The Plastic Phenomenon Underlying the Associative Processes in the Addictive Properties of Diazepam and Other Psychoactive Drugs

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Abstract: Benzodiazepines are commonly prescribed for the therapy of disorders such as anxiety and sleep disturbance, but develop dependence in many patients. In this review we discuss the impact of different brain areas that modulate the reward system in the development of tolerance and dependence to benzodiazepine and the associative processes underlying those fenomena.

INTRODUCTION

Chemical Structure of Benzodiazepines

The basic chemical structure of benzodiazepine is a 7-membered ring fused to an aromatic ring, with four main substitutent groups that can be modified without loss of activity. The most important effects of benzodiazepines (BDZs) on the central nervous system (CNS) consist of reduction of anxiety and aggression, sedation, induction of sleep, reduction of muscle tone and anticonvulsant effect. BDZs are some of the most commonly prescribed psychoactive drugs for the therapy of disorders such as anxiety and sleep disturbances. However, this practice runs the risk of dependence developing in many patients [37]. Furthermore, many studies using experimental animals have demonstrated the development of tolerance to the sedative effects, motor disturbances, and motor relaxation produced by BDZs [14, 24, 25, 92].

The pharmacological actions of BDZs are mediated by a high-affinity site on the $GABA_A$ receptor which is widely distributed on post-synaptic neurons into the central nervous system. The binding of BDZ agonists results in the facilitation of GABA-operated chloride channels (Cl^-), that is to say, enhancement of the inhibitory actions by GABA [59, 86, 98, 99]. Endogenous ligands for BDZ receptors, which would regulate the action of $GABA_A$ have been isolated from the brain and exhibited an opposite effect to BDZs, namely the inhibition of Cl^- channel opening.

Benzodiazepines are commonly prescribed for the treatment of anxiety and sleep disorders. However, prolonged treatment may lead to dependence with evident withdrawal syndrome [37]. It is generally understood that the neurophysiological activity of the mammalian brain is maintained by the balance between inhibitory (such as GABA) and excitatory (such as glutamate) neurotransmission. Indeed, there is close interaction between $GABA_A$ receptors and the N-methyl-D-aspartate (NMDA) receptors in the CNS [13, 101]. For example, kindling induced by the $GABA_A$ receptor channel blocker pentylenetetrazol was prevented by NMDA receptor antagonist treatment [14, 28]. A protective effect of muscimol against NMDA-induced neuronal injury has also been reported [76]. Furthermore, Tsuda *et al.* have demonstrated that pentylenetetrazol and BDZ site inverse -agonist DMCM-induced seizures are suppressed by the non-competitive NMDA receptor antagonist dizocilpine [108, 109].

Previous studies on rodents have shown that chronic exposure to BDZ produces tolerance and physical dependence [25, 29]. Clinical studies have also demonstrated that the long-term use of BZDs often results in tolerance to and dependence on many of the therapeutic actions of BZDs [41, 89]. Furthermore, severe withdrawal syndrome has been reported with seizures and even death in humans [77, 83]. Indeed, the mechanisms by which BZD tolerance and dependence are mediated have recently been the focus of much interest.

Conditioned Tolerance and Dependence

Pavlovian conditioning is a form of associative learning related to the contingency between two stimulus events. Repeated administration of drugs often results in the conditioning of physiological responses. These conditioned responses can be distinguished from other direct and indirect drug effects by the fact that, under appropriate circumstances, they can be elicited without administering the drug. This form of classical conditioning is important because it may occur whenever drugs are chronically administered. The drug administration ritual may act as the conditioned stimulus that will eventually elicit a conditioned response. These conditioned responses have been suggested to play a role in drug tolerance and sensitization [35, 60, 96, 97, 117, 118].

Repeated drug exposure results in a variety of changes at molecular, neuronal and behavioral levels, with some changes occuring during exposure to the drug while others are expressed during absence of the drug. Often, the effects of the drug decrease in magnitude with repeated exposure, a phenomenon referred to as drug tolerance; changes observed after the cessation of drug exposure are often the opposite to

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the initial effects of the drug and are referred to as withdrawal symptoms.

