Psych 3102
Introduction to Behavior Genetics

Lecture 26

Substance use and abuse

Alcohol

Genetics of substance use disorders (SUDS)

- abuse of drugs is one of the leading public health problems

- societal and personal burdens
  – health care, lost productivity, broken families, ruined careers, violent victimization, increases risks for chronic disabling illness

- aims of behavior genetic research is to get better understanding of origin of use disorders , so that better prevention and intervention methods might be developed

- behavior genetic research has helped transform field - these disorders are no longer viewed as result of moral weakness or as an outcome of unresolved conflict

- widespread recognition there is a neurological basis with genetic influence

- evidence is that these are chronic conditions - the person cannot be ‘cured’

REVIEWS

Transcriptional and epigenetic mechanisms of addiction

Alfred J. Robison and Eric J. Nestler

Abstract | Investigations of long-term changes in brain structure and function that accompany chronic exposure to drugs of abuse suggest that alterations in gene regulation contribute substantially to the addictive phenotype. Here, we review multiple mechanisms by which drugs alter the transcriptional potential of genes. These mechanisms range from the mobilization or repression of the transcriptional machinery — including the transcription factors ΔFOSB, cyclic AMP-responsive element binding protein (CREB) and nuclear factor-κB (NF-κB) — to epigenetics — including alterations in the accessibility of genes within their native chromatin structure induced by histone tail modifications and DNA methylation, and the regulation of gene expression by non-coding RNAs. Increasing evidence implicates these various mechanisms of gene regulation in the lasting changes that drugs of abuse induce in the brain, and offers novel inroads for addiction therapy.

Drug addiction exacts an enormous medical, financial and emotional toll on society in the form of overdose and health complications, family disintegration, loss of employment and crime. The National Institute on Drug Abuse (NIDA), part of the US National Institutes of Health, estimates that the total cost of drug abuse in the United States exceeds US$600 billion annually, and it is particularly alarming to note a sharp increase in the abuse of prescription drugs and in drug abuse by teenagers (see the NIDA web site). These data substantiate the need for more research into the neuronal effects of drugs of abuse and the mechanisms of addiction, in the expectation of uncovering novel targets for treating and preventing addictive disorders.

Although most individuals are exposed to drugs of abuse, only a subset experience the loss of control over drug use and compulsion for drug seeking and taking that defines the addicted state. Entrance into this state is strongly influenced by both an individual's genetic constitution and the psychological and social context in which drug exposure occurs[1–3]. Although the genetic contribution to risk for addiction is roughly 50%[1], the specific genes that are involved remain almost completely unknown. The addictive phenotype can persist for the length of an individual's life, with drug craving and relapse occurring even after decades of abstinence. This persistence suggests that drugs induce long-lasting changes in the brain that underlie addiction behaviours.

The many cells of an individual organism, although they contain essentially identical complements of DNA, differentiate to form distinct tissues and organs through regulated changes in the transcriptional potential of each gene, based on environmental cues, cell-to-cell signals and other, probably random factors[4]. It is becoming clear that many of the same processes of gene regulation that are involved in the normal differentiation of cells and tissues during development are also engaged in the adult organism to mediate cellular adaptation to environmental stimuli[5,6]. The processes that are involved in the regulation of transcriptional potential are varied and highly complex, and include activation and inhibition of transcription factors, modification of chromatin and DNA structure, and induction of non-coding RNAs. Increasing evidence supports the hypothesis that each of these mechanisms of epigenetic regulation is directly affected by drugs of abuse, and that such adaptations are one of the main processes by which drugs induce highly stable changes in the brain that mediate the addicted phenotype. This Review summarizes the findings that support this hypothesis, and highlights areas in which future research will extend this fundamental knowledge of addiction and exploit it for new therapeutics.

