Isoquinolines, beta-carbolines and alcohol drinking: Involvement of opioid and dopaminergic mechanisms

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Summary. Two classes of amine-aldehyde adducts, the tetrahydroisoquinoline (TIQ) and beta-carboline (THBC) compounds, have been implicated in the mechanism in the brain underlying the addictive drinking of alcohol. One part of this review focuses on the large amount of evidence unequivocally demonstrating not only the corporeal synthesis of the TIQs and THBCs but their sequestration in brain tissue as well. Experimental studies published recently have revealed that exposure to alcohol enhances markedly the endogenous formation of condensation products. Apart from their multiple neuropharmacological actions, certain adducts when delivered directly into the brain of either the rat or monkey, to circumvent the brain's blood-barrier system, can evoke an intense and dose-dependent increase in the voluntary drinking of solutions of alcohol even in noxious concentrations. That the abnormal intake of alcohol is related functionally to opioid receptors in the brain is likely on the basis of several distinct lines of evidence which include: the attenuation of alcohol drinking by opioid receptor antagonists; binding of a TIQ to opiate receptors in the brain; and marked differences in enkephalin values in animals genetically predisposed to the ingestion of alcohol. Finally, it is proposed that the dopaminergic reward pathways which traverse the meso-limbic-forebrain systems of the brain more than likely constitute an integrative anatomical substrate for the adduct-opioid cascade of neuronal events which promote and sustain the aberrant drinking of alcohol.

Key words. Alcohol; brain; tetrahydropapaveroline; drinking; opiate receptors; dopamine; beta-carboline; aldehyde adducts; tetrahydroisoquinolines; ethanol.

Introduction

One of the major clinical-scientific issues in this field today centers on the synaptic events which take place in the brain of the individual who exhibits an addictive liability to alcohol with repetitive drinking. Clearly, an alcoholic beverage can be rewarding in the short term because of its hedonistic properties. With repeated usage, alcohol tends to lose its potency of effect and tolerance to it develops. However, the mechanisms in the brain responsible for these actions of alcohol, although scientifically fascinating, do not necessarily underlie the remarkable craving for the drug and the irreversibility of its powerful addictive quality in the genetically predisposed person.

In the 1970s, a new concept began to emerge, centering on the functional role of those substances metabolically related to alcohol which might play a part in its addictive property. It was known then that alcohol apparently has neither an affinity nor selectivity for pre- or post-synaptic receptor sub-types in neurons of the brain. Thus, a scientific search began which diverged into studies of endogenous metabolic by-products of alcohol as well as those endogenous factors which in their own right could be involved in the fundamental addictive mechanism. In the first instance, tetrahydroisoquinoline (TIQ) alkaloids such as tetrahydropapaveroline (THP) and salsolinol became the focus of investigation. In the second case, endogenous opioid substances of the endorphin family, the enkephalins, were examined in terms of their mediation of alcohol's addictive nature.

Endogenous formation

A question has arisen in past years concerning the mechanisms of endogenous formation and sequestration of a TIQ or beta-carboline in the brain[27,45,112]. Clearly, a pivotal criterion for the putative involvement of an aldehyde adduct in the neuronal processes underlying the addictive liability to alcohol rests in its functional activity in cerebral tissue. Otherwise, the central pharmacological evocation or suppression of volitional drinking of alcohol by a condensation product would in effect constitute little more than an experimental curiosity.

Shortly after the demonstration that the TIQ condensation reaction could be driven in tissue by the presence of alcohol or an aldehyde[22,33], salsolinol and THP were detected in the urine of the L-dopa-treated Parkinson's patient who had consumed alcohol[111]. Whether or not a metabolic by-product in the urine is of neurophysiological relevance to the miniscule quantity of the respective metabolite active in the CNS, particularly in relation to the ingestion of alcohol, was most assuredly uncertain in the 1970s[61]. It is the case even today. Nevertheless, a succession of papers on urinary measures of excreted salsolinol in conjunction with the administration of alcohol did provide clearcut support of the corporeal synthesis of numerous aldehyde adducts[26,112].

