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CONTEMPORARY FRAMEWORK FOR ALCOHOL CRAVING

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SUMMARY

Objective: *Fifty years ago, craving was defined as an "urgent and overpowering desire, or irresistible impulse", but subsequently, craving definitions have been modified by many authors and no unique definition of this phenomena, or a consensus in regards to its manifestation and significance exists. This review discusses the contemporary views of alcohol craving. Issues such as definition and different types, dynamics of craving, its mediators and moderators and clinical correlations are explored.*

Subjects and methods: *We focused on the literature search (MEDLINE, PSYCHLIT, and EMBASE) and new findings in the addiction field, especially paying attention on the study of craving.*

Findings: *There is growing evidence to suggest that craving is associated with different aspects of addiction (i.e. withdrawal, relapse) and clinical characteristics such as depression and anxiety. These different phenomena contribute individual differences in intensity, frequency and types of craving. At present, there are several different models to better describe the complexity of craving.*

Conclusions: *Craving is not an exact, precisely measurable value but it is rather an uncertain, descriptive phenomenon. Further research (biological, sociological and psychological) should be orientated primarily toward exploration of the relationship between environmental factors and personality variables and craving and its maintenance, with special attention to gender differences.*

Key words: *craving - alcohol addiction - models*

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INTRODUCTION

The researchers and clinicians dealing with alcohol-related disorders, in recent years have put the focus on the "craving phenomenon" (Drobes & Thomas 1999). Even though craving was described as a central component of alcohol dependency more than half a century ago, intensive research in the last decades have showed that this phenomenon is very complex and there exists the need for a multidimensional and integrative approach to its assessment (Jellinek 1955). Particularly, the Expert Committee on Alcohol and the Expert Committee on Mental Health of the World Health Organization (1954) defined craving as an "urgent and overpowering desire, or irresistible impulse". From then on, different authors have comprehended craving in different ways (i.e. Marlatt 1978, Kozlowski & Wilkinson 1987, Tiffany 1990). There in no unique definition of this phenomenon nor a consensus in regards to its manifestation and significance (Anton 1999).

The concept of craving comes from popular psychology and means the mental state (i.e. the desire for achieving a certain goal or feeling), which sometimes persists for months or years after alcohol abstinence is achieved. (Vukovic 2006, Mathew et al. 1979). International classification of diseases, version 10 (ICD-10 1992) includes craving as one of the diagnostic criteria of addiction, defining this term as a strong desire or compulsion to take drugs (i.e. alcohol). This definition points out certain aspects of craving, but does not make a clear distinction between desire, craving for alcohol and its compulsive use. Kozlowski and Wilkinson (1987) thought that researchers should limit the use of the word craving to particular cases of urges to use a drug (i.e. alcohol). In this way craving is a conscious feeling of a desire or uncontrollable impulse to take an alcohol (Verheul et al. 1999). In line with this is the Elaborated Intrusion Theory of Desire (EI), suggested by Kavanagh et al. (2005). EI assumes that the craving for alcohol is analogous to any other type of desire. Kavanagh considers craving to be a "conscious wish to obtain pleasure, to relieve discomfort or to engage in behavior associated with these outcomes" (Kavanagh et al. 2005).

Contrary to this, some authors have concluded that craving is an epiphenomenon (e.g. Tiffany 1999, Drummond et al. 2000). More specifically, it is an interpretation of relapses by the alcoholics themselves. According to Tiffany's cognitive processing model, craving can be labeled as non-automatic cognitive processes occurring merely when efforts to obtain alcohol are impeded (Tiffany 1999, Toneatto 1999). This formulation is interesting as it suggests an explanation for occurrence of craving after extended periods of abstinence.

It is clear that today's conceptual status of craving has no comprehensive etiological model that explicitly makes possible the distinction between correlates and/or the basic components of craving on one side, and its consequences on the other. Verheul emphasizes that craving for alcohol presents a wide concept which includes many aspects (Verheul et al. 1999). Firstly, there exists the urge for positive effects of alcohol (i.e. reward craving). Secondly, alcohol can be craved for the expected negative reinforcing properties when we talk about negative-reinforced craving. And thirdly, craving can be the consequence of the feeling of control lack over the use of alcohol (i.e. obsessive craving) (Franken et al. 2000, Verheul et al. 1999).

The aim of this review is to demonstrate the contemporary views of the craving phenomenon for the purpose of better understanding of addiction, it's nature and treatment possibilities.

