The Psychopharmacology and Neuroscience of Substance Use Disorders: The Anti-Reward Brain System

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The Neuroscience and Pharmacology of Addiction 2015
Addiction Depression 2015

Reward Brain

BDNF

cAMP

Anti-Reward Brain

CREB
Increased cAMP produced in post-synaptic cell
Factors Contributing to Vulnerability to Develop a Specific Addiction

use of the drug of abuse essential (100%)

Genetic (25-50%)
- DNA
- SNPs
- other polymorphisms

Environmental (very high)
- prenatal
- postnatal
- contemporary
- cues
- comorbidity

Drug-Induced Effects (very high)
- mRNA levels
- peptides
- proteomics
- neurochemistry
- behaviors

Kreek et al., 2000
This is your brain

This is your brain
Thanks to BDNF

Think of it like fertilizing and pruning your rose bushes
So What’s New in Psychopharmacology?

- Vilazodone (Viibryd)
- Levomilnacipran (Fetzima)
- Vortioxetine (Brintellix)
- Asenapine (Saphris)
- Iloperadine (Fanapt)
- Lurasidone (Latuda)
- Zolpidem Spray (Zolpimist)
- Clozapine Oral Suspension (Versacloz)
- Fentanyl Oral Tablets (Abstral and Fentora)
- Fentanyl Nasal Spray (Lazandra)
- Fentanyl Buccal Film (Onsolis)
- Buprenorphine Transdermal (Butrans)
- Buprnorpine SL Tablets (Zubslov)
- Tapentadol (Nucynta)
- Hydrocodone (Zohydro)
The Impact of Current Substances of Abuse on the Brain
"Street Drugs"-2015

- Absinthe
- Alcohol*
- Bath Salts*
- Caffeine
- Cannabis*
- Cocaine
- DXM
- GHB
- Heroin
- Inhalants
- Ketamine

- LSD
- MDMA
- Mescaline
- Meth
- Mushrooms
- Nutmeg
- Opiates*
- Peyote
- Salvia*
- Spice*
- Tobacco
Peaks of Brain Plasticity

The word “plasticity” is a term used to describe the brain’s ability to physically change its internal structure (by making more dendrites) when we learn new things or have new experiences.

During peaks of plasticity the brain must make key neural connections to wire us to become a responsible, thoughtful, intelligent adults

Drinking alcohol during peak periods of plasticity can seriously damage brain wiring
Moving To A Dependent State

Craving
Today’s Psychopharmacology – Can It Rescue A Drug Damaged Brain?

9/23/2015 Dr. Merrill Norton
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**CROSS SECTION OF THE HUMAN BRAIN**

**Corpus callosum**
A large band of nerve fibres through which information flows back and forth between the left and right hemispheres of the brain.

**Thalamus**
The relay station for most information going into the brain.

**Hypothalamus**
Regulates sex hormones, blood pressure and body temperature.

**Pituitary Gland**
The master gland of the body - produces its own hormones and also influences the hormonal production of the other glands in the body.

**Amygdala**
Regulates the heartbeat and other visceral functions and process the emotion fear.

**Hippocampus**
Helps establish long-term memory regions of the cerebral cortex.

**Basal ganglia**
A control system for movement and cognitive functions.

**Cingulate gyrus**
Cooperation, cognitive flexibility, and ability to see options.

**Cerebellum**
Essential for coordination of movement.

**Pons**
Control of breathing, circulation, heartbeat and digestion.

**Medulla oblongata**

**Spinal cord**

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**One-PFC-Parietal Lobe-Temporal Lobe (Cognitive Function)**

**Two- Control Lobe (Transition Between Cognitive and Instinctual Functioning)**

**Three-Amygdala-Hypothalamus-Thalamus (Instinctual Functioning)**
Serotonin and Norepinephrine in the Brain

Depressed Mood Problems Concentrating

Psychomotor Retardation Agitation

One- PFC-Parietal Lobe-Temporal Lobe(Cognitive Functioning)

Two- Control Loop(Transition of Cognitive and Instinctual Functioning)

Three- Amygdala-Hypothalamus-Thalamus(Instinctual Functioning)

Guilt Thoughts of Death

Loss of Appetite Weight Gain/Loss Loss of Pleasure

Insomnia Hypersomnia

Mechanisms of Actions of New Substances of Abuse

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5-HT levels in monkey after MDMA (two 5 mg/kg daily for 4 days)


Result:
- long-term loss of 5HT fibers in monkeys
- some recovery (caudate nucleus)

Figure 4. Dark-field photomicrograph, sagittal plane, of 5-HT immunoreactive axons in the caudate nucleus of a control monkey (A), a 2 week MDMA-treated monkey (B), and a 7 year MDMA-treated monkey (C). Scale bar, 100 μm.

