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Naloxone and Ethanol Addiction Reinforcement

by

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Abstract

The research presented here explored the role of endogenous opioid mechanisms in alcohol reinforcement. Alcohol was introduced to naïve mice under food deprivation or ad libitum food availability three times. Deprived and non-deprived mice were administered naloxone or vehicle after each exposure to ethanol or water. The animals were subsequently given a two bottle test of alcohol preference. The animals exposed to alcohol under deprivation and given vehicle showed a preference for alcohol over all other groups. Animals given naloxone after exposure to alcohol while deprived showed lower alcohol preference and did not differ from controls. These data show that the enhanced reinforcing and incentive effects of alcohol when initially presented under high food need is blocked by the opioid antagonist naloxone and suggests that these motivating effects of alcohol are mediated in part by endogenous opioid systems. Naloxone in suppression of alcohol preference and intake may be an effective tool in the treatment of alcohol addiction.

Key words: Naloxone, Ethanol, Reinforcement, Dopamine, Opioid, Mouse.
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1.1 Statement of purpose

Recent figures from the National Institute of Drug Addiction indicate that alcoholism affects upwards of 17.3 million Americans, more than 6% of the total population. (“Nationwide trends”, 2015), and that deleterious health outcomes for individuals struggling with alcoholism are a strain on our national healthcare system (“Excessive drinking is draining the U.S. economy”, 2016). In order to create clinical programs that can cope more effectively with this issue, it’s essential to investigate not only the physiological changes that accompany addiction, but also the motivational changes that arise both as a consequence of and a determinant of addiction reinforcement. While current research has explored many of the external conditions that motivate reinforcement in alcohol addiction (i.e. incentive mechanisms), our understanding of the internal mechanisms that mediate these motivational factors and how intervention might disrupt these mechanisms remains an important research issue.

1.2 Defining addiction

To understand how addiction develops and is reinforced is to stand at the crossroad of motivation where issues of need, want, liking and other behavioral states intersect with physiology, neurochemistry, and genetics. It is a complex state that is difficult to unravel. This is further complicated by the fact that alcohol is the only drug of abuse that provides nutritional value - delivering around 80 calories per ounce - and that nutritional content may constitute up to 50% of the caloric intake of an alcohol dependent individual (Lewis, 1996). The mechanisms that mediate reinforcement of alcohol addiction are many and varied, and their study requires multiple behavioral and neurobiological approaches.
Neurochemical Mechanisms

Many neurochemical systems are involved in the development and maintenance of addiction such as glutamate (D’Souza, 2015), GABA (Tan et al., 2011), and cannabinoids (Maldonado et al., 2006); however, dopamine (DA) has been implicated most widely in neurochemical accounts of addiction (Wise, 1980) and its continued study has produced the most consistent and reproduced models of addiction reinforcement. Originating in the ventral tegmental area (VTA) of the brain, DA neurons then ascend through the nucleus accumbens (NAc) and ventral striatum to the prefrontal cortex (PFC) (Berridge & Kringlebach, 2015). In this way, the mesocorticolimbic DA system connects that which is most reptilian in the brain with that which is most singularly human. DA receptors (DAR) types are differentiated by their mode of action: members of the D1 receptor family are G-coupled receptor proteins which increase the concentration of cAMP in the cell, whereas members of the D2 receptor family are G-coupled receptor proteins which inhibit the formation of cAMP in the cell (Carlson & Birkett, 2016). Both types have been implicated in reward, motivation and addiction (many references).

A growing body of literature suggests that D2 receptor availability specifically plays a significant role in addiction. This includes genetic data: Bice et al. (2008) selectively bred high alcohol-preferring mice and then mapped their genome. Compared to control mice, high alcohol-preferring mice expressed lower levels of the gene responsible for the production of the D2 receptor. Additionally mice given chronic intermittent alcohol exhibit a massive loss of D2 modulation (Trantham-Davidson et al., 2014). Finally, this hypothesis is bolstered by clinical data showing that Type II alcoholics show lower striatal D2 receptor availability than healthy controls (Volkow et al., 2002).

