CRAVING - NEUROBIOLOGY AND THERAPEUTIC APPROACHES IN ALCOHOL USE DISORDERS

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Abstract: *Craving plays an important role in addiction and correlates with vulnerability to relapse and with the severity of alcohol dependence. The allostatic burden of chronic alcohol misuse in relation with genetic and environmental factors may explain craving and alcohol-seeking behaviours. Better understanding of the neurobiology and pathophysiology of craving may improve therapeutic approaches, thus reducing craving is becoming an increasingly valued perspective of treatments for alcohol use disorders. Here, we review some important aspects of neurobiology of craving and summarise some therapeutic implications targeting craving reduction.*

Craving, as a subjective statement, has a multidimensional approach; there are multiple definitions attempting to describe the intermediary states between the healthy desire to drink and pathological compulsive urge to use alcohol. Terminology used to describe craving refer to psychological, behavioural, autonomic responses to a subjective experience and its temporal dynamics are described as continuous or discontinuous, pulsatile, phasic or tonic. Difficulties proposing a standardised and uniform definition for this heterogeneous concept correlate with challenges in finding a valid and feasible method to evaluate and measure craving.

Nevertheless, craving has been included as a diagnostic criterion for alcohol use disorders in DSM 5, as it has been in ICD-10. This emphasises the core role played by craving in the complexity of addiction. There are multiple studies linking craving to relapse and severity of alcohol use disorder; the COMBINE multi-site clinical study among 1370 patients with alcohol dependence in USA, showed that for each 1-unit increase in the craving scale, the likelihood of drinking in the following week was 31% higher. Routinely assessing craving using simple self-report scales is becoming a part of addiction management plan in clinical practice.(1)

Research on craving may contribute to an improved knowledge and understanding complex neurobiology of alcohol related disorders. Neural processes underlying craving and relapse are complex and reflect the neuroadaptative changes (due to allostatic load after chronic alcohol abuse), interacting with genetic and environmental factors. Reducing or even reversal of craving has become an increasingly important goal of addiction therapeutic approaches because is viewed as an opportunity to prevent relapse and interfere with the chronic course of addiction. Many studies focus on craving therapy and many pharmaceutical, psychotherapeutic and other complementary methods, single or combined, were proposed and used in addiction treatment. Results were so far mostly inconsistent, with few significantly useful in clinical practice.

Craving and mechanisms of alcohol dependence

Identification of brain activity associated with craving

Craving refers to a pathological motivational state that usually precedes the addictive behavior (compulsive seeking of drugs in order to obtain and use them). Understanding the neurobiological basis of craving is essential for understanding the pathophysiology of addiction. Moreover, measuring physiological correlates of craving, instead of relying on self-report, could provide a better index of treatment response.(2) Functional Magnetic Resonance (fMRI) can identify specific brain regions that become active with presentation of drug-use cues or during the subjective experience of craving.

There are three methods used to induce craving:

1. presentation of videotapes of people using drugs;
2. directed recall of past drug experiences;
3. pharmacological stimulants

The following facts were observed:

- Activation of anterior cingulate gyrus through video cues and pharmacological stimulants.(3,4,5,6)
- Activation of dorsolateral and orbitofrontal cortex with video-cues.(4,7,8)
- Other studies using video-cues have shown activation of the amygdala and the temporoparietal or peristriate areas (5,7)

Studies using pharmacological stimulation showed activation of nucleus accumbens, subcallosal cortex(3) or the striatum, cerebellum, thalamus.(6)

These craving-related activations of specific brain regions have at least two physiological links:

a. an association of craving with differential activation of limbic structures with important roles in motivation and affect;
b. many of these regions are part of or receive input from the mesoaccumbens pathway which appears to be important for the reinforcing effect of cocaine in animal studies.(9)

It is important to note that these are not the brain regions most consistently activated in imaging studies of emotions in healthy individuals, i.e. medial frontal cortex - superior frontal gyrus following presentation of stimuli that evoke either happy or sad emotions.(10,11,12), or thalamus, hypothalamus, caudate nucleus, putamen, amygdala primarily activated in response to fear-associated stimuli.(13,14)

The remarkably limited overlaps between the regions

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active during positive or negative emotional normal responses and those active during the pathological motivational stage of craving suggest a fundamental neurobiological difference between craving and normal emotional states.(2)

The question arising is if the brain activation during craving is definitely different of brain activation during other emotional states. Is the susceptibility to craving associated with other abnormalities in emotional response?