Drug action and gene transcription

A seemingly similar syndrome of addiction can result from exposure to a wide variety of chemical substances or even rewarding activities, from cocaine to gambling to sex. One common mechanism in these various forms of addiction is thought to be activation of the brain's reward circuitry, which centres on dopaminergic neurons in

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Biological basis

- brain is hard-wired to increase pleasure, decrease pain – underlies use of all drugs
- all drugs increase dopamine levels in nucleus accumbens (main reward center of brain)

nicotine, amphetamines do this directly cocaine blocks reuptake

alcohol, narcotics (heroin, pain relievers) suppress neurons that inhibit release

- all drugs seem to act by inducing transcription factor changes, leading to gene expression changes

fos family – act in NAc, increase reward, produce sensitized response to drugs, increase in spiny neurons, induce positive emotional state, drug craving, relapse

- changes in gene expression are lasting (epigenetic), lead to addiction, even after use ends genes are 'marked' – react quickly to cues, relapse

- genetic vulnerability in some individuals makes them more likely to become addicted

The substance use and disorder phenotype

- disorders are relatively common
  – most common mental health problem in nearly all Western countries
  - community based samples, population twin studies will provide large #s with clinically relevant levels of abuse/dependence

- both clinical and sub-clinical patterns of use have health consequences
  - research not limited to disorders

- developmental framework is apparent, with different influences acting at different stages

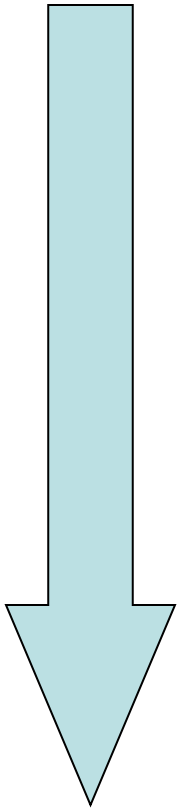
- a use disorder rarely occurs in isolation
  – comorbidity with other drug use and with psychopathology, personality disorders

- access to substances is obviously necessary
  – there will be genotype/environment interaction and correlation
- temporal and geographic variation in availability of substances makes the phenotype even more highly complex

Levels of substance use

- use is viewed as occurring on a developmental continuum
- different influences act on the different levels
- influences are both substance-specific and substance non-specific

Measured by quantity and frequency



Abstinence those who do not use

Initiation onset of use early or late use onset?

Use on a regular basis

Abuse ← DSMIV criteria

Dependence ← DSMIV criteria

early or late onset of dependence

Influences on substance use and abuse

Research shows substance use runs in families

Family risks (over no use)

	Alcohol	Cannabis	Other drugs .
Use	1.8	2.7	3.2
Abuse	3.5	2.9	1.6
Dependence	3.0	3.2	0.8

- only a small fraction of those who experiment with or use substances proceed to harmful use

- research indicates health efforts may be more effective if directed

a) at those who are more likely to abuse substances and suffer social and personal impact and

b) at the transition from use to abuse rather than on experimentation

Abuse of prescription drugs

psychiatric **medications**

ADHD stimulants anti-anxiety medications

pain relief drugs

opiates

Abuse of these dwarfs other illicit drug problems:

hospitalizations related to these up x5 over last 10 years

more high school seniors report recreational use of these drugs than heroin and cocaine combined

Alcohol use and use disorders

- Abuse and dependence are complex genetic traits that are influenced by environmental factors

- 2002 WHO report: alcohol is 5th leading cause of death & disability worldwide
  - liver disease (cirrhosis)
  - cancer (especially breast cancer in women)
  - cardiovascular disease (weakening of heart muscle, stroke, hi BP, irregular heartbeat)
  - shrinkage of cerebral cortex, related changes in behavior

- Heritability for alcoholism (alcohol dependence) = 50-60%
- Similar for alcohol abuse (to be no distinction in DSMV)
- Influences on use (NOT abuse, dependence) of alcohol are largely environmental

developmental framework

–different influences at different ages and levels of use

Sex differences

- prevalence rates

  males : females 2:1

- influences, both genetic and environmental

  low genetic and environmental correlations

- women alcoholics are more likely to have comorbid disorders

  eating disorders (70%?) depression anxiety

- women are more likely to have alcoholic partners due to assortative mating on the part of females only

  49% alcoholic females are in relationships w. alcoholic men

  only 6% of alcoholic men are in such relationshps

  puts females at high risk for abusive treatment (risk = x9)

- health problems caused by abuse and dependence are worse in women

  liver cirrhosis high blood pressure breast + other cancers

  risk increases at just 2 drinks/day vs 4-6 for men

What's one drink?