While initially conceived of as the neurochemical most associated with pleasure in the brain, a waystation for the translation of stimulus into hedonic salience, many today believe that
DA may play a more limited motivational role (Berridge & Kringlebach, 2015). Some now believe that the mesocorticolumbic DA system may be a key part of our motivational system that encodes memories of reward experiences with events that preceded them (Volkow et al., 2017). With drugs of abuse like alcohol, the initial exposure produces an increase in striatal DA (Lewis, 1996), phasic activation results in widespread downregulation of D2 receptors (Volkow et al., 2017).

D2 receptor availability not only mediates addiction but eating disorders as well. This is not surprising, given the fact that addiction and food intake share a common pathway by way of the mesocorticolumbic system via the hypothalamus (Volkow et al., 2011). VTA DA neurons express receptors instrumental in the homeostatic control of food intake such as leptin, amylin, and ghrelin (Volkow et al., 2017). Clinically, subjects with morbid obesity were found to have decreased striatal D2 levels (Volkow et al., 2008), and, furthermore, that chronic high-fat diet consumption decreased the brain reward threshold as a consequence of D2 receptor downregulation, leading to the individual consuming more of the diet in order to attain the same level of reward (Reyes, 2012).

If changes in the DA system reflect changes in motivation, changes in hedonic tone may involve other mechanisms. Endogenous opioid systems have been hypothesized to play a role in the positive hedonic qualities of motivational stimuli. Endogenous opioid receptors are of four types - three “classical” receptors (mu-opioid (MOP) receptor, delta-opioid (DOP) receptor, and kappa-opioid (KOP) receptor) and one “non-classical” receptor (nociceptin orphanin FQ peptide receptor) - and are present in high concentration, among other locations, along the mesolimbic and mesocortical pathways associated with reward and motivation (Nutt, 2014). Pro-opiomelanocortin (POMC), a key opioid precursor, is of particular import to the study of
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addiction: it gives rise to β-endorphin. A neural system which projects from the arcuate nucleus onto regions associated with the mesolimbic DA system such as the VTA and NAc, β-endorphin binds to both MOP and DOP (Gianoulakis, 2001).

Research with other drugs of abuse (e.g. cocaine) has shown that activation of the D2 system recruits activation of an endogenous opioid peptide that binds to MOP (Soderman & Unterwald, 2009). Likewise, ethanol diets have been shown to “cause an increase in the maximum number of both μ- and δ-receptors in experimental animals” (Herz, 1997). Also the release of endogenous opioid in response to ethanol administration is similar to that of DA. Ethanol administration increases β-endorphin in the short-term which interacts with specific MOP and DOP receptors to mediate the neurobehavioral effect of the drug. Prolonged exposure to ethanol, however, results in a decreased β-endorphin release as an adaptive measure to counterbalance the effect of alcohol retain functioning at baseline levels which produces a hedonic change in the absence of ethanol (Gianoulakis, 2001). This change in hedonic quality may reflect neurochemical changes that occur with the development of physical dependence (withdrawal) with chronic administration of opioids. The presence of the withdrawal symptoms intensifies motivation leading to increased opioid intake and other aspects of additive behavior.

Motivational Mechanisms

The mechanisms in the development of addiction involve those that mediate changes with chronic administration (withdrawal) and motivation. One principle change is the activation of brain aversion systems that mediate negative hedonic effects produced by the absence of the drug of abuse. Whereas initial exposure activates positive reinforcement through increased DA and endogenous opioid receptor activation, prolonged exposure may lead to a homeostatic response to repetitive activation of reward systems producing aversion mediated by corticotropin-releasing
factor (CRF) and dynorphin in the amygdala. These responses are components of stress and may lead to other consequences in addition to aversion (Koob, 2017).

Over time, consumption of drugs of abuse that may have started as goal-directed behavior becomes habitual, leading to a significant change in motivation and a resistance to devaluation of the stimulus. This is mirrored by the change in positive reinforcement (seeking positive hedonic effects) to negative reinforcement (avoidance of negative hedonic effects) (Koob & Volkow, 2010). These motivational behavioral changes are enhanced by observed changes in neural connectivity: electrophysiological data of animals performing a food reinforced task showed dorsal medial striatum (DMS) activation during the acquisition phase of the experiment that transitioned to dorsal lateral striatum (DLS) activity during habitual performance (Everitt & Robbins, 2015). Changes in DLS DA signaling have been associated with cue-induced cocaine craving (Everitt & Robbins, 2015), and may represent a site of relevance to the negative affect that leads to feelings of need in avoidance of withdrawal.