The relationship between drug tolerance and physical dependence has been repeatedly debated. A common proposition of different theories of drug actions is that, after repeated drug exposure, the changes in the drugged and in the non-drugged state share common physiological features. The same physiological adaptations that underlie drug tolerance also underlie the observed changes seen in the absence of the drug, in physical dependence or in compensatory responses [48, 53, 85]. Different neuronal models have been proposed in order to account for the ways in which conditioned environmental stimuli can reproduce drug effects or even modify the action of drugs themselves, with different neuronal circuitry been thought to be responsible, for example the dopaminergic [117] and glutamatergic [15, 51] systems. It has been reported that the systemic injection of the noncompetitive NMDA receptor antagonist, MK - 801, blocks the development of tolerance and changes the expression of physical withdrawal signs for Diazepam (DZ) [26, 102] and other psychoactive drugs [113]. Furthermore, it impairs the development of sensitization to both amphetamine and cocaine by blocking the plastic changes brought about by repeated drug administration [104]. Because of the known role for NMDA receptors in several types of learning, it seems likely that these receptors participate in the conditioning of the behavioral activation observed after chronic psychoactive drug administration [62, 91].

The development of "rapid" tolerance to the hipolocomotor effects, after 4 days of DZ administration, has been described [24, 63]. Moreover, early previous exposure to the environment related to the drug administration impaired tolerance to these hypolocomotor effects reported after 4 days of (5mg/kg) DZ administration [62] Fig. (**1A**). These results are in agreement with the learning hypothesis, put forward as a mechanism of the conditioned tolerance development to different psychoactive drugs [34].

LTP Description

Long term potentiation (LTP) of synaptic transmission is a relevant phenomenon, seemingly linked to neural information storage [105]. In the hippocampal formation, LTP can be produced by the repetitive activation of afferent pathways [19, 58]. It is believed that glutamatergic receptors, such as NMDA, participate in the induction of LTP [42]. Phosphonovaleric acid derivative (APV), an antagonist to NMDA receptors, and the ionic channel associated blocker, MK-801, impair the induction of LTP and the acquisition of different behavioral responses [70].

We previously demonstrated an increase in the hippocampal synaptic plasticity associated to the development of tolerance to the hipolocomotor effects of DZ [63]. Preexposure to the drug environment administration impairs both the tolerance and the increase of the associated hippocampal dentate gyrus plasticity Fig. (**1A** and **B**) [62]. Long-term potentiation of synaptic transmission in the hippocampus has been extensively studied as a model of learning and memory, with drugs blocking the LTP also been effective in impairing behavior in different tests [69, 70]. If the development of tolerance to DZ is a learning or contingent phenomenon, and the environmental clues are also relevant, then our results concerning the impairment of the development of tolerance to the sedative effects of DZ, and the concomitant lack of increase in hippocampal synaptic plasticity (observed in animals after pre-exposure to the drug environment), may suggest the role of the hippocampal plasticity as a biological explanation for the contingent or learning interpretation of tolerance to DZ. Supporting this view is the fact that antagonists of NMDA receptors block the development of tolerance to the effects of cocaine on locomotor activity [18], to the analgesic effects of morphine [61] and to the motor-impairing effects of ethanol [52, 121]. Kalant *et al.* [47] pointed out that it was impossible to know, when comparing tolerant with non-tolerant animals, whether a particular change in the brain of the tolerant subject was the mechanism responsible for the production of tolerance, or merely a consequence of tolerance. Nevertheless, we can speculate that the change in the hippocampal synaptic plasticity is at least, either one of the biological mechanisms causing the development of tolerance to different neurological depressor drugs or a consequence of the phenomenon underlying this learning process.

Nmda Glutamatergic Receptor

The NMDA receptor subtypes of glutamate receptors may play a very important role in the use-dependent plasticity of synapses [12] and LTP [42]. Cloning studies have identified two families of NMDA receptor subunits in rat brain. These comprise the NR1 and NR2 (NR2A, NR2B, NR2C and NR2D) families [66, 68]. Homomeric receptors of the NR1 subunit have all the characteristics of the native NMDA receptors, although at a lower efficacy, whereas homomeric receptors of the NR2 subunits are not functional [66]. Co-expression of the NR1 subunits with NR2 subunits enhances the individual functional properties of the subunits, such as channel conductance, and agonist, antagonist, and co-agonist sensitivities [66, 68]. Ya-Ping *et al*. [122] have demonstrated that the over expression of the recombinant NR1/ NR2B subunits results in a prolonged opening of the NMDA receptor channel for detecting coincidence, and in an enhanced NMDA receptor activation in individual synapses. Furthermore, a tyrosine phosphorylation of NR2B subunit has been observed following long-term potentiation induction "*in vivo*" [93, 94]. It has also been consistently reported that epileptiforme seizures and excitotoxicity are caused by the large influx of calcium into the cell as a result of NMDA receptor activation [109]. Furthermore, an over expression of $_{m}$RNA for the NR1 - NR2B NMDA receptor subunits in the hippocampus *dentate gyrus* of rats tolerant to DZ has been described [81]. All these findings show a relevant participation of hippocampal glutamatergic transmission during the development of tolerance to DZ.

