



Neurobiological Evidence in Alcohol Addiction Can Help Pharmacological Treatment Personalization

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Introduction

Addiction is a burden disease that affects a wide part of the world population and is the most harmful form of abuse for users and for society [1]. Nevertheless pharmacological treatment for alcohol use disorders (AUD) have a modest efficacy and none of the molecules accepted in North America and Europe (Disulfiram, Naltrexone, Acamprostate, Sodium Oxibate, Nalmefene) can be considered a gold standard for the treatment of alcohol use disorders [2-7].

On the light of this consideration many researchers are underlying the importance of personalization in pharmacotherapy by matching patient features with drug hallmark as a strategy to improve the efficacy of the treatment [3,6]. In the perspective of personalizing treatments, the chance to include our neurobiological knowledge, though challenging, can't be overlooked.

Indeed, in the last years, thanks to neuroimaging non-invasive techniques, we had the chance to explore the central nervous system involved with the genesis of addiction and speculate on new interpretative models [8]. In particular the scientists agree on the presence of two complementary pathological neurobiological alterations: on one hand the improvement of positive reinforcement and negative reinforcement as drive mechanisms toward the use of drugs of abuse, and on the other hand the lack of control ability due to cognitive prefrontal control deficit and changes in thalamic-cortex circuitry of habit [9].

This article tries to match clinical features corresponding to specific neurobiological pathological addiction and pharmacotherapy of alcohol use disorders as a new frontier of personalization of treatment.

Personalization of pharmacological treatment

Between the few alcoholism pharmacological treatment guidelines, the most renowned are NICE (National Institute of Clinical Excellence) Guidelines [10] that identify Naltrexone and Acamprostate as the first treatment line due to the presence of a high level of efficacy. Recent international reviews adopt the same position [5,11] but there are also other points of view that highlight the value of Sodium Oxibate and Disulfiram for the treatment of AUD [6,12,13].

In particular Skinner review article concluded indicating the blind studies with placebo as an incorrect methodology to research Disulfiram efficacy and, based on results with open-label studies, pointed out that Disulfiram is a safe and efficacious treatment compared to other pharmacological treatments for AUD [13]. The Leone et Al Cochrane Review establishes that Sodium Oxibate is better than Naltrexone and Disulfiram in maintaining abstinence and these side effects are not statistically different from those with BZD, NTX or Disulfiram [14]. Moreover Caputo et Al, analyzing 20 year of Italian physician experience with Sodium Oxibate treatment clarifies that the drug is safe if it is used at therapeutically dosage and under medical supervision [15]. On the light of these considerations there aren't efficacy based criteria or side

effects based criteria for choosing between the four abovementioned molecules, that have got the same treatment indication (maintaining abstinence from alcohol or preventing relapse) but widely different mode of action. Personalization of treatment is therefore suggested by many authors as the correct approach to alcoholism pharmacological treatment [3,6,16].

On the light of this consideration neurobiology of addiction and in particular of alcohol dependence can give us a key to differentiate the clinical use of these four drugs and can be added to other matching variables for treatment personalization as psychiatric and internal comorbidity and typology of alcoholism and craving.

Neurobiological Evidence

Behavioural control is not only a cognitive function but depends on the dynamic and interconnected relations between reward impulsive system and control inhibitory system [17]. The first involves basal ganglia and limbic system and sustain hedonic state, gratification and motivations to act, the second involves prefrontal cortex and cortico-striatal connections and sustain regulation of drives, anticipation of adaptive behavioural strategies, integration of drives to act and personal goals [18].

Chronic alcohol abuse causes critical changes in neural reward and motivational systems, and simultaneously induces deficits in inhibitory control [19]. These neurobiological adaptations are thought to account for compulsive alcohol use despite negative consequences and for the emergence of negative emotional state when the alcohol blood level decreases [9].

The progression of alcohol dependence consists in a worsening dysfunction of the interconnected reward and control circuits, which becomes increasingly imbalanced [19].

Drive System Disregulation

Positive reinforcement

This theory focuses on enhancement of dopaminergic mesolimbic-cortical circuitry of gratification by alcohol repeated consumption. In particular there is an increased dopamine transmission in the nucleus

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accumbens and associated ventral striatal areas [20] that initially mediates the gratification effect of drug and subsequently is able to increase salience and appetitive value of substance related stimuli [21]. This mechanism is called positive reinforcement of the drug. Alcohol related positive reinforcement is mediated by GABA_A receptor activation that induces a disinhibition of GABAergic neurons in the VTA and subsequently a disinhibition of dopaminergic neurons that project from the VTA to the NAcc [22]. Moreover alcohol promotes the release of endogenous opioid peptides within the mesolimbic dopamine circuitry [23] causing the disinhibition of dopamine release to the NAcc [24].