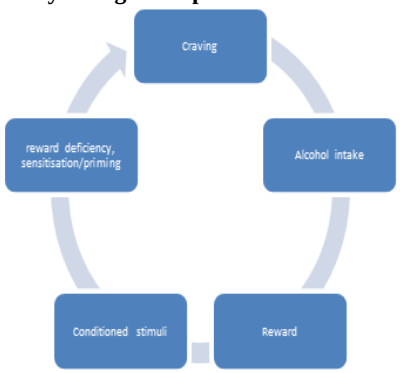
The answer may delineate from the fact that cues related to cocaine use lead to abnormally high cingulate and low frontal lobe activation in cocaine addicts. These activations appear to be specifically associated with the drug-taking experiences of the addicts and precede the self-reported onset of feelings of craving. Addicts also show more general abnormalities in affect-related brain activation.(2)

Mechanisms of alcohol dependence - therapeutic connotations

Cyclic interactions and overlapping of neurobiological and psychological mechanisms of addiction translate in treatment difficulties and maintain the high relapse risk and chronic course of the disease.

The psychological dependence is viewed from a behavioural perspective as a result of positive reinforcing and is probably sustained through opioid / dopaminergic mechanisms (figure no. 1).

Figure no. 1. Psychological dependence



Rewarding effects of alcohol may be mediated by dopamine and opioid systems.

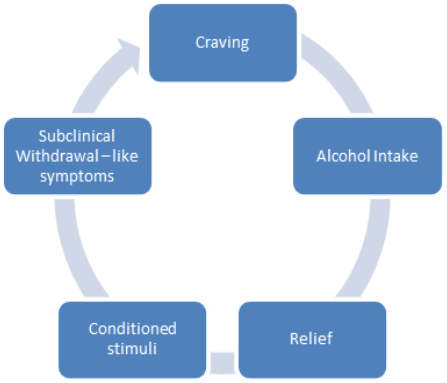
Acute alcohol intake induces increased dopamine transmission in reward brain circuitries. Ethanol stimulates dopamine release in mesolimbic reward pathways (nucleus accumbens) through endogenous opioid system.(15) Chronic alcohol abuse was associated with dysregulation of reward-related brain processes, thus perpetuating the increased vulnerability to relapse through craving, altered decision-making, alcohol-seeking behaviors. Studies targeting craving using dopamine modulators (antipsychotic agents - Olanzapine, Quetiapine, Aripiprazol) showed limited effect on craving and relapse, athough they exhibited some benefit especially in patients with comorbid psychiatric disorders.(15) Opioid system targeting agents will be discussed further.

Physical dependence would be the result of negative reinforcement from a behavioral point of view and sustained probably by GABA/glutamatergic mechanisms (figure no. 2).

Withdrawal symptoms associated with alcohol use may be associated with GABA – and glutamatergic systems.

Serotonergic pathways are dysregulated in alcohol addiction, although there is an inter-individual variation. Altered serotonin modulation occurs both in acute and chronic alcohol exposure and may explain the anxiety, mood dysregulation, withdrawal symptoms, obsessive thinking and behaviors related to craving.(15)

Figure no. 2. Physical dependence



There are studies showing that serotonin levels in nucleus accumbens, prefrontal cortex, striatum are elevated in acute exposure and decreased after 1-7 weeks post ethanol exposure, correlating with anxiety, negative emotions induced craving and relapse. SSRI (fluvoxamine, citalopram, sertraline) showed some eficacy in reducing alcohol consumption, craving and preventing relapse, especially in patients with comorbid depression and in type A of alcoholism (as proposed by Babor and collegues). Aripiprazole (atypical antipsychotic with 5-HT 1A/2A partial agonist/antagonist activity) showed some efficacy in reducing craving and heavy alcohol intake.(16)

Do insensitive pleasure centers lead to addiction?