It has been widely demonstrated that the previous administration of MK-801, a non-competitive NMDA receptor antagonist, impairs the development of tolerance to DZ and other psychoactive drugs [26, 52, 61, 107, 121]. Furthermore, previous MK-801 administration not only prevents the enhanced hippocampal synaptic plasticity, but also the increased $_{m}$RNA for the NR1-NR2B NMDA receptor subunit associated with the development of tolerance to DZ [3].

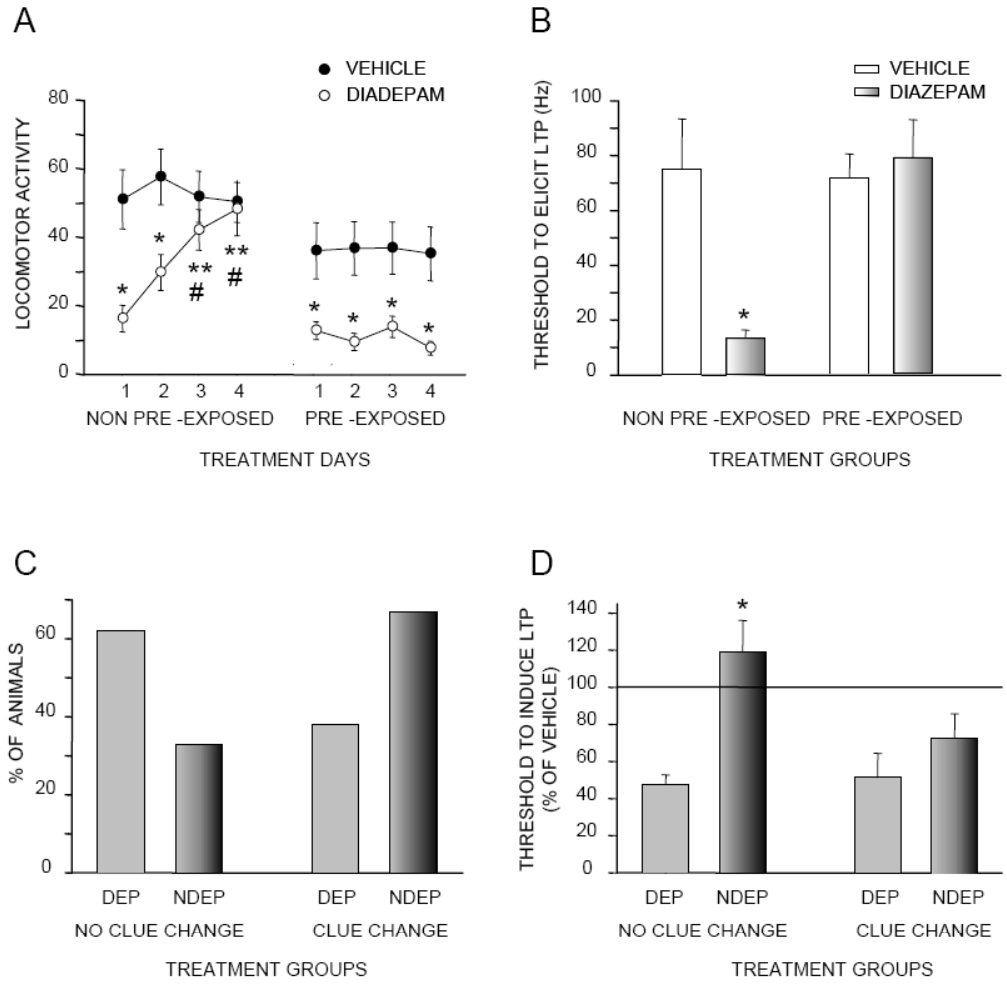

Fig. (1). Environmental clues are relevant for development of tolerance and dependence to benzodiazepines. A. Time course of changes in locomotor activity of pre-exposed (n=14 for each group) and non preexposed (n=9 for each group) rats to the context of drug administration with vehicle or diazepam treatment. Circles represent mean, and vertical bars the SEM. * p <0.01 compared with their respective vehicle rats on the same day. **p <0.01 compared with DZ non-pre-exposure rats on day 1. # p <0.01 compared with DZ pre-exposed rats on the third and fourth day. **B.** Threshold frequency to elicit LTP in hippocampal slices from pre-exposed (n=7 for each group) and non pre-exposed (n=6 for each group) rats, treated with vehicle or diazepam (four days). Bars represent the mean and vertical bars the SEM. * p <0.01 compared with their respective vehicle non-pre-exposed rats and compared with the pre-exposed groups. **C.** Percent of animals that develop dependence with or without contextual change. The distribution between groups with different environmental clues is different, Chi-square test 10.54; p=0.0012. **D.** Threshold to induce LTP in hippocampal dentate gyrus, expressed as a percentage of control group (VEH). Each bar represents a mean and vertical bars ± SE. * p< 0.02 group non dependent (NDEP) respect to dependent rats (DEP), dependent rats with clue change and non dependent rats with clue change groups (n= 7 for each group).

It has been suggested that the rapid development of tolerance to the action of DZ and other psychoactive drugs is a learned or contingent form of tolerance [26, 63, 66, 121]. Furthermore, it seems likely that a plastic phenomenon underlies, as an adaptive mechanism, the chronic psychoactive drug administration [71, 72]. Recently, several authors have postulated that drugs of abuse cause long-lasting changes in the brain that may underlie the behavioral abnormalities associated with drug addiction [72, 106, 119]. These molecular mechanisms could be similar to those connected with learning and memory processes.

Considering all these findings together, it can be postulated that the increased hippocampal synaptic plasticity may be the neurobiological substrate responsible for the behavioral alteration observed after chronic DZ administration. Also, the over-expression of the mRNA for the NR1- NR2B NMDA receptor subunit could be one of the biochemical mechanisms responsible for the increased synaptic efficiency in the hippocampal glutamatergic transmission. However, a concomitant decreased hippocampal gabaergic transmission during the development of conditioned tolerance to DZ can not be ruled out.