(Hatzidimitriou et al., J. Neurosci. 19 [1999] 5092)
Cathinone is a naturally occurring beta-ketone amphetamine analogue found in the leaves of the Catha edulis plant. Synthetic cathinones are derivatives of this compound. Those that are being used as drugs of abuse include butylone, dimethylcathinone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, mephedrone, methedrone, methylenedioxyxpyrovalerone (MDPV), methylene, and pyrovalerone. Synthetic cathinones are phenylalkylamines derivatives, and are often termed "bk-amphetamines" for the beta-ketone moiety. They may possess both amphetamine-like properties and the ability to modulate serotonin, causing distinct psychoactive effects. Desired effects reported by users of synthetic cathinones include increased energy, empathy, openness, and increased libido. Cardiac, psychiatric, and neurological signs and symptoms are the most common adverse effects reported in synthetic cathinone users who require medical care. Deaths associated with use of these compounds have been reported.

Salvia divinorum: A Psychopharmacological Riddle

- Combined NMDA/serotonin/norepinephrine/Kappa opioid agonist - this would indicate only supportive therapies available.

- Dysphoria, “somatic” sensations such as hypo or hyperalgesia and proprioceptive feverish sensations that suggest opiate receptor involvement.

- Used in the Amazon as “Trance inducing drug”

- Diaz, JL, Current Drug Abuse Reviews, 2013, 6, 43-53

Synthetic Cannabinoids- A Pharmacological Dilemma

A case report describes the dependence syndrome and withdrawal phenomena of a 20-year-old male patient who initially smoked 1g (increased to 3g after decreasing effects) of "Spice Gold" for 8 eight months.

He continued to use Spice despite negative cognitive effects and potential loss of employment. Due to experience with previous unpleasant withdrawal symptoms, the patient requested voluntary hospital admission and medical assistance to help him in drug withdrawal.

On admission, he appeared anxious and insecure, and on day two he complained about increasing internal unrest and trouble sleeping. By day four he had developed a strong craving for Spice, profuse sweating, nightmares, nausea, tremor, and headaches. He also experienced a heart rate of 125 beats/min and a blood pressure of 180/90 mmHg that remained elevated for two days.

The patient was eventually released and returned to the hospital four months later with a good report. It should be noted that the phenomena reported are confounded by the patient's underlying diagnosis of ADHD and longstanding "inner unrest" for which he self-medicated with Spice and cannabis. Although dependence is rare among cannabis users, it may be more common among users of synthetics.

LaDow,T., Seltzer, J., "Spice" it Up - A New Way to Get High What Pharmacists Need to Know Drug Information Alert University of Texas College of Pharmacy, 2014
### Synthetic Cannabinoids: The Major Compounds

- **a) Naphthoylindoles**
  - JWH-018
  - JWH-398
  - JWH-081
  - JWH-122
  - JWH-019
  - AM-2201
  - JWH-387
  - JWH-412
  - 5-Fluoropentyl-JWH-122

- **b) Cyclohexylphenoles**
  - JWH-073
  - JWH-200
  - JWH-015
  - JWH-210
  - JWH-007
  - AM-1220
  - CP-47,497-C8

**SOURCE:** Agudelo et al. (2012). *Effects of Synthetic Cannabinoids on the Blood Brain Barrier*, Presented at 74th Annual CPDD.
Reefer Madness 2015: The Science of Medical Cannabinoids

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Current Marijuana Use

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Reefer Madness 2015: The Science of Medical Cannabinoids

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STRUCTURE OF THC

$\Delta^9$-TETRAHYDROCANNABINOL ($\Delta^9$-THC)

(The primary psychoactive molecule)
Marijuana (2010)

• Stats and Facts:
  – 2010: 15 States and DC approved Marijuana for medical purposes
  – 2009: 25% of U.S. teens had smoked MJ in the past month
  – Not much cross-tolerance with other drugs
  – Doesn’t produce anesthesia, coma or death in high doses
  – Highly controversial drug
  – 2010: CA attempted to legalize MJ for recreational use with Prop 09-0024
Marijuana (2010)