Individuals who respond only at higher doses may have insensitive pleasure centers, therefore external substances have greater effect on those centers, are more reinforcing and patients seek repeated exposure at high doses to achieve a "normal state" (pseudo – normal state). Responders (especially with euphoria) to low doses of substances are less likely to become abusers. Those responding only at higher doses are more likely to become abusers, hence repeated exposure to larger doses is necessary for the effect of a "high" – this may lead to dependence and addiction. Insensitive pleasure centers may not mediate substance abuse, but may link substance abuse with psychiatric disorders.

Brain areas contributing to dependence may include the frontal cortex, amygdala, and hippocampus.

Alcohol: a promoter of stress?

Regulatory agents of stress (e.g. CRF, NPY) may be altered by the alcohol abuse. Bottom line is that increased CRF activity and decreased neuropeptide Y (NPY) activity in the amygdala and / or bed nucleus of the stria terminals (BNST) may mediate the increased consumption of alcohol associated with acute withdrawal and protracted abstinence.(17)

Potential pharmacological treatments

- Aversive drugs: Disulfiram
- Opioid receptor antagonists (Naltrexone, XR - NTX) - to block the euphoria and make drinking less pleasurable
- NMDA / GABA agents (Acamprosate) – to reduce craving
- 5-HT antagonists (off-label)
- Topiramate (off -label)

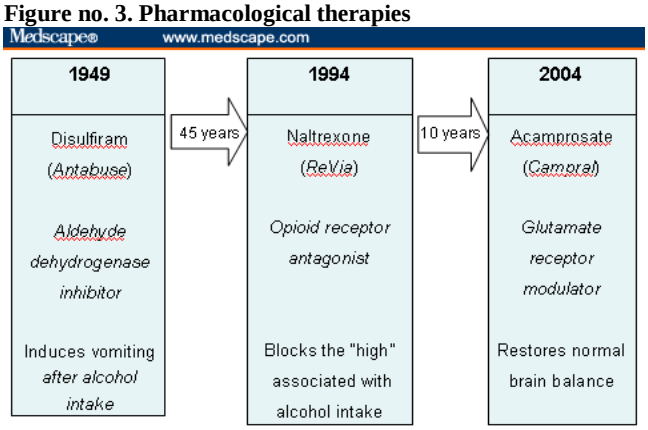
Disulfiram

- Action: Irreversible inhibition of acetaldehyde dehydrogenase which converts alcohol to carbon dioxide and water. If alcohol is taken, this creates toxic levels of acetaldehyde in the bloodstream causing unpleasant symptoms like headache, nausea and vomiting, flushing, tachycardia. It may also block dopamine B hydroxilase, increasing dopamine and decreasing noradrenalin, with consequent reduced craving.
- Patient adherence is crucial for benefits; compliance is increased if the taking of the drug is monitored by another

person (e.g. spouse, relative).

- Dose: 250 – 500 mg on alternate days; - one year duration.(18)
- Side effects: rare reports of hepatotoxicity and psychotic reactions.

Figure no. 3. Pharmacological therapies



Naltrexone (NTX)

Action: Beta – endorphin antagonist and opioid receptors antagonist. Blocks the effects of endogenous endorphins released by alcohol intake. Reduces dopamine release at the nucleus accumbens. Reduces "positive reinforcement" and "reward" of alcohol consumption.(19)

Dose: 25 mg/day initially (one week), maintenance 50 mg/day.

Side effects: nausea, headache, anxiety, fatigue, flu-like symptoms, sleep disturbances, sedation. A dose – related hepatic effect was described, therefore transaminase levels are to be determined monthly for the first 3 months, and then quarterly.

Contraindication: poor liver function, ongoing or recent opioid use.

The risk of relapse with oral NTX was evaluated by previous studies.(20,21,22,23,24,25,26,27) With oral NTX, most effects were seen on number of drinking days, number of heavy drinking days, number of patients who engage in heavy drinking, latency to first heavy drinking day. Beneficial effects were seen mostly in patients who take 70 – 90% of the medication. Adherence is an important factor.(28)

Most common adverse effects are sedation, nausea, headache, anxiety.