When DZ is administered for a longer period (i.e. 18 days), animals exhibit withdrawal signs such as anxiety. In addition, they also show a facilitated threshold to induce LTP in the hippocampal formation [80]. These phenomena have a strong dependency on the drug administration context, since both are reversed after the introduction of some

changes in the drug administration environment [79] Fig. (**1C** and **D**). Furthermore, the alteration of some environmental cues increased the locomotive activity in animals that did not show anxiety as a withdrawal sign [79]. Therefore, we conclude that a common neural system could underlie the behavioral expression of conditioned tolerance and dependence on DZ.

Contextual cues linked to drug experience have been frequently associated to craving and relapse, with this phenomenon been described in both human and experimental animals.

Hippocampal synaptic plasticity has been related to learning memory and adaptive processes developed during the chronic administration of drugs of abuse. We have recently observed that the re-exposure to the initial environmental context associated with the drug experience (retrieval) was able to evoke the same behavioral alteration during withdrawal to BDZ. When the hippocampal synaptic plasticity was studied during withdrawal and retrieval, we observed an increased hippocampal synaptic plasticity, on dentate gyrus, in both cases in animals dependent on DZ. In addition, we observed an over expression of Arc protein on dorsal dentate gyrus and CA1 after one day of DZ withdrawal and retrieval for the animals dependent on DZ (Unpublished observation).

POSSIBLE CIRCUITRY INVOLVED IN BEHAVIORAL ALTERATION AFTER CHRONIC BENZODIAZEPINE ADMINISTRATION

Locus Coeruleus Noradrenergic Neurons

LC is the major noradrenergic nucleus in the pons, influencinf a wide range of brain functions and behaviors, such as the sleep-waking cycle [10], neural plasticity [8, 100, 111], drug abuse [56] and stress responses [9, 77]. In addition, this system has been proposed to modulate several cognitive functions, including learning and attention involved in arousal and vigilance [11, 90, 111]. Its activation is one of the major promoters of the physical withdrawal symptoms in different types of psychoactive drugs, involving autonomic and spinal cord functions [56]. Clinical and laboratory reports on BZD withdrawal have described symptoms such as anxiety, insomnia, and hyperexcitability, which suggest enhanced adrenergic activation. Biochemical studies in both humans and animals showed that the acute and long-term use of BZD was associated with decreased levels of NE and its metabolites, while BZD withdrawal was associated with increased NE levels [73, 74].