- **History:**
  - Earliest evidence of use: 10,000 years ago during Stone Age
  - Pharmacological use recorded in China ~2700BC
  - Important crop in U.S. since 1611 (Hemp for rope)
  - Mind-altering properties not discovered until 1850s
  - Napoleon’s troops brought back recreational use to France after war with Egypt
  - 1920s: Prohibition: led to increase in MJ use
  - 1937: Marijuana Tax Act made recreational use illegal and taxed Rx’s
What is Marijuana?(2010)

• Cannabis plant
• 3 Types:
   – C. Sativa (hemp)
   – Indica (grown in India—higher THC)
   – Ruderalis (grown in Northern Europe and Asia—low potency)
• Active ingredients: over 80 known cannabinoids
   – Most common: delta-9-tetrahydrocannabinol (THC)
• Hashish: dried resin; most potent 10-20% THC
• Ganja: dried material from top of plant; 5-8% THC
• Marijuana: dried remainder (leafy portion); 2-5% THC
Pharmacokinetics
Pharmacokinetics (2010)

- Routes of Administration
  - Oral
    - Solid or liquid form
    - Larger dose needed for same effect as inhalation (Liver clears much of the THC)
    - Effects longer/more sustained
    - Peak effect: 1-2hrs
    - Lasts 4-6hrs
  - Inhalation
    - Rapid effect (reaches brain in ~30 seconds)
    - Peak effect: 30-60 min
    - Lasts 2-4hrs
    - Subjective state for ~12hrs
Pharmacokinetics (2010)

- Distribution, Metabolism, Excretion
  - THC is water insoluble
  - It is absorbed in fatty tissue throughout the body
  - 25-30% of dose may remain in tissue for a week
  - 2 weeks to clear from tissues
  - Metabolized primarily by liver
  - Excreted via urine and feces
  - Detectable in urine
    - Frequent smokers: 7-21 days
    - Infrequent smokers: 1-3 days
    - Daily users: 30 days or more

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and Caitlin Payne, Research Assistant
Marijuana Standards (2015)
Pharmacology

CBD
- Aids sleep
- Reduces inflammation
- Inhibits cancer cell growth
- Treats fungal infection
- Stimulates appetite
- Relieves pain
- Inhibits cancer cell growth
- Promotes bone growth
- Slows bacterial growth
- Reduces seizures and convulsions
- Reduces blood sugar levels
- Reduces function in the immune system
- Reduces inflammation
- Reduces risk of artery blockage
- Reduces small intestine contractions
- Reduces vomiting and nausea
- Relieves pain
- Relieves anxiety
- Slows bacterial growth
- Suppresses muscle spasms
- Tranquilizing
- Treats psoriasis
- Vasorelaxant

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D8-THC
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CBD
Pharmacology(2015)

• **Marinol (Dronabinol)**
  – Reduction of nausea and vomiting in chemotherapy
  – Increase appetite in HIV-wasting disease
  – Potential New Indications
    • Reduction of spasticity, analgesia, agonist-replacement in cannabis dependency

**Kinetic Profile after a single oral dose (10mg of THC)**

– mean peak conc found 1-2 hours post dose
  • THC: 3.8 ng/ml *(1.1-12.7 ng/ml)*
  • 11-OH-THC: 3.4 ng/ml *(1.2-5.6 ng/ml)*
  • THC-COOH: 26 ng/ml *(14-46 ng/ml)*
Cultivation methods have been developed to reproducibly produce plants with defined THC or CBD concentrations. *GW Pharmaceuticals* has produced two standardized extract preparations, *Tetranabinex®*, which is high in THC, and *Nabidiolex®*, which is high in CBD. *Sativex®* contains equal proportions of *Tetranabinex®* and *Nabidiolex®*, and, hence, almost equal amounts of THC and CBD.

Drug Interactions (2015)

• **Stimulants**
  – Cocaine, Amphetamines, etc
    • increased hypertension
    • tachycardia
    • cardiotoxicity.