Human subjects. The formation of TIQ products has been repeatedly demonstrated to occur in vivo as measured in urine of the human subject following exposure to alcohol[25,27]. However, different results obtained in early experiments can now be attributed to either the diversity

of technical problems associated with the detectability of a TIQ or procedural variables including the duration of alcohol administration [28]. For example, the technique of mass fragmentography has revealed that in the alcoholic patient undergoing withdrawal, the output of salsolinol rises progressively in 24-h samples of urine collected over a 5-day interval [112]. Recently it was shown that the level of salsolinol increases significantly in the urine of the moderate drinker of alcohol in comparison to the non-drinker [59]. Clearcut differences exist also in the amounts of urinary salsolinol excreted by light and heavy drinkers after ingestion of a salsolinol-enriched diet [42, 44]. These findings thus suggest that each of the mechanisms of metabolism of salsolinol and its absorption and distribution can play a vital role in the alcohol drinking response [20].

In a population of Japanese males exhibiting different levels of isozymes of aldehyde dehydrogenase, alcohol when administered orally evoked a significant elevation of urinary salsolinol which is much greater in the enzyme-deficient individual than in the normal volunteer [1]. Of significance is the fact that the values of blood acetaldehyde correlate more highly with the quantity of urinary salsolinol than that of blood alcohol. In alcoholics undergoing withdrawal, approximately half of the patients show a significantly higher urinary excretion of salsolinol on admission than the non-alcoholic individuals. On the other hand, 50% of acutely intoxicated individuals exhibit urinary values of salsolinol resembling those of healthy volunteers [2]. In these studies, the importance of the diet of the alcoholic or non-alcoholic individual could be a critical variable, since a salsolinol-containing foodstuff such as chocolate can contribute to the appearance of salsolinol in the urine [43, 44].

In relation to the etiology of alcoholism, an equally important issue concerns the presence of a pharmacologically active amine-aldehyde adduct in the brain of an individual consuming alcohol. Following several early reports, the issue of detectability seemed to resolve the discrepant findings on the in vivo formation of a TIQ as a result of exposure to alcohol [39, 93]. The unusual characteristics of salsolinol metabolism also could contribute to the earlier difficulty of its unequivocal detection [94].

In an extensive series of investigations, scientists in Sweden have documented the occurrence of salsolinol in samples of both urine and cerebrospinal fluid obtained from alcoholic and non-alcoholic individuals. The values of the aldehyde adduct generally are significantly higher in the alcoholic patient than in the control, although these distinctions are time-dependent in relation to the ingestion of alcohol as well as to the specific interval of abstinence [117, 118, 120]. In contrast to the sober alcoholic, a significant elevation in salsolinol occurs in dopaminergic-rich regions of brain tissue collected postmortem from the intoxicated alcoholic patient. The cerebral structures within which these changes are observed include the basal ganglia, hippocampus and cerebral cortex [122]. In the sober individual, a lower level of salsolinol in the lenticular nuclei could reflect a decreased metabolism of pyruvate which in turn would lead to a decline in the synthesis of salsolinol [121]. The identification of 1-carboxy-salsolinol in the urine of the healthy volunteer given a challenge dose of alcohol further indicates that alternative forms of salsolinol may underlie the distinctive properties of metabolites of alcohol or aldehydes on the brain [119] in terms of their addictive action [74].

Animal studies. In parallel studies with the rat, the chronic administration of alcohol induces a significant rise in the concentration of salsolinol in limbic-forebrain structures, inclusive of the corpus striatum [120]. Treatment with the aldehyde dehydrogenase inhibitor, calcium carbamide, combined with exposure to alcohol sharply augments the endogenous level of salsolinol in the corpus striatum of the rat within 90 min following the administration of alcohol [11].

Other experiments have now validated beyond scientific doubt the synthesis in vivo of both isoquinoline and beta-carboline alkaloids as contingent upon administration of alcohol to the animal. In the Long-Evans rat which had consumed 10% alcohol for 10 months, the concentrations of both dopamine and salsolinol rose significantly in the medial basal hypothalamus when compared to controls [89]. One conclusion to be drawn from this observation is that chronicity of exposure to alcohol is a key factor in the ultimate identification of a TIQ in brain tissue. Of interest here is the fact that in the rat which self-injects acetaldehyde intravenously for one hour per day for 20 days, the concentration of salsolinol again in the medial basal portion of the hypothalamus as well as in the corpus striatum is likewise significantly elevated [88]. When the rat consumes alcohol for periods of 3, 4, 5 and 6 months, the significant increases in the level of salsolinol in both hypothalamus and corpus striatum are linearly correlated to the interval of the chronic exposure regimen [60]. Further, the concentrations of dopamine and norepinephrine remain constant, and upon removal of alcohol from the rat's diet, the increased values of salsolinol return gradually to normal [60].

