began to reduce by 55% at the 1-month mark and were almost gone by the end of the 2nd month.
- His cravings to "use" were about 80% less by the end of the 3rd month.
- He started exercising, and on those days he had little no cravings at all.
- He signed up for 5 km race and a natural body building contest.
- 6 weeks into his training he began forgetting to take his Wellbutrin with no side effects.
- 2 months later he came off of Wellbutrin and transitioned to L-Tyrosine Macuna combo 2 BID empty stomach with no problems as long as he kept all other supplements and exercise up.

Differential Treatment Plan

Dale

- Issue: stress impairing sleep triggering inflammation and lower BDNF.
- Requires stress and neural health support to maintain dopamine in the PFC.
- Should not have dopamine boosting.

David

- Issue: low dopamine production and poor neural health and repair.
- Requires L-tyrosine combo and neural health support always to maintain dopamine levels.
- Needs dopamine boosting.

Case Study #3

- Susie is a 26-year-old female who describes herself as an “all or nothing” person.
- She is a competitive in everything she does – sports, school, work.
- Recently started training for a triathlon and pushed herself quite quickly into OverTrainingSyndrome.
- She was instructed not to workout at all for 3 months and soon found herself unmotivated to work, see friends and started binge drinking and eating potato chips almost every night.
- After a family intervention, she stopped drinking. Within 5 days the cravings were so bad she started sneaking the alcohol.`

Susie's Genotyping

- DRD2- AG: less dopamine production and receptors.
- DRD2/ANKK1– GA: less dopamine production and receptors.
- COMT- GG: fast clearance of dopamine and stress hormones.
- FKBP5-AA: significant increased loss of negative feedback in HPA axis.
- CRHR1- TC: increased loss of negative feedback in HPA axis.
- IL6- CG: increased inflammation and neural receptor blocking.
- TNFa- GA: increased inflammation and neural receptor blocking.
- BDNF – CT: decreased neural repair, increased neural inflammation.

Susie's Interpretation.

- Susie had kept her dopamine high through daily exercise and academic success.
- Stress of not being able to workout triggered her FKBP5 and CRHR1 genes increasing inflammation and lowering dopamine.
- Not working out lowered her dopamine production further, causing her to drink and eat fatty foods, further triggering inflammation through her IL6 and TNFa genes.
- The increased inflammation and HPA stimulation with lower BDNF meant decreased neural repair and higher inflammation, further blocking dopamine and increasing cravings.

Susie's Program

- L-Tyrosine, Macuna combo – 2 caps BID empty stomach for 8 weeks then reduce to 1 BID empty stomach until she could exercise again.
- Lactium, l-theanine combo– 2 BID empty stomach until she could exercise again and then 1 BID.
- Resveratrol 200mg – 1 BID empty stomach for 8 weeks and then reduce to 1 per day.
- Liposomal Glutathione– 400 mg per day with or without food for 8 weeks and then reduce to 1 per day.
- NAC (900mg) – 1 cap BID empty stomach for 8 weeks and then reduce to 1 per day.
- Created a mini challenge/goal every week.

Susie's Outcome

- Within 1 week her desire to eat fatty foods and drink alcohol reduced by 40%.
- By the end of the first month, motivation to see friends was returning but not back to her norm.
- By the end of the 3rd month, she started running and swimming in the pool for 30-45 min sessions every other day. On these days she had very little desire to drink or binge.
- Over the next 3 months as the intensity of her workouts increased, Susie rarely gave alcohol a thought, and when she did have a drink socially, she could easily stop.

Case Study #4

- Annie is a 53-year-old female who also considered herself an all or nothing individual but most often fell to the negative side of this.
- She started drinking at a very young age, would go into depressive bouts before and after drinking, and slowly shut out the world.
- She went through AA many times, often relapsing weeks after finishing the program.
- This would upset her even more and drive her to drink larger quantities until she lost her job.
- Her GP put her on Celexa which made her more anxious.
- She still fought urges to drink daily.

Annie's Genotyping

- DRD2- GG: much less dopamine production and receptors.
- DRD2/ANK1– AA: much less dopamine production and receptors.
- COMT- AG: faster dopamine clearance, slower catecholamine clearance. (other stress genes normal)
- TPH2- GG: normal serotonin production.
- 5HTTLPR-AA: decreased serotonin transportation.
- MAOA- GA : faster serotonin clearance, slower catecholamine.
- BDNF – CC: Normal neural repair.
- IL6 – CG – increased inflammation and neural receptor blocking.

Annie's Interpretation

- Annie genetically has very poor dopamine metabolism, normal serotonin production and very poor serotonin transportation (why celexa made things worse).
- She didn't exercise as a child but rather started drinking triggering her dopamine and serotonin genes and the addictive binge cycle.
- AA and OA did not address the hormonal side, so she continued to relapse.
- The inflammatory response from drinking triggered her IL6 which further blocked dopamine and serotonin from binding.
- This took years to "kick-in" due to her normal BDNF helping to repair neural damage.

Annie's Program

- L-tyrosine, macuna combo– 2 caps BID empty stomach for 8 weeks then reduce to 1 BID empty stomach.
- Lactium, l-theanine combo- 2 caps BID empty stomach for 4 weeks and then reduce to 1 cap BID for 4 weeks then 1 prn (normal stress genes and reduce serotonin syndrome symptoms).
- Took her Celexa with her GP. Discussed the use of Wellbutrin if above combo did not work.
- 30-minute walks in the morning.

Annie's Outcome

- Annie reduced her binge drinking by 30% in the first month.
- She reported her moods were lifted and she started engaging with her family again.
- By the end of the first month, she was fully off Celexa and feeling much calmer despite still having urges and cravings to drink.
- 9 months later she had not binged in 3 months and tried to reduce her L-tyrosine, Macuna combo to 1 per day. Within 10 days she was binging again.
- 2 yrs later she remains on on her supplements at the reduced doses, and when a craving hits is able to redirect behaviour.

Differential Treatment Plan

Susie

- Issue: stress triggering inflammation, and lower dopamine and BDNF.
- Able to control dopamine and stress through exercise.
- Requires supplementation to keep stress genes stable and dopamine in the PFC.

Annie

- Issue: dopamine and serotonin.
- Requires supplementation always to maintain dopamine levels.
- Doesn’t require stress gene support.

Questions?

www.pkrhealth.ca

www.generx.ca