• **Depressants**
  – Benzodiazepines, Barbiturates, Ethanol, Opioids, Antihistamines, muscle relaxants, etc.
    • increase drowsiness
    • CNS depression

• **Alcohol**
  • greater impairment
  • decreases in function
  • less likely to react appropriately
  • increased reaction times

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Cannabis Plant Anatomy

- **Cannabinoid Concentration**
  - 30,000 cannabis preparations confiscated in the U.S. between 1980 and 1997 were
    - Average Concentrations
      - 3.1% THC
      - 0.3% CBD
    - Influencing Factors
      - Plant sex, age/developmental stage, environment, genetic makeup
- **Medical species are grown to produce similar levels of THC and CBD**
- *Sinsemilla* is derived from the unpollinated female cannabis plant
  - preferred for its high THC content (up to 17% THC)
- **Concentrations of cannabinoids in the body (parent or metabolite) are dependent on use and dose**

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Cannabinoids (2015)

R = H  \Delta^9\text{-Tetrahydrocannabinol (THC)}
R = OH  11\text{-Hydroxy variant (11-OH-THC)}

\text{Cannabidiol (CBD)} \quad \text{‘11-Nor-9-carboxy-}\Delta^9\text{-Tetrahydrocannabinol’ (THC-COOH)}

But Is THC Toxic???

• **2009 study from American Scientist on the relative toxicity of recreational drugs showed that using only 10 times the "effective" dose of alcohol could be fatal, whereas more than 1,000 times the effective dose of marijuana would have to be used to be possibly fatal.**

• The toxic dose of THC in a 65kg adult would be 8.45kg.
But is THC Toxic???

- The tachycardia almost invariably produced in acute intoxication, combined with the sensory alterations and increased tremor commonly reported, probably contribute to the affective components of these reactions. CNS and respiratory depression are noted with high doses, which in severe overdose may be life-threatening (Rosencrantz, 1983). These effects are, of course, more dangerous to those with pre-existing cardiac irregularities. Because of the large effective to lethal dose ratio in humans (probably in excess of 1:1000 in non-tolerant users) the risk of experiencing severe toxic effects of cannabis is limited by the aversive psychotropic effects of high doses, which usually lead to cessation of use before the onset of dangerous physical consequences.
New Types of Concentrates

- Kief
- Water Hash
- CO2 Oil
- Butane Hash Oil (BHO)
- Rosin
Concentration: Kief

- Also known as dry sieve (sometimes “dry sift”) hash, kief is the simplest of concentrates. Kief is composed of the trichomes (the crystalline structures coating the outside surface of the flowers) broken away from the dried plant material, usually via specialized filtering screens and a little elbow grease. Kief is generally considered a lower-quality extract, but some top-flight extractors can produce an extremely clean and flavorful product using this method. THC content can range from 20 percent to 60 percent. This process at its highest level yields nothing but the largest, most perfect trichome gland heads and none of the gland stems, plant matter, etc. that generally clouds the quicker, lower-quality kief extractions. While it is certainly available in Colorado dispensaries, compared to three years ago, it is much harder to find because of the prevalence of solvent extracts and the low return that it provides to commercial growers.

Concentrates of Water Hash

• There are various techniques used in the production of water hash, and the resulting products have many forms (bubble hash, solventless wax, ice wax, among others). The basic principle is this: plant material (either dry or fresh-frozen generally) is mixed with cold water and ice, then agitated manually or mechanically in order to break off the now-brittle trichome heads. This solution is then filtered through specifically-sized screens to remove anything undesirable, leaving behind a relatively pure finished product that typically tests between 50 percent and 80 percent THC. The most common way that water hash is extracted is using a series of microscreen fabric bags (generally referred to as “bubble bags”) which remove various grades of product according to the size of particles they allow through.
Concentrates of CO2 Oil

- This variety of extract is created using carbon dioxide compressed at high pressures until it becomes what is known as a "supercritical fluid," which then is able to strip the essential oils of the cannabis plant much like hydrocarbon solvents. CO2 oil is generally a loose, orange-tinted oil that can be either clear or opaque depending upon the finishing processes used after extraction, and THC content tests between 50 percent and 75 percent. The appeal of this method for many is that it is non-flammable and contains no chemical solvents. The machines required to do CO2 extractions at any kind of commercial scale can cost hundreds of thousands of dollars.
Concentrates of Butane Hash Oil (BHO)