- 5oz wine
- 12oz beer
- 1.5oz liquor (80proof)

Quantity and frequency

- 'light' consumption = 3 drinks/week
- 'moderate' consumption = 4 to 13 drinks/week
- 'heavy' consumption = 2 or more drinks/day

- 2 drinks/day can lead to health problems
- 1 to 2 drinks/day can be beneficial

Fetal alcohol syndrome and spectrum defects

4 necessary features for syndrome (FAS):

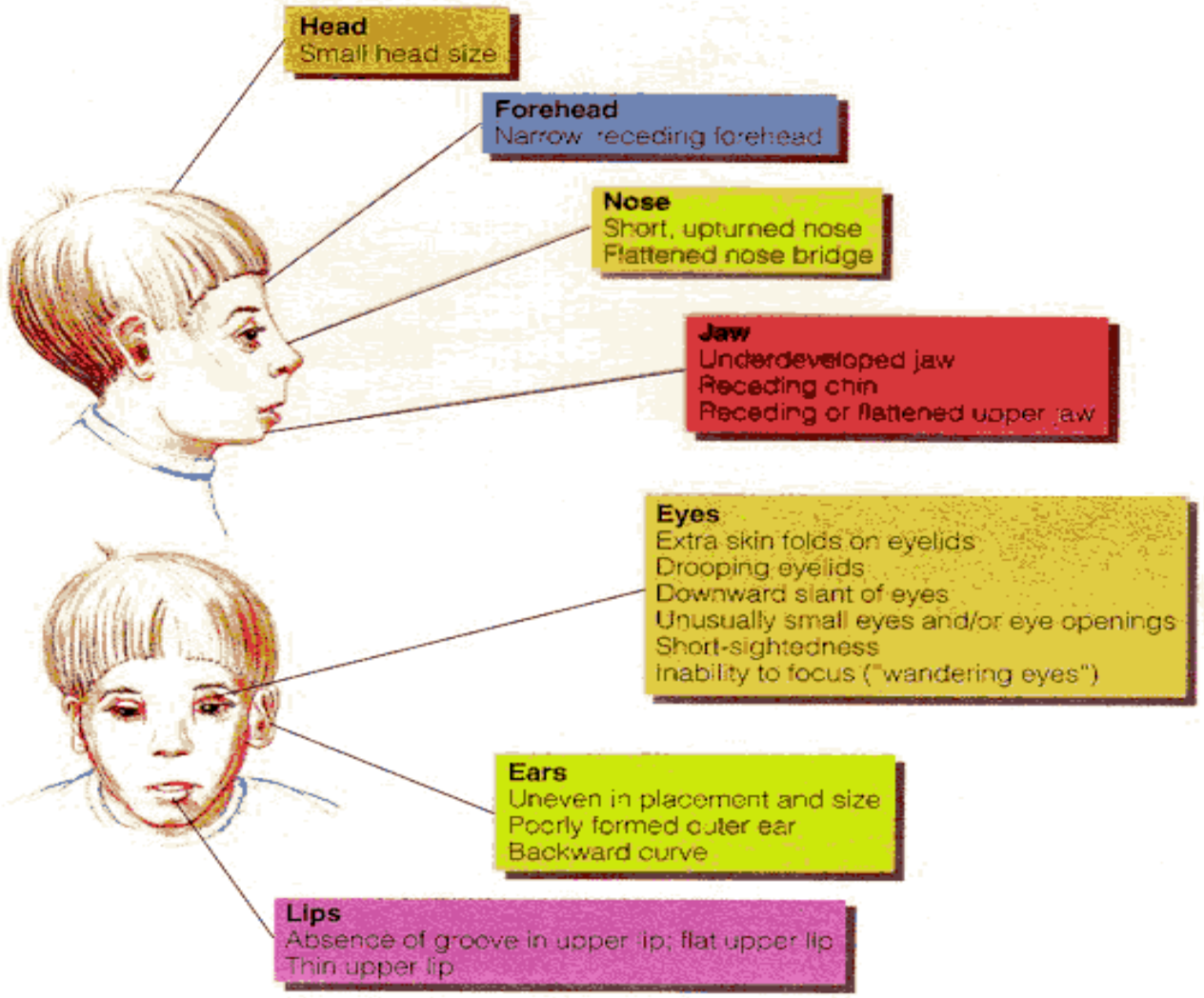
1. maternal alcohol consumption
2. craniofacial features (lack = spectrum diagnosis)
3. CNS dysfunction
4. growth retardation (pre- and post-natal)