Of equal importance is the clearcut demonstration of the alcohol-dependent occurrence of THP in the brain [17]. When alcohol is administered acutely to the L-dopa-treated rat, the level of THP in the brain is raised significantly, by as much as 1000% over that seen in the animal treated with L-dopa alone [18]. Corresponding to this finding are observations of alcohol-related formation of several beta-carboline compounds endogenously [25]. For example, 1-methytetrahydro-beta-carboline has been identified in the plasma of volunteers who have ingested alcohol [98]. In addition, the level of the urinary beta-carboline is increased significantly in the alcoholic patient on admission to hospital, remaining elevated in some in-patients even after 2 weeks [105]. A similar time- and dose-dependent rise in the indole-aldehyde adduct occurs

also in the brain of the rat after its consumption of alcohol[107].

Taken together, therefore, these findings provide unequivocal evidence for the alcohol-contingent in vivo formation in the brain of aldehyde adducts, which are active pharmacologically in inducing alcohol drinking in the experimental animal. Under the conditions of both acute and chronic exposure to alcohol, THP and salsolinol are readily identifiable, given that appropriate and analytically sensitive techniques are employed[17]. It is notable, moreover, that when an animal drinks alcohol chronically, prior treatment with a dopamine precursor is not essential for the demonstration of the presence of an endogenous isoquinoline in brain tissue[88,89].

Pharmacological effects

Since TIQ and beta-carboline derivatives are formed endogenously in the brain as a result of acute or chronic exposure to alcohol, their effect on cellular and subcellular mechanisms in cerebral tissue would be expected to be diverse and widespread. As reviewed previously[14,21,72], both classes of aldehyde adduct can exert specific actions on populations of neurons in different regions of the brain. To illustrate, THP has been shown to: affect presynaptic dopamine receptors in the neostriatum of the rabbit[47]; accumulate in synaptic vesicles of the substantia nigra[52]; bind to both alpha2 adrenergic receptors[91] and opiate receptors[35] in the rat; be a potent dopamine agonist[12]; alter significantly the metabolism of cerebral serotonin[40]; induce withdrawal-like symptoms[116] impair behavioral responses independent of alcohol drinking[58]; and possess pharmacological properties similar to alcohol in terms of its behavioral discrimination by the rat[13].

Concerning the central actions of indole-aldehyde adducts, beta-carboline derivatives can act variously to: inhibit type A monoamine-oxidase in brain tissue[67]; release both 5-HT and dopamine from cerebral tissue stores[106]; bind to both tryptamine and 5-HT_1 and 5-HT_2 receptor sites in the cerebral cortex[16]; increase or otherwise influence fluidity in nerve cell membranes to a greater extent than alcohol[97]; and mediate the discrimination of alcohol in a behavioral task[115].

Alcohol drinking

It has long been known that the presence of even the most minute amount of acetaldehyde in the brain can evoke the spontaneous preference for alcohol[71] presumably through neuronal mechanisms promoting the formation of an aldehyde adduct[73]. When acetaldehyde is self-administered intravenously in the rat, which constitutes a reinforcing condition itself, measures of subsequent voluntary selection of alcohol show a marked increase in intake[87].

When alkaloid metabolites are given by the peripheral route different pharmacological effects on alcohol drinking are produced. To illustrate, the parenteral administration of a high dose of a beta-carboline can inhibit alcohol drinking, presumably because of its inhibition of liver aldehyde dehydrogenase[36,68]. However, when 3-carboxy-salsolinol is administered either subcutaneously[101] or orally[26], the consumption of alcohol is enhanced significantly in a rat given a free choice with water. To what extent this TIQ derivative penetrates the blood brain barrier as a result of the peripheral route of administration is still unknown. Nevertheless, these findings provide a physiological corollary to the view (see previous section) that an alkaloid adduct can be synthesized in peripheral tissue in a pharmacologically significant amount following the administration of alcohol.