- Perhaps the most common type of extract on the market, BHO has a variety of names (wax, shatter, crumble, oil, errl, honeycomb, moon rock, nectar, etc.) but like water hash, the basic principles of extraction are the same across all of them, with the variations in appearance and texture mostly coming in finishing processes. To make a butane concentrate, butane is pressurized in a vessel and washed over plant material (usually dry, but sometimes fresh-frozen — more on that below), then the resulting solution is collected. The hashmaker must remove any residual solvent from this solution, so the next step generally is applying heat (butane has a low boiling point) and vacuum (which lowers the boiling point further) in order to make this process easier and faster while retaining the highest amount of flavorful terpenes and cannabinoids in the finished product. BHO generally tests between 60 percent and 90 percent THC, making it perhaps the strongest concentrate on the mainstream market.
Concentrates of Rosin

- The newest and hottest type of extract on the scene right now, rosin is extracted from either dried buds, trim, or lower-grade water hash/kief. What is unique about rosin is that it can be made with nothing more than a standard hair straightener, parchment paper and some hand-applied pressure. When the material is smashed and heated quickly between the parchment sheets, it extrudes some of the essential oils present in the plant, resulting in a golden shatter or oil-like extract that looks similar to pressed high-quality water hash or even solvent-extracted shatter. Rosin is a fairly recent development, so its availability in dispensaries is still somewhat limited, as is data about its potency; but early reports on some rosin extracts have showed numbers **between 50 percent and 70 percent THC**, similar to that of high-quality water hash.
Edibles
Anti-Craving Medications

Campral

Revia and Vivitrol

Antabuse

Suboxone

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**Antabuse (Disulfiram)**

- Alcohol abuse *deterrent*
- Prevents second step in alcohol metabolism
- When alcohol is consumed:
  - Causes buildup of acetaldehyde
  - Flushing, nausea, and palpitation will occur
  - If effects are ignored and drinking continues, results may be fatal!
Antabuse (Disulfiram)

- Wait at least 12 hours after drinking alcohol before beginning Antabuse
- Avoid alcohol in sauces, foods, and medications
  - Read Labels
- Avoid paint fumes, paint thinner, and shellac (nail polish)
- Use caution with colognes, aftershave, and rubbing alcohol
Antabuse (Disulfiram)

Black Box Warning

Disulfiram should never be administered to a patient when he is in a state of alcohol intoxication, or without his full knowledge. The physician should instruct relatives accordingly.
Campral (Acamprosate)

- Used in conjunction with a treatment program
- Helps restore chemical balance
  - Increases GABA activity
  - Decreases glutamate activity
  - End result = blocking pain and less cravings

GABA                GLUTAMATE     =    PAIN and
CRAVINGS

Campral (Acamprosate)

- Reduces SECONDARY withdrawal symptoms
  - Insomnia
  - Anxiety
  - Restlessness
  - Uncomfortable moods

- Proven to help patients with severe dependence to remain abstinent for several weeks to months
Campral (Acamprosate)

- Will not reduce or eliminate PRIMARY alcohol withdrawal symptoms
- Minor side effects including nausea, diarrhea, and dizziness may be due to alcohol abstinence not the medication
- Must report feeling of depression, anxiety, or any suicidal thoughts to your health care provider
Suboxone (Buprenorphine + Naloxone)

- Buprenorphine: opioid partial agonist
- Naloxone: opioid antagonist
- Prevents withdrawal symptoms
  - Buprenorphine: too weak to give a “high”
  - Naloxone: blocks the “high” from stronger opioids
- Serious side effects and death can occur if taken with benzodiazepines, sedatives, and alcohol
Vivitrol/ Revia (Naltrexone)

- Vivitrol- monthly injection
  - $$$expensive$$$
- Revia- daily tablet
- This medication is a narcotic antagonist
- It does not decrease alcohol or opioid withdrawal symptoms
- Treats the cravings, NOT the addiction
- A person cannot have any opioids in system because sudden withdrawal symptoms will result
- Must be opioid free for 7 to 10 days before starting naltrexone
Vivitrol/ ReVia (Naltrexone)

Black Box Warning

**Hepatotoxicity:** Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone does not appear to be hepatotoxic at the recommended doses. **Warn patients of the risk of hepatic injury and advise them to seek medical attention if they experience symptoms of acute hepatitis.** Discontinue use of naltrexone in the event of symptoms and/or signs of acute hepatitis.
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