The participation of the NA system in promoting a full withdrawal syndrome after the long-term use of BDZ has been well established in many studies [30, 87]. Moreover, drugs with a strong direct effect on LC-NE activity have a higher potential for tolerance and withdrawal effects [88]. In our studies, rats chronically treated with DZ for 18 days displayed an increased LC-NE electrical activity, which was assessed by an increased number of spontaneously active cell/track, and a higher firing rate when compared with rats treated with vehicle Fig. (**2A**). Interestingly, DZ treated rats without physical signs of withdrawal, such as increased anxiety in an elevated plus maze, showed no differences in their LC electrical activity compared with controls Fig. (**2A**).

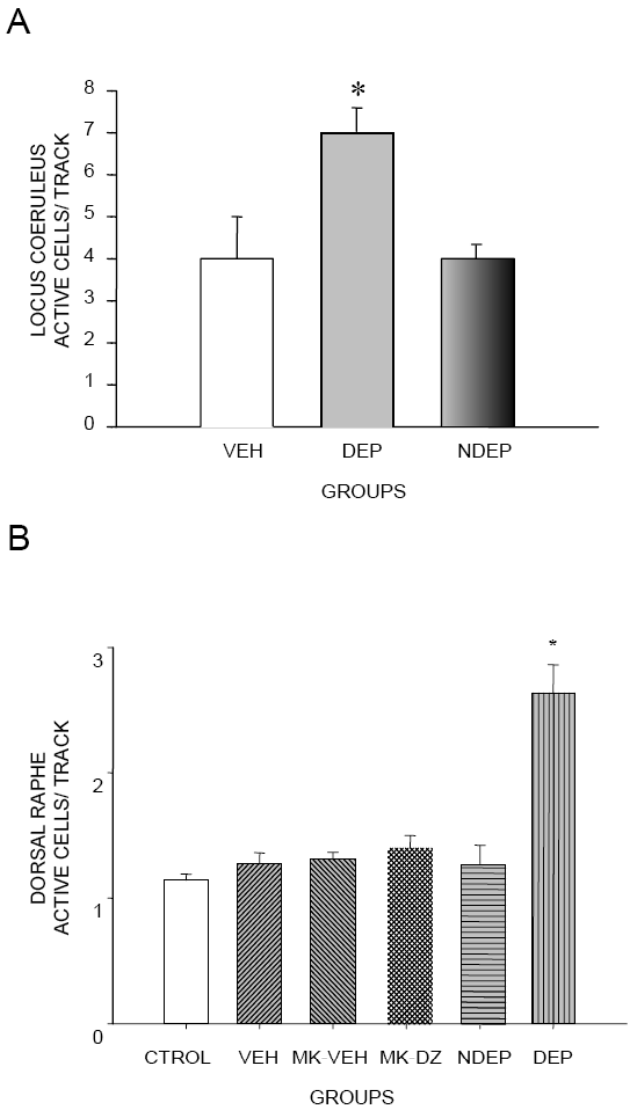

Fig. (2). Withdrawal from benzodiazepine increases Locus coeruleus and Dorsal Raphe neurons activity. A. Bar graph showing number of active cells per track in Locus Coeruleus. Each bar represents a mean and vertical bars ± SE * $p < 0.01$ significantly different from control (VEH) and non dependent (NDEP) groups. **B.** Represent means ± S.E.M. of the number of DNR spontaneously active cells/track in Ctrol, VEH, MK-VEH, MK-DZ DZ-NDEP and DZ-DEP groups. Numbers in brackets indicate numbers of rats. * P< 0.01 respect to VEH, MK-VEH, MK-DZ and DZ-NDEP groups.

The enhancement of LC NE activity, observed after the discontinuation of DZ chronic administration, may account for both physical withdrawal symptoms involving the autonomic function and the increased hippocampal synaptic plasticity. In agreement, it has been demonstrated on hippocampal slices of adult rats, that the perfusion of adrenergic agonists promotes lasting synaptic plasticity in the adult central nervous system [43].

BZD withdrawal symptoms may be a heterogeneous phenomenon, involving a number of different underlying signs mediated by different mechanisms [31-33]. In our research, we have used the increase in anxiety as a behavioral

