DRUGS OF REWARD AND DEPENDENCE

Drug Dependence – physiological state of neuroadaptation produced by repeated administration of the drug – to prevent withdrawal

Cross Dependence – drugs used to maintain the physiologically dependent state

Cross Tolerance – the ability to use one drug to suppress physical dependence of another drug

DETOX

1. Slow tapering of a drug that has caused dependence and withdrawal if stopped too quickly
2. Can also use a cross tolerant drug

RELAPSE

- Reoccurrence of disease prior to drug treatment

REBOUND

- Exaggerated expression of original condition

MESOLIMBIC DA PATHWAY

REINFORCEMENT AND REWARD

Brains NT’s
- Naturally occurring
- Morphine/Heroin (Endorphins)
- Marijuana (Anandamide)
- Cocaine and Amphetamine (DA)
All psychotropic drugs of abuse – cause mesolimbic pathway to release DA

1. More intense
2. Postsynaptic limbic – DA receptors
3. D2 sites crave DA
4. Addiction depends on how many D2 sites a person has

Few receptors – no effect at first

Drug will become more rewarding with use

Low initial response to a drug is a poor prognosticator (natural reward system may be poor)

High initial response to a drug predicts a low risk of abuse

Low initial response, high risk of abuse

**COCAINE**

1. Local Anesthetic
2. Inhibitor of monoamine transporters (inhibits DA reuptake at DA transporter)
3. May also release DAC or NE or 5HT by reversing NT out of the presynaptic neuron via the monoamine transporters

Use antipsychotropics to relieve symptoms of cocaine intoxication

DA synapse becomes more sensitized to cocaine

--With long-term abuse – DA receptors become desensitized (down regulated)

Euphoria

Decreases “crashing”


**Amphetamines**

d-amphetamine and methamphetamine

1. Releases DA
2. NE increases
3. 5 HT increases

(CART)

NT system (Cocaine and Amphetamine-Regulated Transcript)

Peptides – role in drug abuse and feeding behaviors

Less intense euphoria

**Hallucinogens**

1. Changes in sensory experiences
2. Visual illusions – hallucinations
3. Enhanced awareness of external and internal stimuli

- Macropsia, Micropsia, subjective slowing of time
- Colors are heard
- Sounds are seen
- Intensification of sound perception
- Depersonalization
- Derealization
- “Bad trip”

Intoxication can produce an acute confusional state
2 classes of Hallucinogens:

Indolealkylamines – 5 HT include classical hallucinations
D-Lysergic Acid Diethycamide (LSD)
Psilocybin
Dimethyltryptamine (DMT)

Phenylalkylamines

Related to Amphetamine
NE, DA, Mescaline, 2,5-Dimethoxy -4 Methamphetamine

MDMA 3.4 Methyl Enedioxymethphetamine
“Ecstasy”
Euphoria, disorientation, confusion

Hallucinogens

5 HT 2A Agonist
5HT 1AC Somatodendritic
Autoreceptors

Flashbacks – emotional conditioning

Tolerance – neurochemical adaptor of the 5HT system

Phencyclidine (PCP) – hallucinogen
Ketamine “Special K”
- Can cause amnesia, delusion, vertical nystagmus

1. Allosteric Modulator of NMDA subtypes of glutamate receptor

Blocks calcium flowing into cell

2. May be neuroprotective

Disrupts memory
THC – Endocannabinoids

Delta tetrahydrocannabinol

Marijuana – smoked

1. Interacts with the brain’s own cannabinoid receptors to trigger DA release from the mesolimbic reward system

Two known cannabinoid receptors CB1 (brain) couples to G proteins

Modulates adenylate cyclase and ion channels – also for alcohol

CB2 – immune system

NATURAL CANNABINOID SYSTEM IN BRAIN – ENDOCANNABINOIDS

1. Anandamide – is a lipid fatty acid (Ethanolamides)

THC – Antagonist SRI 41716A

Marijuana

- Sense of well being
- Loss of temporal awareness
- Slowing of thought process
- Impairment of short term memory

Long-term use – Amotivational Syndrome

Long term marijuana abuse – decreases occupational goals

1. Shortened attention span
2. Poor judgment
3. Easy distractibility
4. Withdrawal does occur
Nicotine

DA cells in the mesolimbic DA pathway receive direct nicotinic cholinergic input stimulated by cigarette smoking

1. Smokers down regulate DA receptors because of excessive DA stimulation
2. Nicotine users up regulate their nicotinic cholinergic receptors to help compensate for nicotine turning them off

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Opiates

Receptors:

MU
DELTA
KAPPA

“Brain’s own Morphine”

endogenous opiates

- Peptides – derived from precursor proteins (POMC)
  - PRO-OPiomelanocortin
  1. Pro Encephalin
  2. Prodynorphin

Stored in opiate neurons

PAIN – MU receptors

Produce BRIEF EUPHORIA
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Alcohol

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BLOCKING CANNABINOID RECEPTORS REDUCES CRAVING FOR ETOH

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Weight Loss

Agonizing 5HT2C – anorexia and increases reuptake blocking 5HT

Butramine

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Beta 3 adrenergic receptors – adipose tissue stimulates thermogenesis – increases oxygen consumption – decreases weight loss

LEPTIN – peripheral leptin
-- Member of the INTERLUKIN 6 cytokine family found in white adipose cells

1. Regulation of insulin secretion and energy metabolism in fat cells
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CHAPTER 14 – Sexual Function

3 Sexual Stages

- Libido
- Arousal
- Orgasm

Arousal

Ach and Nitric Oxide

Parasympathetic smooth muscle of the innervations of the genitals

Ach and Nitric Oxide – promote erections in men and lubrication and swelling in women

STAGES OF SEX

Message of arousal starts in the brain relayed down the spinal cord (then into peripheral autonomic nerve fibers; both sympathetic and parasympathetic into vascular tissues, into genitals

NO = gas – brain blood vessels control erections

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NO
1. Relaxes smooth muscles in blood vessels in the penis
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Target of NO is not a receptor
Target is IRON in GC
NO binds to iron
GC is activated
cGMP is formed
cGMP is terminated by (PDEs)
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Opiate Antagonists

NALOXONE
NALTREXONE
- Compete as antagonists at opiate receptors

Cause rapid *tolerance* and *dependence*

1. Need for higher doses for pain
2. Opiate receptors decrease their sensitivity to agonists

Opiates act at MU – especially Delta, Kappa

Dependence and tolerance occurs rapidly

Dependence – withdrawal can occur as soon as opiate wears off

NALOXINE – opiate antagonist can precipitate withdrawal symptoms in a dependent person

**WITHDRAWAL SYMPTOMS**

- dysphoria
- Craving
- Autonomic hyperactivity
- Tachycardia
- Tremor
- Sweating
- pilo erection

Can use CLONIDINE Alpha 2 adrenergic agonist to reduce autonomic hypersensitivity

**METHADONE** – another can be given to assist with *tapering* off to detox

A partial MU opiate AGONIST BUPRENOPHINE – can be used and tapered for WITHDRAWAL

BUPRENOPHINE combined with NALOXONE can be taken so IV opiates will have no effect
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