- spectrum prevalence = 1 in 100

30,000 babies / year born with alcohol-related defects

- billions of dollars spent on treatment for these babies each year
- not all women who drink whilst pregnant produce children with FAS, genetics of Mom, child and also environmental circumstances (education, SES, time of consumption) are important
- alcohol can act very early in development (gastrulation) probably by changing methylation patterns (ie. epigenetically)
- some syndrome features produced by consumption later in gestation (eg. hyperactivity – may be produced by effect of alcohol on 3rd trimester brain growth spurt)

Typical Facial Characteristics of FAS



Lifetime rates of dependence

= history of dependence at any time in a person's life

- rates are increasing in younger cohorts
- there is tendency to earlier age of onset of dependence

  USA mean age of onset of alcoholism = 20

DSMIII-R criteria: USA prevalence of alcoholism

males = 20%

females = 8%

illicit drug dependence males = 9.2%

females = 5.9%

nicotine dependence ~ 20% in young adults (same both sexes)

- high rate of male alcohol dependence
- family risks are higher: first degree (sibling) relative risk = 50% males

  25% females

DSMIV criteria for substance abuse

- a maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring within a 12-month period:

  Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
- Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
- Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).

- Note: The symptoms for abuse have never met the criteria for dependence for this class of substance. According to the DSM-IV, a person can be abusing a substance or dependent on a substance but not both at the same time.

DSM-IV Substance Dependence Criteria

- Substance dependence is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by **three** (or more) of the following, occurring any time in the same 12-month period:

  Tolerance, as defined by either of the following: (a) A need for markedly increased amounts of the substance to achieve intoxication or the desired effect or (b) Markedly diminished effect with continued use of the same amount of the substance.

- **Withdrawal,** as manifested by either of the following: (a) The characteristic withdrawal syndrome for the substance or (b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
- The substance is often taken in larger amounts or over a longer period than intended.
- There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
- Important social, occupational, or recreational activities are given up or reduced because of substance use.
- The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (for example, current cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Subclinical use

substantial burden from those with no diagnosis:

- health effects – especially in women where health consequences accrue at low levels of consumption
- increased risk of driving accidents, violence
- decreased productivity
- increased risk of progressing to abuse and dependence, especially with early use (early adolescence) since use and disorders occur on a continuum
- Subclinical use has largely environmental influences

  some genetic influences on preference, reaction to alcohol

Behavior Genetic Human studies

Which has the greatest influence on drinking behavior?

friends? parents? genes? personal experiences ?

Depends on what age and what level of use we are discussing

at 14 - genes contribute very little, shared e = 40% of variance

at 23 – shared e contributes very little, genetic variance = 40%

Levels of use

1. Abstinence what influences a person to decide NOT to drink?
2. Initiation (onset of use) what influences a person to start drinking at a particular age? what determines the person's response to alcohol?
3. Progression to abuse and dependency

what makes a person increase quantity and frequency enough to lead to abuse and dependence?

1. Influences on decision to use alcohol versus abstinence

Most MZ and DZ correlations indicate very small gene effect

shared environment is large influence

family history

religion

cultural factors

access to alcohol

- environmental variables more important than genetic

- assortative mating for use spousal correlations = 0.38 – 0.45

  initial selection not shared e

  could inflate shared e estimates

  could create gxe correlations - both genetic and environmental risks experienced by children

2. Influences on initiation and use

- initiation (USA) typically early to mid adolescence
  initiation after mid-twenties is uncommon

ADD Health study (very large population sample)