Changes in incentive relevance accompany and make possible changes in need to consume drugs of abuse: the importance of environmental cues associated with drugs of abuse reflects a neurochemical imbalance that directed consumption seeks to rectify. The neurochemical imbalance focuses and enhances the effects of environmental cues that are associated with consumption of the drug of abuse. In this respect, we can understand compulsive drug use as a need of a kind similar to the need for food. As has been explored previously, drug reward and motivation pathways share neural connectivity with pathways mediating food consumption. In the same way that nutritional deficit motivates food consumption behavior, mesolimbic D2 dysregulation can be conceptualized as creating a need that motivates drug consumption behavior (Atzram, 2015).
The way these systems interact with one another and create compounding effects can be seen in research on addiction reinforcement and deprivation. Studies using food deprivation and ethanol intake have been explored since 1901, but early explanations for increased ethanol consumption following deprivation attributed this outcome to alcohol’s caloric content; it wasn’t until the paradigm was used as part of an operant conditioning protocol that this was shown not to be the case, since ethanol drinking decreased but still remained higher than water consumption in control group rats when the intermittent schedule of food administration was removed and the animals were allowed to eat until sated (Carroll and Meisch, 1984). Indeed, the effect has been replicated with other drugs of abuse that do not have caloric content like stimulants and depressants, and there, too, a period of deprivation preceding drug administration increased intake (Meisch, 1984). The neurochemical explanation for this effect could be attributable to enhanced functional activity of DA receptors during food deprivation, either enhancing release, minimizing reuptake, or augmenting the D1 receptor pathway (Carr, 2002), which in turn enables an increased effect of D1/D2 synergism in the NAc (Hasbi et al., 2011).

1.3 The C57Bl/6 Mouse

The C57BL/6 mouse (C57) is the standard model for mouse research - not only is the strain possessing of a remarkable stability, widespread use, and is easily bred (Battey et al., 1999), but for those very reasons it was selected as the first organism to have its genome recorded outside of humans. This popularity may have been motivated in part by to the strain’s outsized preference for ethanol consumption. In a survey of voluntary ethanol consumption in 15 commonly used inbred mouse strains, the C57 reigned supreme in the amount of ethanol consumed at low and high concentrations (3% and 10% respectively) in addition to exhibiting the lowest incidence of avoidance (Belknap et al., 1993).
Part of this effect can be explained by genotypic variation. Compared to DBA/2 mice, a strain with just as strong of an outsized avoidance for alcohol, the C57 mouse has a lower density of D2 receptor mRNA abundance in the hypothalamus (Ng et al., 1994), a finding consistent with assumptions of the DA hypothesis of addiction explored above.

1.4 Naloxone antagonism of ethanol and reinforcement effects

First patented in 1961 to treat constipation induced by chronic opioid use (“The history of naloxone”, 2017), naloxone is now widely used as an over the counter tool to reverse acute opioid overdose (“Is naloxone accessible?”, 2018). Naloxone acts as an opioid antagonist, reversing the effect of opioids by competing for the same binding sites with higher affinities and thereby resolving attendant central nervous system depression, sedation, and hypotension in an individual experiencing overdose (“Narcan prescribing information”, 2017). Naloxone is not a selective antagonist - though it has a predominantly high nanomolar affinity for MOP, it also demonstrates a nanomolar affinity for KOP (Nutt, 2014).

Naloxone administration has been shown to modulate the reinforcing and motivational components of drugs of abuse (e.g. cocaine) in subjects as shown by Kuzmin et al. (1997). In their first experiment, mice were pre-treated with either naloxone, naloxone-methyl iodide (NMI) (a form of naloxone that does not cross the blood brain barrier), or saline solution before a period of self-administration of cocaine at graded doses. The administration of naloxone shifted the dose-response curve to the right, and significantly blunted the reinforcement effect (i.e. less self-administration) of 0.4µg cocaine at 1 mg/kg compared to both equal concentrations of placebo or NMI. Furthermore, 1mg/kg of naloxone had a significant effect on conditioned place preference for animals conditioned with 10 mg/kg cocaine, significantly decreasing the amount of time spent in the drug paired side of a two compartment box compared to equal concentrations
of placebo or NMI. Because neither of these effects were exhibited with the administration of NMI, the opioid blockade’s influence on reinforcement occurs centrally, not peripherally.