Considerable experimental research followed the discovery in 1977 that addictive-like drinking of alcohol can be produced by THP given directly into the brain of a test animal. Initially, the central effect of this TIQ was characterized in the rat by an unusual set of behavioral or physiological responses[77]: first, the absolute amount of alcohol consumed is frequently greater when the test concentration offered to the animal is increased to an aversive level[64]; secondly, withdrawal-like symptoms occur spontaneously in the THP-infused rat and can even be evoked by auditory stimulation[64]; thirdly, after discontinuation of infusion of the TIQ, the intense preference for alcohol is seen to persist for months when the animal is re-introduced to the alcohol-water, free choice test situation[34,64,77]. Fourthly, although salsolinol is not as potent as THP in inducing alcohol preference[65,79]; certain beta-carboline compounds given by the same i.c.v. route cause significant increases in alcohol imbibition even in the presence of a highly palatable sweetened solution[78].

A theoretical assumption made in early experiments[77,78] that a TIQ must be present chronically in the brain to promote the abnormal consumption of alcohol is not necessarily valid. That is, experiments with the rat in which single injections of THP or salsolinol are given acutely by the i.c.v. route demonstrate a dose-dependent and significant rise in the self-selection of alcohol[79]. In an experiment[19] which replicated the observation on acute i.c.v. administration of THP, the higher dose of the alkaloid was found to suppress drinking whereas the lower dose enhanced the rat's preference for alcohol. The dose-dependent nature of the effects on alcohol preference produced by either salsolinol or THP was replicated also in the paradigm utilizing chronic infusion of the compounds[34]. Further, in the unanesthetized Macaque monkey, acute i.c.v. infusions of THP repeated over several days induce a significant enhancement in alcohol consumption with a dose-dependent response curve characterized by an inverse U-shaped response function[84].

Equally potent effects on alcohol drinking are observed when a beta-carboline is administered directly into the

brain by an acute or chronic procedure. Given by the i.c.v. route, tryptoline (noreleagnine) elicits alcohol drinking virtually identical to that produced by THP, which is again characterized by a marked and persistent increase in the intake even of aversive concentrations [78, 79]. Moreover, alcohol consumption is augmented significantly in the rat, particularly at concentrations ranging from 11 to 30%, following the chronic i.c.v. infusion of 1-methyl-THBC which is present endogenously in blood following exposure to alcohol [125]. However, 6-methoxy-THBC injected under the same experimental condition is essentially without effect in comparison to the other beta-carbolines [4]. These findings taken together with the observation of the central action of the TIQs have led to the 'Multiple Metabolite' theory [73], which has implicated both classes of aldehyde adduct in the abnormal intake of alcohol.

Recently, it has been shown that a beta-carboline is specific in its action in inducing voluntary drinking of alcohol. Whereas harman is either ineffective or attenuates the consumption of other addictive drugs when they are offered in a similar self-selection paradigm, alcohol drinking is enhanced by harman under the same condition [104]. In another experiment, reactive sites of action of a beta-carboline in evoking alcohol drinking have been identified in the dorsal hippocampus [49]. In this case noreleagnine micro-injected in nanogram doses into this structure twice daily enhances alcohol intake significantly [49]. Noteworthy is the fact that the anatomical region reactive to the β-carboline is homologous morphologically with an area of the hippocampus where this compound acts to evoke an intense, anxiety-like response in the rat [48].

Although in one report the THP-induced increase in alcohol drinking apparently was not statistically significant [13], at the highest concentrations of alcohol offered, i.e., 15–30%, the rats' alcohol preference ratio following THP increased to twice that of the baseline level, while the g/kg intake also increased correspondingly. A number of methodological variables can contribute to the magnitude of increase or decrease in alcohol drinking following the central injections of a TIQ or THBC [15]. These factors include neurosurgical techniques [85], the chemical characteristics of the TIQ itself [83], selection of animals with a strong initial preference for alcohol [13] and screening procedures of the test animal [73, 74].

Mechanisms of aldehyde adduct-induced alcohol drinking

Several hypotheses have been proposed to account for the central action of a TIQ or beta-carboline in inducing alcohol drinking. Each of these centers on a possible mechanism in the brain.