CONCEPTUAL MODELS OF CRAVING

Contemporary theoretical framework of the craving phenomenon includes behavioral theories of classical conditioning, cognitive and motivational mechanisms, and anatomo-functional and neurobiochemical considerations (Vukovic-Simic et al. 2004).

Phenomenological models

From the phenomenological point of view, craving presents the symptom of addiction, in the same way as for example, lack of energy is a symptom of depressive disorder (Drummond 2001). Based on his clinical observation, Isbell (1955) differentiates physical ("non symbolic") from "symbolic" craving. The first type usually begins during the withdrawal phase, while the second begins later, during the prolonged period of abstinence. Moreover, Caetano (1985) believe that craving is likened to an obsession and compulsion. Modell et al.

(1992) agree with this assumption because they noted that many of the patients who abuse alcohol describe craving in a similar way. These authors assume that emotions which follow the craving for alcohol are similar to the phenomena in obsessive-compulsive disorder (OCD).

Behavioral and cognitive models

Singleton and Gorelick (1998) suggest the classification of craving models based on behavioral and cognitive theories. Behavioral models are based on the theory of classical conditioning. If for any reason, during the exposure to alcohol-related stimuli, the person does not consume alcohol, the phenomenon of craving appears. The three leading models of cue-reactivity are: (1) cue-reactivity resembles unconditioned alcohol withdrawal (Wikler 1948); (2) cue-reactivity is similar to the unconditioned alcohol effects (Stewart et al. 1984); and (3) cue-reactivity opposes the unconditioned alcohol effect (Siegel 1975). All these are described in terms of classical conditioning, cue-reactivity being a conditioned response (CR).

In contrast to the previous, it is assumed that cognition plays an important role in the development of craving. The cognitive models derive from the assumption that the reactions derived from the exposure to alcohol and/or conditioned stimuli which include different cognitive processes such as anticipation of pleasant feeling during the consumption of the alcohol, and the attitude of the person that he is not able to stop or deal with the appearance of the desire for the alcohol. Large numbers of cognitive models have been suggested, which Singleton and Gorelick classify into cognitive-behavioral models, cognitive model of urges and alcohol use behavior and neurocognitive models. In conclusion, all of these models attempt to explain the nature of craving, although no single model accounts for all aspects of this phenomenon (Vukovic et al. 2001).

Neurobiological models

During the last decade, the neurobiological basis of craving has been increasingly researched. Progress in the field of neuroscience, especially in functional brain-imaging techniques, has made better understanding of this phenomenon possible (Park et al. in press, Chang et al. 2006). Exposure to alcohol-related cues activates a wide range of brain areas including frontal and temporal cortex regions and limbic structures such as the anterior and posterior cingulate cortex (i.e. Lingford-Hughes et al. 2006).

Based on the accumulated data, neuroanatomical models were suggested, by which the researchers are trying to make a connection between certain aspects of craving for alcohol and specific neuronal systems (Vukovic et al. 2001). Among the first is the model of Modell et al. (1992). On the basis of the aforementioned literature, the model is based on the phenomenological similarities between alcohol addiction and an obsessive-compulsive disorder. In fact, craving may result from a driven obsession, from over-activity within the strio-thalamo-cortical neuronal loop. Also, the loss of control of alcohol use may be a driven compulsion resulting from the impairment of the basal ganglia/limbic striatal portion of this loop, caused by the acute dopaminergic effects of intoxication.

Recently, researchers are pointing out the significant role of specific neurotransmitter systems in the pathogenesis of certain aspects of craving (Verheul et al. 1999). Therefore, reward craving is related to dopaminergic/opioidergic dysfunction, relief craving can be the consequence of alteration of GABA-ergic/glutamatergic neurotransmission, while serotonin

deficiency is present at the basis of obsessive craving (Wrase et al. 2006, Szerman-Bolotner & Peris-Diaz 2007).

DYNAMICS OF CRAVING

Some authors accentuate the dynamic nature of craving (Drummond et al. 2000). In this framework, different types of craving are mentioned - for example linear, curvilinear or a discontinuous phenomenon; "trait" (i.e., a persistent, general desire, referred to as "craving-past") vs. "state" phenomenon (i.e., an instant desire triggered by cues, referred to as "craving-now") (Drummond et al. 2000, Ooteman et al. 2006). By using a structured instrument, Mathew et al. (1979) have found that the craving manifestation can be found on a continuum, not an all-or-none phenomenon, whereby the environmental and/or endogenous factors modify its appearance. The second option is that craving is a non-linear phenomenon, existing on the inverted U-curve of the classic Yerkes–Dodson law (Abrams 2000).