Due to the close interrelation of the DA mesolimbic systems and endogenous opioid receptor systems explored above, naloxone has been explored as a potential avenue to interrupt patterns of alcohol dependence. Indeed, administration of opioid receptor agonists have been shown to increase ethanol consumption. Wild and Reid (1990) demonstrated that Sprague-Dawley rats given intracerebroventricular doses of morphine consumed more ethanol than their vehicle counterparts during two bottle choice period following 22 hours of water deprivation, and that this effect is due to central, rather than peripheral, mechanisms in the brain. This effect is not confounded with other appetitive factors like sugar content; having been administered a subcutaneous dose of morphine, Sprague-Dawley rats have been shown to have an increased preference for a sweetened ethanol-sucrose solution over water during a two bottle choice period following 18 hours of food and water deprivation, but not for the sucrose solution without ethanol (Reid & Hunter, 1984).

Non-specific opioid receptor antagonists have been shown to decrease both ethanol dependence and locomotor effects. In Swiss-Webster mice made physically dependent on alcohol via ethanol vapor exposure, those mice that had been given naloxone exhibited withdrawal behaviors 14 times less than those given a saline solution of equal volume, even though both groups had equivalent concentrations of blood alcohol (Blum et al., 1977). Moreover, mice (BALB/c, C57, or DBA/2) given a subcutaneous naltrexone (a non-specific opioid receptor antagonist similar to naloxone; like naloxone it has preferential binding for MOP and KOP, but has a higher affinity for DOP than naloxone (Nutt, 2014)) administration before being injected intraperitoneally with ethanol did not exhibit ethanol hypnosis compared to
experimental groups that received only saline injections and, with the exception of C57, did not exhibit loss of righting reflex following ethanol exposure (Kiianmaa et al., 1983).

Non-specific opioid receptor antagonists alter ethanol preference. A 1mg/kg administration of naloxone in Wistar rats following the development of behavioral dependence on ethanol acutely lowered ethanol consumption without affecting water consumption as part of a two bottle choice, whereas behaviorally dependent rats given saline demonstrated no difference in preference (Marfaing-Jallait et al., 1983). Likewise, subcutaneous naltrexone administration in C57 mice following 2 weeks of ethanol exposure as part of a continuous two bottle choice transiently reduced ethanol consumption and produced a long-lasting reduction in ethanol preference (Middaugh & Bandy, 2000). Additionally, naloxone has been shown to decrease motivation effects of alcohol. Rats implanted with lateral hypothalamic electrodes were operantly trained to self-administer brain stimulation; following a pre-test control session, the animals were then injected with saline or naloxone and then saline or ethanol and tested for 10 minutes .5, .2, 3.5, and 5 hours following injection (Lorens & Sainati, 1978). Those subjects that received an ethanol and naloxone administration did not exhibit the increase in self-administration present in those subjects that received an ethanol and saline administration. Because naloxone was not shown to affect blood alcohol level, this indicates that naloxone effectively blockaded the motivational effect of ethanol with regard to lateral hypothalamic self-stimulation.

2.1 Thesis Objectives

Endogenous opioids have been shown to play a significant role in motivation, enforcement and addictive behaviors. Moreover, they have been found to interact with other neurochemical systems in mediating alcohol behavioral and physiological effects. Opioid
antagonists have been shown to effectively interrupt preferential and motivational effects of alcohol consumption, and, by the same token, opioid agonists have been shown to effectively raise preferential effects. In the research explored above, the blunting effect of opioid blockade on the performance of extant addiction oriented behaviors has been demonstrated. What is of interest, however, is if naloxone can block the consolidation of addiction reinforcement in the first place, not only depressing preference or physical dependence with extant addiction, but rather the learning about reward salience mediated by activation of the mesocortical dopamine pathway during the first exposure to the drug of abuse.