Toxic hypothesis. One proposal suggests that an isoquinoline adduct which is formed and sequestered in the parenchyma of the brain acts as an endogenous neurotoxin [27]. Although theoretically plausible, studies undertaken using i.c.v. infusions of neurotoxins which destroy catecholaminergic and serotonergic neurons fail to demonstrate changes in the self-selection of alcohol in the order of magnitude noted after only a nanogram quantity of a TIQ or beta-carboline is similarly delivered [63, 76]. Chemical lesions produced by kainic acid injected into hippocampal sites which mediate aldehyde adduct-induced alcohol drinking do not enhance alcohol intake [86]. In addition, when a toxic amount of 1,2,3,4-tetrahydroisoquinoline is administered to the mouse, little if any neurotoxicity arises centrally in the nigrostriatal system [95]. Thus, it is unlikely at present that a neurotoxin hypothesis could explain the long-lasting central effect of an aldehyde adduct in enhancing alcohol intake.

Dopamine reward hypothesis. An involvement in alcohol drinking of monoamine neurotransmitters in the brain has been presumed since the late 1960s. Drugs administered to alter the cerebral content of serotonin, for example, modify alcohol self-selection under a variety of experimental conditions [71]. Studies with serotonergic and catecholaminergic neurotoxins [63] also supported a role in alcohol self-selection for neurons containing norepinephrine, dopamine and serotonin [51, 76, 103]. Further, drugs that affect the release of catecholamines as well as their receptor function also implicate both norepinephrine in the alcohol preference mechanism [54] and dopamine in the reinforcing aspect of the fluid [96]. Either the acute or chronic administration of alcohol can affect markedly the content and turnover of dopamine in specific regions of the rat's brain [4, 32], with differences observed also in an alcohol-preferring strain of rat which is either tolerant or intolerant to the actions of alcohol [70]. From the standpoint of endogenous neurotransmitter activity, dopamine is released by THP and other condensation products perfused locally at circumscribed sites within the forebrain [66]. Similarly, alcohol liberates dopamine from sites in the corpus striatum and nucleus accumbens [50, 108]. Moreover, the prolonged ingestion of alcohol alters also the density of striatal dopamine receptors as well as their sensitivity [53, 55, 113]. In this connection, THP is a most potent inhibitor of haloperidol binding to the D_2 sub-type of dopaminergic receptor in cerebral cortical membranes [92]. When aldehyde dehydrogenase is inhibited by a drug such as cyanamide, which in itself induces a sharp increase in alcohol drinking [30, 31], the turnover of dopamine shifts in discrete regions of the brain [126].

Taken together, therefore, it would appear that dopaminergic neurons in cortical and subcortical structures could play a multifaceted role in the rewarding property of alcohol. The presence of an aldehyde adduct, generated in the brain by prolonged consumption of alcohol could thus act to modulate the dopaminergic reward pathway. That the lower level of salsolinol in the brain of the sober alcoholic, in contrast to the intoxicated individual, would thus cause the alcoholic individual to drink more alcohol in a compensatory fashion in order to augment the

brain's reduced salsolinol concentration is indeed conceivable [69, 121]. Since salsolinol binds to receptors on dopaminergic neurons, this in turn would thereby subserve either the reinforcing effect of alcohol, as mediated in part by the dopaminergic reward system, or the intoxicating action of alcohol, or both. An important observation related to this concept has recently been made: those structures in the brain-stem which are specifically reactive to the local injection of a TIQ in either evoking or suppressing alcohol drinking comprise, in large part, the mesolimbic and nigro-striatal pathways which are characterized anatomically as dopaminergic [80, 99].

Opioid mechanisms in adduct-induced drinking. The probable involvement of an opiate receptor mechanism in the brain in the volitional intake of alcohol has been recognized for many years [6]. A 'common-link' hypothesis relating the pharmacological and other properties of alcohol to endogenous opioids has served as the basis for much intensive research [8, 124]. To illustrate, certain opiate receptor antagonists such as naloxone or naltrexone can reduce alcohol drinking either in the rat pretreated i.c.v. with THP [75], or in an untreated rat which is acclimated to a selected concentration of alcohol [110]. Naltrexone also antagonizes the self-administration of alcohol in the monkey [5, 82]. Although morphine can attenuate alcohol drinking induced by THP [31], this action of the opiate agonist occurs presumably through a separate class of receptor which presumably is affected specifically by the chronic exposure to alcohol [57].