According with this theory the patient will look forward using alcohol to exert its hedonic effects with increased motivation and gratification due to positive reinforcement. In this case the pharmacotherapies that we can speculate to be more sensible to the neurobiological mechanism are two, depending on patient goal:

- if the patient goal is total abstinence: Sodium Oxibate, that exert an alcohol mimic effect acting on GABA_B receptor and GHB receptor that result in a disinhibition of dopaminergic neurons in ventral tegmental area neurobiologically [25].
- if the patient goal is consumption control: Naltrexone or Nalmefene that antagonizes opioid specific effect decreasing the rewarding effects of alcohol [26] and reduces alcohol and alcohol cues stimulated dopamine output in striatum [27] accounting for a reduction in positive reinforcement power.

Negative reinforcement

Chronic alcohol consumption is associated with several neuroadaptations: decreased activity of the mesocorticolimbic dopamine system determined by increases in reward thresholds [28], sensibilization of dynorphine system [29] increased deregulation of brain stress system [30], decreases GABA_A receptor function [31] and development of hyperglutamatergic state [32]. The clinical correlation of this neurobiological adaptation is chronic irritability, hyperkatifeia, malaise, dysphoria, alexithymia, loss of motivation for natural rewards [33] and increasing motivation for alcohol intake: this pathological mechanism is called negative reinforcement.

According to this theory, chronic alcohol consumption causes an alteration of the homeostasis of the reward/stress system by decreasing the reward threshold on one hand and increasing the responsiveness of stress system and anti-reward molecules on the other hand. This would determine the research of alcohol to rebalance the system. In this case the pharmacotherapies that we can speculate to be the more sensible to the neurobiological mechanism are:

- Acamprosate that prevents the increase in glutamate in the nucleus accumbens [34] and the escalation in the hyperglutamatergic state [35].
- Sodium Oxibate that restore homeostasis both potentiating dopaminergic hedonic activity (as described below) and through the conversion of Sodium Oxibate in GABA that activate GABA_A and GABA_B receptors obtaining anxiolytic and sedative effects [25].
- Novel molecules not yet approved that involve stress system (neuropeptide Y and CBR antagonist) [36].

Inhibitory System Disruption

In advanced phase of addiction, the disruption of orbitofrontal cortex, a brain region implicated in salience attribution and motivation,

results in compulsivity and the disruption of cingulate gyrus, a brain region implicated in inhibitory control and conflict resolution, results in impulsivity [37].

Moreover, the gradual engagement of dorsal striatum, in the place of ventral striatum, in response to alcohol related stimuli, is the neurobiological base of habitual compulsive alcohol use [38].

Chronic alcohol consumers show frontal brain regions biases that impact on reward circuitry [19] and worsen inhibitory control tasks [39] due to neurobiological degeneration, possibly linked to neuroinflammatory sequelae of alcohol-related chronic microglial activation [40], in the anterior cingulate cortex, dorsolateral prefrontal cortex, and orbitofrontal cortex [41,42].

According with this theory drug seeking habit, elicited by drug associated stimuli or emotional cues (both associated to drug reward through pavlovian conditioning), is divorced by patient goals and can rise automatically (not depending on conscious awareness) and in contrast with major cognitive intentions [38].

In this case, premising that the clinical severity of the disease is often high and a residential treatment could be needed, the pharmacotherapy that we can speculate to be more sensible to the neurobiological mechanism is:

-Disulfiram: due to habit neurocircuitry enhancement and cortical deficits, the behavioural control ability is greatly compromised and the aversive effect of Disulfiram can play a role in enhancing it [43,44]. In particular the patient can assume the medication in a specific moment of the day that can be free from alcohol related stimuli or emotional cues and gain a control improvement for the rest of the day. Moreover the good clinical practice expect that Disulfiram should be administered by a care giver that can help the patient to fill the gap of cortical deficit by daily brief medical management: from this perspective Disulfiram and care givers assume the role of extended mind [45] that supply neurodegeneration.

Combination Treatment

Since neuroadaptations often coexist in a single patient, we can find contemporary enhancement of drive system (through positive and/or negative reinforcement) and a lack of inhibitory ability. Thus it is rational to associate pharmacological treatment, in particular the association between Disulfiram and Sodium Oxibate [46], Disulfiram and Naltrexone [47] and Disulfiram and Acamprosate [48] have already been studied demonstrating their safety and efficacy [6,49].

Conclusion

Neurobiology is an important key to develop pharmacological treatment for alcohol dependence, especially focusing on the neurocircuitry target of pharmacotherapy. Since there is a strict connection, from a theoretical point of view, among neurobiological adaptations in both reward and control systems, and behavioural manifestation of addiction, this article has explored a possible rational match between medication and patient, based on the consistency between drug mechanism of action and patient behavioural manifestation derived from neurobiological adaptation. This scientific speculation needs experimental research to be validated. In the meanwhile, considering the absence of guidelines for pharmacological treatment personalization in AUD, this rational match could be taken in consideration for a good clinical practice.

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