Mean age of 1st use , 3 age categories

Early	9 -11
Medium	12-13
Later	14 -16

- for initiation, h^2 ~ 26%, shared e ~ 65% (Fowler et al 2007)

Shared sib and peer environment more important than parent

McGue et al (1996) J. Studies on Alcohol Disorders

adoptive sibs: reared together, not biologically related

biological sibs, parents all rated for drinking behavior

Adoptive sibs, age 12-18 same-sex, < 2 years apart in age r = 0.45

opposite-sex, > 2 years apart r = 0.05

adoptive P/O r = 0.04

P/O biological children = 0.30, so parental contribution genetic not environmental

Influences on level of use

- majority will try alcohol (and tobacco)

- age of initiation and how rapidly use escalates is more important than use itself for predicting future problems

- for most, environment moderates use in young adults
  marriage career
  responsibilities multiply
- use is higher in more 'permissive' environments: unmarried, lack of religious upbringing, less strict, less close families, regions of high alcohol sales, more deviance in peers

So far - most influences have been environmental

Where do genetic risk factors enter into this?

Some genetic influence on onset of use
genetic variants of cholinergic nicotinic receptor gene cluster
- genes code for various subunits of nACh receptor
- influence onset of use of tobacco, alcohol, cannabis, other drugs

3. Progression of drinking towards abuse/dependence

Different people are going to have different risk factors for abuse/dependence

Response to first drink

Protective factors: genetic tendency for low preference

genetic tendency to react badly to alcohol

alcohol dehydrogenase alleles

3 categories of risk factors identified by behavior genetic research:

1. Hypersensitivity "whoa, this is awesome!"

- increased sensitivity to the stress-response dampening effects of alcohol may put some individuals at greater risk for alcoholism

measurable greater attenuation of cardio-vascular response to unavoidable shock in offspring of alcoholics compared to non-alcoholics, when given alcohol

+ other neurophysiological differences

eg. offspring of alcoholics show more relaxed, comfortable state after drinking

2. Hyposensitivity "what 'whoa'? maybe I need more?"

Why?

- lower response to stress dampening effects - may lead to overconsumption
- lack of feedback inhibition
- need to consume larger amounts to achieve perceived desired effects

tolerance is naturally high, even before much consumption

non-alcoholic sons of male alcoholics show reduced sensation of intoxication after standard dose compared to non-alcoholic sons of non-alcoholics (matched for drinking history)

within 10 years: 43% of alcoholics' sons were alcoholic
11% of non-alcoholics' sons were alcoholic

Sensitivity and tolerance to effects of alcohol are genetically influenced
- leads to increased risk for use disorders in some

3. Externalizing behavior

traits associated with behavioral disinhibition increase risk for alcohol use disorders

Conduct disorder
– puts individual at greater risk of encountering alcohol at an early age (environmental)
- lack of ability to inhibit risky behavior increases likelihood of early use and overuse (genetic)

Common genetic risks found in ADHD, other externalizing disorders

Ball & Collier,2002

14 year-old twins (Review of 9 twin studies)

Community-based (clinical samples give biased results through overrepresentation of severe & comorbid individuals)

1% met dependence criteria
3% met abuse criteria
13% met CD criteria males > females

for alcohol symptom counts: $h^2 = 0$, $c^2 = 80\%$ no sex difference

for CD symptom counts: $h^2 = 50\%$ in males 30% in females
$c^2 = 30\%$ in both sexes

correlation between CD and alcohol counts = 0.5 mediated by shared e

genes are not an important influence on early alcohol use

CD behavior, shared environment are important influences

other studies (McGue et al 2001) have reported higher heritabilites in boys for early drinking, but still large shared e

Early use of alcohol is predictive

Grant & Dawson (1997) National Longitudinal Alcohol Epidemiological Survey

27,000 ever-drinking adults

- those trying alcohol before age 15, lifetime rate of dependence = 4 times higher than those trying alcohol after age 20

Males: 55%
Females: 25%
} of those whose first drink was prior to age 14 became alcoholic

males, risk ~ 45% at 15, 14% after age 19

- early age of first alcohol use is a manifestation of generalized disinhibition (which has a strong genetic component)

early alcohol use was also associated with nicotine dependence, other drug use, ADHD CD later ASPD decreased levels of constraint
decreased educational attainment