In considering the opioid-alcohol interaction from the perspective of endogenous substances, the whole brain of the inbred alcohol-preferring mouse has a significantly lower level of enkephalin in contrast to the mouse of a non-alcohol preferring strain [9]. Enkephalin values in these strains are anatomically differentiated specifically within tissue of the hypothalamus and corpus striatum, with other structures in the limbic system exhibiting little or no differences between strains [9]. Another compound of the endorphin family, beta-endorphin, reportedly is released from the hypothalamus of the animal following an alcohol challenge [38] (see paper in this multi-author review). This result is concordant with a possible mechanism for the rewarding property of alcohol at the level of the diencephalon. Since morphine is found endogenously in samples of human CSF [15], it is conceivable that the endorphin system, as reflected by concomitant fluctuations in CSF concentration, is directly affected during the intake of alcohol, during alcohol intoxication and withdrawal [10]. For example, in the detoxified alcoholic patient tested 3–10 days after withdrawal from the fluid, the content of beta-endorphin in the CSF is 3-times lower than that of control volunteers [37]. Whether or not the genetic factors that influence enkephalin levels in brain tissue is a part of or related to the 'alcogene' [73], which has been proposed to mediate the abnormal response to alcohol, is not yet known.

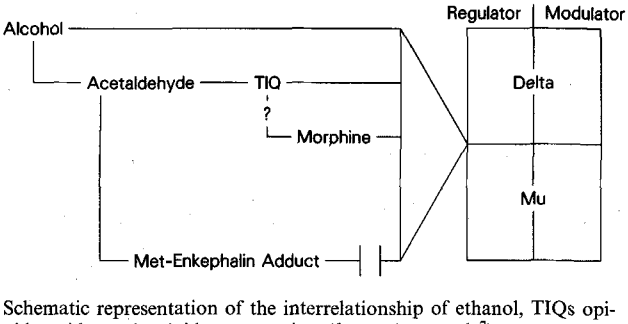
Conclusion

A hypothetical model to explain the functional interactions among alcohol, acetaldehyde, a TIQ, an enkephalin and morphine is presented in the figure [7]. This schema serves to illustrate the order of one possible cascade of events which theoretically could take place in the brain on the input side of the δ and μ opioid receptors. Clearly, conformational modifications in receptor protein at this molecular level would explain neurochemically the irreversibility of the syndrome of alcoholism as well as its hallmark of temporal longevity.

An exciting era is now at hand in which intelligent research strategies are being integrated to examine functional interactions, within a neuroanatomical context, between aldehyde adducts, endorphin systems and alcohol. New technologies which now make this possible include an implantable mini-pump which can chronically deliver a pharmacologically relevant aldehyde metabolite into the brain [20, 104], and sophisticated procedures for evaluating the binding of beta-carbolines or TIQs to opioid, dopamine and other receptor subtypes [53]. Even given its low rate of synthesis and rapid degradation [62, 90], the identification is now certain of salsolinol in CSF and in different anatomical regions of the brain [88, 89], as well as in the CSF in relation to alcohol exposure, drinking and abuse [60, 121]. In this connection, THP which has been linked most strongly to the etiology of alcoholism [72, 73] has at last been identified in the brain following an alcohol challenge [19].

Another crucial endeavor of the future continues to be the delineation of anatomical regions which are specifically involved in the adduct-opioid receptor link [49, 50]. However, it is clear that certain of the acute effects of alcohol can be reversed pharmacologically by centrally acting compounds such as a Ca^{++} chelating agent, EGTA [81], a Ca^{++} channel blocker [102] and a compound which affects benzodiazepine receptors [41, 56, 109, 123] (other subjects in this multi-author review). Similarly, the chronic drinking of alcohol can be experimentally reversed by drugs as structurally diverse as the novel anxiolytic, buspirone [23, 100], and a centrally acting enzymatic inhibitor of L-aromatic-amino acid decarboxylase [69].

Theoretical and interpretive controversy to some extent may be an issue in the minds of the participants in this



Schematic representation of the interrelationship of ethanol, TIQs opioidpeptides and opioid receptor sites (from Blum et al. [7]).

difficult field of research. Nevertheless, the factor of reconciliation of data should never provide a basis for an impediment to rational experimental approaches. Hence, the intricate puzzle surrounding the etiological role in the addictive process of endogenous neurochemical factors in the brain will ultimately yield to this new thrust in scientific research.

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