2.2 Subjects

Subjects consisted of 25 C57 mice all of which had no prior ethanol exposure from Taconic Laboratories (New York, NY, USA). Subjects were individually housed in ventilated Plexiglas cages in a room maintained on a 12-12 reverse light dark cycle. The mean body weight was 28.8 grams. This study was conducted in accordance with guidelines of the Guide to the Care of the Use of Laboratory Animals, of the National Institutes of Mental Health. The animals were maintained on ad libitum food (lab chow) and water except for the 24 h before exposure to ethanol when food was withheld. Animals were returned to ad libitum conditions at other times. Food deprivation was followed by two or three days of ad libitum food and water before each deprivation period.

2.3 Procedure

Subjects were divided into four equal cohorts: two experimental cohorts, and two control cohorts. Members of the first experimental cohort \((n = 5)\) received a 5 mg/kg administration of naloxone immediately after their first exposure to ethanol \((2 \text{ cc of } 3\% \text{ ethanol})\), while members of the second experimental cohort \((n = 5)\) received a 5 mg/kg administration of saline \((2 \text{ cc } 0.9\% \text{ saline})\).
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NaC) vehicle immediately after their first exposure to ethanol (2 cc of 3% ethanol). The first of the control cohort (n = 5) received a 5 kg/mg administration of naloxone following the fasting period, but did not receive ethanol exposure. Likewise, the second control cohort (n = 5) received a 5mg/kg administration of saline solution, but did not receive ethanol exposure. After three days of exposure to ethanol under deprivation conditions accompanied by administrations of either vehicle or naloxone, subjects then resumed a chow diet and were run on a two bottle choice paradigm (Martinetti et al., 2000). One hour into the dark (active) cycle, each subject was presented with a bottle of water and a bottle of 10% v/v ethanol solution. For one hour, each subject was allowed to freely consume from either of the two bottles. The bottles, having been pre-weighed, were then collected and re-weighed to determine the difference.

3.1 Statistical Analysis

Ethanol consumed

It was hypothesized that subjects which had been administered naloxone immediately following ethanol exposure would consume less ethanol than subjects administered vehicle immediately following ethanol exposure during a two bottle choice test. A one-way analysis of variance (ANOVA) comparing the means of ethanol and water consumption supports this hypothesis. While there is no significant between groups difference in the amount of water consumed during the two-bottle choice test \(F(3, 21) = 1.14, p = 0.36\), there is a significant between groups difference for the amount of ethanol consumed \(F(3, 21) = 13.64, p < 0.05\).

This difference is characterized by the outsized consumption of ethanol of the naloxone-/ethanol+ group \(M = 2.44, SE = 0.26\). Compared to each other group – naloxone+/ethanol+ \(M = 1.00, SE = 0.07, p < 0.01\), naloxone+/ethanol- \(M = 1.34, SE = 0.18\),
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$p < 0.05$), and naloxone-/ethanol- ($M = 1.24, SE = 0.13, p < 0.05$) – the naloxone-/ethanol+ group consumed a significantly larger amount of alcohol according to a Tukey’s range test.

The naloxone-/ethanol+ group is also the only cohort to exhibit a significant difference in the amount of water and ethanol consumed within the group. An independent samples t-test shows that whereas the naloxone+/ethanol+ ($p = 0.36, t = 0.99$), naloxone+/ethanol- ($p = 0.93, t = 0.93$), and naloxone-/ethanol- ($p = 0.13, t = 1.69$) cohorts all had no statistically discrete difference in the amount of water and ethanol consumed, the naloxone-/ethanol+ cohort ($p < 0.01, t = 5.29$) consumed significantly more ethanol than water. These data are summarized in figure 1 below.

Figure 1: Figure 1 illustrates discrepancies in the amount of liquid consumed by each group, measured in grams, during the two-bottle choice test.

**Percent alcohol consumed**

It was hypothesized that subjects which had been administered naloxone immediately following ethanol exposure would not only consume less ethanol, but would consume less
ethanol preferentially (i.e. ethanol would represent a smaller fraction of the total amount of liquid consumed) than subjects which had been administered vehicle immediately following ethanol exposure during a two bottle choice test. The percent alcohol consumed for each group was calculated by taking the amount of ethanol consumed in grams and then dividing it by the total amount of liquid consumed in grams.