Event-related potential endophenotype common to all externalizing disorders:

p3 amplitude – low amplitude correlates with age of 1st drink, predates alcohol use predicts onset of new SUDs h^2 = 60-65%

- alcohol use is NOT causal in CD behavior

4. Alcohol abuse and dependence

- typically onset is late adolescence, early adulthood
- factors affecting abuse and dependence seem similar
- differences in diagnostic criteria between DSMIII-R and DSMIV make little difference in estimates of heritability
- studies on adult community-based samples produce consistent results
- studies on younger cohorts give less consistent results and have focused on studies of quantity & frequency rather than abuse & dependence criteria, but not always looking at age of use
- heritability rises and shared e influences get less as age of ascertainment goes up

Dutch longitudinal twin sample (van Beek et al,2012)

Heritability for alcohol abuse and dependence

Age	15-17	18-20	21-23	30-32
h^2	28%		58% →	
c^2	57%	18% →		
e^2	15%			48% →

Evidence for **same** set of genetic factors acting at all ages

- other factors are important at different ages, modifying heritability

Adoption studies confirm size of genetic influence – no correlations in adoptive parent-offspring

Adult, community-based twin studies - heritabilites

Criteria		Abuse	Dependence
DSMIIIR	males	55%	49%
	females	56%	50%
DSMIV	males	58%	51%
	females	66%	59%

Remainder of variation was e^2, no c^2 found for lifetime abuse or dependence, no sex differences

Results are supported by adoption studies – the adopted away offspring of alcoholic parentage retain higher risk

Samples that include only people who have sought (or been court-ordered to seek) treatment do show shared e:

abuse	h^2 = 48%	c^2 = 34%	e^2 = 18%
dependence	= 63%	= 17%	= 20%

Adolescent/young adult studies report lower heritabilities and more shared environmental influences

Sex differences in genetics of alcohol abuse/dependence

- heritabilities for males and females look similar in recent studies but past studies show inconsistencies, males more frequently found to have higher heritability
- studies of opposite-sex DZ pairs indicate a low correlation for genetic effects r = 0.24

  - this indicates gender-specific genetic factors

Subtypes of alcoholism

1. Early and late onset alcoholism

Age of onset = person's age at first symptom

Early onset = age 20 or younger

Late onset = age 21 or later

McGue et al (1992) clinical sample from treatment centers

Dependence	Males			Females		
	h^2	c^2	e^2	h^2	c^2	e^2
Early onset	73%	23%	4%	0%	73%	27%
Late onset	30%	37%	33%	0%	53%	47%

- genetic influences are less for later onset alcoholism – found in several studies

In this sample:

- environment (both $e^2$and c^2)is more important in male late onset and late and early onset in females
- no genetic influence in females
- age of first drink correlated with dependence but less with abuse

dependence - 29% of total variance accounted for by age of first drink, both in males and females

abuse – only 12% in females, 3% in males

not all studies, therefore, indicate raising age of first drink would reduce alcoholism

2. Type I no tendency towards aggression when drinking

Type II 20-50% alcoholics display alcohol-related aggression

more common in males higher heritability

associated with variation in 5HT genes influencing 5HT and GABAergic neurotransmission, increased amygdala activity, impaired prefrontal function – predisposes to increased intake, impulsive aggression, intake increases impaired executive function → facilitates aggressive behavior further

Genotype/environment interaction

Cloninger, Swedish adoption data:

Type I alcoholism 3% prevalence

+ve biological background → -ve adoptive home 10-11% risk

+ve biological background → +ve adoptive home 27% risk

Type II alcoholism 2% prevalence

no change in risk with adoptive home risk = 17-18%

Role of genes in use and abuse of alcohol

Animal studies mice rats Drosophila

psychopharmacogenetics genetic effects on behavioral responses to drugs

Rodents

selection, cross-breeding, inbred-strain studies all indicate genetic influences on every aspect studied :