In regards to the circumstances of its appearance and time dynamics, we can differentiate two modalities of craving: basic and episodic craving (Drummond et al. 2000). Basic craving is experienced tonically, characterized by the state of stable balance during the day (Drummond et al. 2000), it is endogenous, neither provoked nor modified by external, environmental stimuli. Episodic craving indicates the appearance of sporadic attacks of intensive, throbbing desire for alcohol, generated and modulated by different environmental stimuli or specific affective states. The attacks of episodic craving are considered to be direct precursors of relapse (Shiffman 2000). The attacks of episodic craving are considered to be direct precursors of relapse (Marlatt 1990). The dilemma remains whether these two modalities of craving experience are qualitatively different or they are/they only exist only on different parts of the continuum. Anyhow, we should not disregard the fact that with different people there are different fluctuations of intensity of craving during different time periods.

MEDIATORS AND MODERATORS OF CRAVING

Different contextual variables intensify or eliminate the connection between craving compulsive use of alcohol and therapeutic outcome, and their interaction presents one of the possible reasons of inconsistent results of the studies about the predictive value of craving. Research is pointing out the significant degree of heterogeneity of the factors influencing craving (Vukovic 2006).

External stimuli

Quality and intensity of craving vary depending on the presence/absence of different environmental stimuli or clearly defined experimental conditions (Vukovic 2006). Exogenous stimuli include environmental factors combined with alcohol abuse (i.e. sight, smell and taste of alcohol). In alcohol-dependent subjects, alcohol-related cues (audio-visual, tactile, olfactory, etc.) specifically increase craving and alcohol-like withdrawal (Reid et al. 2006, Lee et al. 2006). It is generally recognized that stress- and alcohol-related cues are the key factors which cause high relapse rates in addictive disorders.

A number of studies showed that stress had an important role in craving and relapse (Breese et al. 2005). Rajita Sinha summarized clinical evidence supporting the hypothesis that there is an increased sensitivity to stress-induced craving in addicts. In the early phase of abstinence, patients who were confronted with a stressful situation showed an increased

vulnerability to relapse (Sinha 2001, Breese et al. 2005). Fox et al. (2007) find different psychobiological correlates (including subjective emotional, cardiovascular, and cortisol responses) in alcohol cue-induced craving and in stress-induced craving. These results could have significant implications for understanding the neurobiology of craving and their possible effects on vulnerability to relapse.

Internal stimuli

Craving has been linked to several aspects of alcoholism and associated psychopathology (Yoon et al. 2006). The analysis of the relationship between craving and the clinical characteristics of dependent patients point out that severity of illness (Yoon et al. 2006), number of previous multiple detoxifications (Malcolm et al. 2000, Hillemacher et al. 2006), age (Turkcapar et al. 2005), gender (Vukovic 2006), anxiety (Lukasiewicz et al. 2005), and depression (Yoon et al. 2006) are the most significant predictors of craving. Ludwig et al. (1974) found that alcohol withdrawal symptoms amplified craving possibly as a homeostatic mechanism to lessen physical symptoms. The analysis of the role of gender is extremely important (Vukovic-Simic et al. 2004). Until now, there has been significantly little research done in regards to the relationship of gender and alcohol craving. In recently conducted research, we demonstrated that certain aspects of craving (obsessive component of craving) are more intensive in men during the early period of abstinence (Vukovic 2006). However, the analysis of gender differences in craving is complicated by hormonal status (Carpenter et al. 2006).

It is known that there are individual differences in the way of experiencing certain aspects of craving. Some authors consider personality as a major modifier of intensity, frequency and the type of craving (Verheul et al. 1999). Studies of cue-reactivity shed some lights on the relationship between certain personality dimensions and craving, showing a significant positive relationship between neuroticism and introversion and craving in alcoholics (McCusker & Brown 1991). Glautier et al. (2000) have found that the reward sensitivity (combination of Eysenck's neuroticism and extraversion) is a significant predictor of reactivity to alcohol related cues.

CLINICAL IMPLICATIONS

Predictive value of craving

Recent researches have confirmed that craving is the predictor of the treatment outcome (de Bruijn et al. 2005, Gordon et al. 2006). In fact, the ICD-10 criterion craving had the highest relative risk of all criteria for dependence at 1 year. Anton (1996) indicates that a positive correlation exists between intensity of craving and the probability of relapse, especially immediately after reaching abstinence. Also it has been found that craving in the first two weeks of abstinence positively correlates with relapse in the next 3 to 12 weeks, as well as that the craving for alcohol induced by negative mood is a predictor of relapse (Anton 1996).