As ways to improve adherence to NTX, there are mentioned the following:

- Increase patient beliefs in efficacy of NTX, convey a positive attitude;
- Manage side effects: - fatigue (take dose at bedtime); - nausea (take with food/antacids.)
- Long-acting injection (XR - NTX): 380 mg/month, may increase compliance; approved by FDA.(18,19,29)

Acamprosate

Action: may interact with glutamate and GABA neurotransmitters to restore a "healthy" balance. It may enhance GABA transmission in the brain.

Actions (if any) on NMDA receptors are not consistent; it is believed that Acamprosate does not have direct effects on NMDA receptors, rather, these effects may be mediated by metabotropic glutamate receptors (mGlu rec.) ; it appears to act as antagonist on group 1 mGlu rec., specifically mGlu5 and perhaps group 2 mGlu rec. as well. Has neuroprotective properties that may result from interaction with mGlu rec. mGlu rec. are G – protein – coupled receptors. Group 1 (mGlu rec. 1, 5), with postsynaptic primary location, regulate neuronal excitability via ion channels; antagonists to this group are neuroprotective.

Activation of group 2 (mGlu receptors 2, 3) receptors may inhibit glutamate release in response to high concentrations of glutamate.

Dose: administer before meals/on empty stomach; - patients >60 kg, 666 mg 3x/day; duration 6 – 12 months.

Was found most effective and was approved in maintaining abstinence; (30) – in a meta-analyse comprising 11 studies, during 1996 - 2000) determined that Acamprosate had the best abstinence rate.

Placebo controlled pivotal studies concerning Acamprosate vs. placebo in complete abstinence, respectively for days abstinence determined the following results:

- 37% vs.13% at 13 weeks, at 1998 mg/day; 65 vs. 29 days (31,32)
- 27% vs. 13% at 48 weeks, at 1998 mg / day; 75 vs. 35 days (31,33)
- 15% vs. 8% at 52 weeks, at 1998 mg; 81 vs. 65 days (31,33)

The combination therapy Acamprosate + NTX significantly increased the rate and extent of absorption of Acamprosate, in the absence of negative interactions:

- 33% increase in maximum concentration
- 33% reduction in time to maximum plasma concentration
- 25% increase in area under plasma concentration – time curve

All patients included in this study also received behavioral therapy.(34,35)

Ondansetron

Action: 5-HT3 antagonist; decreases dopamine release and, therefore, positive reinforcement / reward.

Is not FDA approved, has greater efficiency for early – onset dependence and type 2 alcoholism.

Dose: 4 micrograms/ kg twice daily.

Topiramate

Action: glutamate AMPA receptor antagonist; reduces positive reinforcement resulting from alcohol consumption and may reduce craving for alcohol, number of drinks consumed / day

Is not FDA – approved, might be useful as an adjunctive agent (18,19,29)

In a Topiramate vs. placebo, 12 week, double-bind, randomised, placebo control trial (n = 150), with Topiramate escalating dose schedule, receiving from 25 – 300 mg/day, the following results were found:

- Baseline: 20% topiramate. vs.25% placebo days abstinence
- Endpoint: 42% vs. 16% respectively.(36)

Another problem might derive from the interpretation of the interactions of pharmacotherapy with psychotherapy, since there is evidence that psychotherapy may reinforce the effects of medication.

The skills to avoid or cope with drinking triggers learned in therapy may have contributed to the reduction of drinking and self-reported craving severity across treatment groups. Certainly, further research is needed concerning the interactions between psychosocial interventions and pharmacotherapy.

The role of cues

Cues associated with drinking are known to act like a priming dose of alcohol and to elicit an appetitive motivational response through conditioned endogenous opioid release.

This response in anticipation or actual receipt of alcohol is effectively blocked by naltrexone.

Naltrexone works in maintaining abstinence and,

moreover, seems to be superior to Acamprosate.(37,34,35) Naltrexone might be efficacious in the maintenance of abstinence, and moreover, this hypothesis was reinforced by the results of the meta-analyses.(38,39)

The role of craving

Craving, as one possible target of pharmacotherapy, plays a core role in understanding pharmacological prevention of relapse in patients with alcohol use disorders. Further research on craving may develop new effective treatment for alcohol addiction.

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