- preference for alcohol (C57BL/6 high, DBA/2 low preferrers, can select for it)
- susceptibility to withdrawal symptoms (rate of seizures depends on genotype)
- response to alcohol (short and long sleeptime selected lines)
- development of tolerance (selected short sleep mice can take 4.2g/kgbody mass & show no sleep response - equivalent to drinking 1 quart hard liquor in a human & showing little effect)
- alcohol-related aggression (response to alcohol depends on genotype)

Gene knock-out studies:

DRD2 knock-out – reduced alcohol preference (throughsupersensitivity)

HTR knock-out – increased alcohol consumption

μopioid receptor knock-out – reduced consumption, since alcohol works via the receptor to increase dopamine

PKCε knock-out - reduced alcohol and nicotine consumption and reward

Genes associated with risk for alcoholism in humans

Genes controlling alcohol metabolism in the liver:

alcohol dehydrogenases (ADH)

chromosome 4

possible protective alleles

influence consumption

aldehyde dehydrogenases

ALDH2(mitochondrial) chr 12

more powerful effect

since this is rate-limiting step

Acetaldehyde causes DNA damage - some repair, depends on genotype

- thought to be one of mechanisms behind fetal alcohol syndrome, deficits of lesser kind in offspring of drinkers

- also causes bone-marrow failure and cancers throughout body

ALDH 2 acetaldehyde dehydrogenase

one of the most transparent gene influences on behavior

- *2 allele of ALDH 2 gene (chromosome 12) has protective effect against alcoholism since it produces ‘flushing’ response when alcohol is consumed and acute intoxication
- allele is only present (>1%) in Asian populations

Japanese males

ALHD 2 genotype	*1/*1	*1/*2	*2/*2
population	58%	35%	7%
alcoholics	88%	12%	0%

*2 homozygotes – strongly protected against alcohol abuse

*2 heterozygotes – can develop tolerance for acetaldehyde, less protected

Unemphasized but important fact:

*2 allele also raises risk of digestive system and other cancers due to acetaldehyde build-up

esophageal cancer x6-10 risk with even moderate drinking

ignoring flushing response not recommended

More alcohol pharmacology

- more complex than other drugs

sedative
ataxic
anxiolytic effects
} mediated through GABA glutamate signaling

reward properties
- euphoria
- psychomotor stimulation
} mediated through endogenous opioids, mesolimbic dopamine

Understanding mechanism of action can help with development of new treatments

μ opioid receptor (OPRM1) blockade being developed as treatment

OPRM1 genotype determines response

Variation in genes within pathways is likely to effect vulnerability to overuse, addiction, response to treatment

Current treatments

Antabuse (disulfiram) has same effect as *2 allele (ALDH blocker)

Naltrexone binds to μ opioid receptor to block dopamine release as a result of alcohol consumption

Acamprosate functional glutamate antagonist

Replicated genetic effects besides ALDH

GABA-A receptor genes

- chromosome 4p
- GABA is major inhibitory neurotransmitter in human CNS
- GABA is involved in many behavioral effects of alcohol
- strong association of GABRA2 alleles with alcohol dependence

Nicotinic acetylcholine receptors CHRN A and B genes

- alcohol dependence frequently co-occurs with smoking
- evidence for shared genetic vulnerability
- CHRNA5 gene associated with both dependences

Dopamine system DRD2 and DRD4

- alleles of both genes may have effects on severity of alcoholism as well as overall risk

association 69% of alcoholics carry A1 allele in region of
20% of non-alcoholics DRD2 locus

Legalize drugs?

- is the current ‘war on drugs’ working to reduce drug use and addiction?
- or is it just serving to give us the largest per capita prison population in the world?

1917 - government estimates 1.3% of US population addicted

1970 - ‘war on drugs’ started under Nixon

- at this time, 2% <12 yrs old had tried illegal drugs and overall 1.3% addiction rate

2003 - 46% <12 yrs old had tried illegal drugs (2300% increase)

- over 1 trillion dollars, more people imprisoned per capita than any other country in the world, and 39 million arrests later

in 2008 government estimates 1.3% of us are addicted

DISCUSSION PAPER SERIES

IZA DP No. 6112

Medical Marijuana Laws, Traffic Fatalities, and Alcohol Consumption

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