Manifestations and craving intensity vary during the day, even hours, and with these phenomena have their own variable predictive value, depending on the moment in which it is measured. The significance of the timing of measurement of craving indicates that there exist critical determinants of its predictive value. It is possible that the amount by which craving fluctuates during hours, days, or weeks, presents a predictive factor in itself. For example, if

the average level of craving is relatively low, a person may experience it as a short, extreme "raffles" once per day, thus he carries a higher risk of relapse than if the level of craving is generally high and stable (that it does not fluctuate in time). The second possibility is that only craving correlates, but not the craving itself, are the predictors of relapse. Therefore, mediators and moderators of craving, like personality or gender, have a higher prognostic value than the experience of craving. Meszaros et al. (1999) have shown that the Tridimensional Personality Questionnaire (TPQ) has a clinical use for prediction of relapse of alcoholics. The same authors have found that the dimension Novelty seeking is a strong predictor of relapse in men, but not in women.

Pharmacotherapy

Many researchers have dealt with evaluation or with the efficacy of different medicament therapy in the treatment of addiction (especially alcoholism) and reduction of craving. Previous studies have showed that acamprosate, naltrexone, and possible selective serotonin reuptake inhibitors (SSRI) can reduce the rate of relapse and can also extend the period of abstinence of alcoholics (Jasovic-Gasic & Kunovac 1990, Vukovic et al. 2003, Kiefer & Mann 2005). It has been suggested that these effects are the result of the reduction of the intensity, frequency and duration of craving. However, particular subtypes of alcoholics could have different mechanisms on the basis of alcohol craving (Addolorato et al. 2005). According to the three-part neurobiological model (Verheul et al. 1999), naltrexone most likely reduces the rewarding aspect of craving (by blocking the opioid receptors), acamprosate reduces the relief craving (by reducing hyperexcitability which lies at the basis of withdrawal syndrome and/or anxiety), while SSRIs reduces the obsessive aspects of craving. Also, Kiefer et al. (2005) noted that different types of alcohol addicts might benefit from different treatment options (naltrexone vs. acamprosate). Current research suggests that at the basis of alcohol-effects lie different mechanisms which imply the complexity of neurobiological processes of the craving phenomena. For example, it has been found that there are differential effects of naltrexone and acamprosate. Naltrexone has the effect of reducing cue-induced craving (Ooteman et al. 2007). Acamprosate influences the glutamate and GABA systems in the nucleus accumbens, which may be responsible for the reinforcing effects of alcohol (Boothby & Doering 2005, Castro & Baltieri 2005). It is also assumed that acamprosate modulates both the endogenous opioid system and the mesolimbic dopaminergic system and may thereby decrease ethanol reinforcement processes (Cowen et al. 2005, Kiefer et al. 2006). For the purpose of distinct pharmacotherapeutic interventions, we have to take baseline psychopathology and typology differences into account. For example, applying Lesch's typology, acamprosate was mostly effective in type I, while naltrexone was shown to have the best effects in type III and IV (Kiefer et al. 2005). Ondansetron has shown some promises in early-onset alcohol dependence but needs more extensive study. Some studies of alcohol dependence showed that topiramate was more effective than placebo (i.e. Castro & Baltieri 2005).

Therapeutic efficacy is influenced by the presence of comorbidity (Petrakis et al. 2006). Alcoholics with comorbid depression support the efficacy of naltrexone in the relapse prevention of alcoholism amongst those with mild depression (Petrakis et al. 2005, Morley et al. 2006).

CONCLUSION

Clinical and experimental research has confirmed the validity of the craving concept. However, craving presents a descriptive notion, which is still not possible to measure with reliability and validity. New technological possibilities offer us a new way of research and a better understanding of the mechanisms that lie at the basis of craving and alcohol addiction in general. Today, animal models are used to achieve further understanding of neurobiological mechanisms, as well as the analyses which integrate neurochemical, neuroanatomical and genetic vulnerability. The use of functional imaging techniques, the fact that the era of processes led by subjective feeling has ended as well as the fact that the era of objective parameters has begun, are all aiding in defining the neuroanatomical basis of craving. It is clear that further studies about the influence of environmental factors and internal variables on the expression and maintenance of craving , are necessary as well as the analysis of gender differences in regards to the correlation between personality and craving phenomena. It is obvious that the concept of craving has been ignored for more than 30 years, only to experience its true "renaissance" in the field of interest, research, debate and discussion. Because of this, today we understand this phenomenon much more and we hope that in the near future we will know even more. Such progress will in fact help us both to understand further and to treat alcohol dependency.

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