A one-way ANOVA comparing percent alcohol consumed supports this hypothesis, but not globally. A significant between groups difference was found \( F(3, 21) = 3.78, p < 0.05 \), but this held only for multiple comparisons between the naloxone-/ethanol+ cohort \( M = 0.74, SE = 0.03 \) and the naloxone+/ethanol+ cohort \( M = 0.48, SE = 0.09 \). There was no significant difference in percent alcohol consumed between any of the other cohorts according to a Tukey’s range test. These data are summarized in figure 2 below.

Figure 2: Figure 2 illustrates discrepancies in the percentage of alcohol consumed by each group. Percent alcohol was determined by finding the ratio of alcohol consumed over the total of all liquid consumed by each subject.
3.2 General Discussion

These data clearly indicate that naloxone appears to have a blunting effect on the consumption of alcohol, as seen in both less alcohol consumed and a greater proportion of water consumed. The naloxone+/ethanol+ cohort behaved indistinguishably from those groups that had never been exposed to alcohol in the first place. The key finding of these data, however, is that naloxone can disrupt the acquisition of the reinforcing effects of alcohol addiction during the initial exposure. Addiction is a process of the acquisition of new behaviors that are reinforced by the effects of the drug. The increased striatal dopamine induced by exposure to a drug of abuse creates an aberrantly powerful change in learning and memory compared to natural cues that leads to sensitivity to environmental cues associated with consumption of drugs of abuse (Torregrossa et al., 2011). Naloxone, as suggested by these data, interrupts that consolidation.

The pretreatment of the naloxone+/ethanol+ cohort led to a lower alcohol consumption in comparison to animals that did not receive pretreatment: their relationship to alcohol during two bottle choice exposure was no different than that of either of the control groups. The naloxone+/ethanol+ cohort was in not particularly attentive to or motivated by the presence of alcohol. On the other hand, the naloxone+/ethanol+ cohort seemed, also, to express a lower need for alcohol consumption. This is reflected by the significant difference of ethanol consumption as a fraction of total liquid consumption. To this end, the naloxone+/ethanol+ group was the only cohort that differed in percent ethanol consumed from the naloxone-/ethanol+ cohort, and was the only cohort to have consumed a significant difference of ethanol and water within the group. In other words, members of the naloxone+/ethanol+ cohort had not only a lower preference for alcohol consumption, but also a lower drive to consume ethanol than their naloxone-/ethanol+ cohort counterparts. Both the external (enhanced incentive) and internal (need) components of
reinforcement were interrupted by the administration of naloxone and the attendant blockage of opioid receptors.

This effect cannot be attributed to a difference in performance. Naloxone’s effect on locomotor changes induced by ethanol has been explored above. Naloxone administered before the exposure to ethanol could create changes in locomotor capacities that can be conflated with changes in motivation. Since naloxone was administered after exposure to ethanol, its effect on motivation cannot be confounded with locomotor changes.

An interesting observation is the increase, though non-significant, of water consumption in the naloxone+/ethanol+ cohort. Across multiple animal models, naloxone has been found to decrease food and water consumption following deprivation (Foster et al., 1981; Brown & Holtzman, 1979). This appetitive decrease is tied to the primarily antidipsogenic action of naloxone, which seems to have been counteracted in part by the exposure of alcohol. It could be that the activation and dysregulation of appetitive systems that accompanies the development and reinforcement of alcohol addiction could be responsible for this increase in water consumption, but further research specifically investigating non-regulatory consumption of water is called for.

These data suggest questions for future research endeavors. For example, is naloxone’s interruption of ethanol’s reinforcing effect dose dependent? A graded dose administration could better define the extent of this effect. Additionally, what is the timing of this effect - could naloxone blunt the reinforcing effect of ethanol after only one exposure? Is naloxone the best tool for this effect? Naltrexone has a longer tail in its effect window, and has different nanomolar affinities – would its administration produce the same outcome? Finally, there are observable differences in striatal DA between men and women (Perry et al., 2016) - is there a discrepancy in the extent of this effect between sexes?
Future clinical research could also emphasize the use of naloxone as a potential therapeutic tool for decreasing incentive mechanisms and drive components of alcohol and other drugs of abuse as well as the treatment of obesity. Naloxone has been used in interventions reversing the effects of alcoholic coma (Lyon & Anthony, 1982), so clinical applications have already been explored. Naloxone could very well be folded into clinical rehabilitation protocols in order to create extinction of incentive value during detoxification, for example, and aid in the cessation of addictive behaviors.
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