expression of a mild symptom of discontinuation of DZ chronic administration, which was assessed by the activity of the rat in an elevated plus maze. Under our experimental conditions, an increased hippocampal synaptic plasticity was found after chronic DZ administration (18 days) and withdrawal. This increased plasticity, correspond to an enhanced LC-NE activity during withdrawal but not after chronic DZ treatment. In summary, previous results confirm the potential role of the hippocampus glutamatergic and gabaergic transmission in the mechanisms underlying the altered behavior characterizing diazepam withdrawal. The LC-NE system increased activity reported here is in agreement with previous findings which have demonstrated increased NA levels and metabolites in both human and rodent DZ withdrawal. Furthermore, it has been proposed that the DZ-increased LC-NE activity affects the regulation of NA release indirectly through GABA, a primary inhibiting neurotransmitter system of the brain [21, 75, 103]. The medial prefrontal cortex provides a powerful excitatory influence on LC neurons, which is mediated by excitatory amino acid (EAA) inputs [46]. These findings indicate a source whereby cognitive processing or emotional activity influences the LC function, and reinforces the idea that LC is fully involved in the modulation of higher mental activity. We can also speculate that the increased LC-NE activity may be a consequence of the cortical activation produced by behavioral alterations observed during withdrawal. Another aspect of these results is the fact that the hyper LC-NE activity observed, but only after the presence of increased anxiety, validates this to be further evidence of DZ withdrawal. However, we cannot rule out the participation of other brain areas and cellular mechanisms in the behavioral alterations characterizing withdrawal symptoms.

Dorsal Raphe Nucleus 5-HT Containing Neurons

The dorsal raphe nucleus (DRN) is generally considered to be a serotonergic nucleus, due to the fact that it is the largest source of 5-hydroxytryptamine (5-HT) terminal in the forebrain. It is generally agreed that *in vivo* 5-HT neurons spontaneously fire broad spikes in a slow, and regular firing pattern [1, 2, 40]. However, there are also significant numbers of neurons containing GABA, dopamine, glutamate, acetylcoline or any of a variety of neuropeptides [44]. 5-HT-containing neurons are either silent or spontaneously active, with a slow, regular firing pattern (0.5-2.5 Hz) and a long duration action potential (1.0 - 2.5 ms). In addition, their firing is inhibited by stimulation of inhibitory 5-HT1A autoreceptors. The forebrain 5-HT system is implicated in many aspects of the cerebral function, including emotion and fear processing, cognition, movement, and regulation of the sleep-wake cycle [20, 45, 65]. 5-HT has been implicated in the control of a wide variety of psychiatric functions, with dysfunction of the 5-HT system thought to be involved in the development and/or progression of neuropsychiatric disorders including depression and anxiety [22, 36, 67]. Specifically, agonists of the serotonin 1A receptor have anxiolitic properties, and knockout mice lacking this receptor have shown an increase in anxiety-like behavior [38, 39, 78]. It has been postulated that the anxiety occurring during DZ withdrawal is mediated by an increased 5-HT release in the hippocampus [7].

We have observed, in rats, an increased neuronal activity on the DRN during DZ withdrawal, assessed by an increased number of spontaneously active cells per track on this nucleus and an increased number of neurons firing between 1.01 – 1.50 spike/sec. Furthermore, previous MK-801 administration impaired the development of anxiety signs during DZ withdrawal, with an increase in electrical activity been seen on 5-HT neurons of the DRN Fig. (**2B**) [4]. It has also been demonstrated that a single DZ administration induces a slow neuronal activity in the 5-HT neurons of the DRN [27]. Considering this fact, it is reasonable to speculate that there might have been a development of subsensitivity in the $GABA_A$ receptors located on 5-HT neurons of DRN after 18 days of DZ administration. This effect may account for the increased DNR neural activity observed during DZ withdrawal. It is interesting to note that only DRN neurons (firing between 1.01-1.5 Hz) increased their activity during withdrawal, with MK-801 impairing this effect but without acting on the neurons firing at a lower or higher velocity. The DRN project to different areas of the brain which are involved in a variety of behavioral conditions [1, 2, 45, 65]. Due to their modulatory function, the 5-HT neurons display a wide pattern of discharge, and it seems likely under our experimental conditions that only these cells participate by increasing their activity. The reversal of the rise in DNR neuronal activity by MK 801 observed in our studies, may be explained by an increased density of serotonergic $5\text{-}HT_{1A}$ auto receptors in the DNR neurons and a concomitant autoinhibition in their firing rates, since an increased density of $5\text{-}HT_{1A}$ receptors has previously been described after MK-801 administration on this nucleus [115]. Another reason for the impairment of the higher neuronal activity on DRN after MK-801 administration could be due to MK-801 inhibition on NMDA associated channels in 5-HT neurons of DRN.

Serotonin systems have been implicated in the regulation of hippocampal functions such as hippocampal synaptic transmission [12, 54, 100]. Moreover, it has been demonstrated that an increased hippocampal synaptic plasticity is developed after chronic DZ administration and also on withdrawal [79, 80]. This increased neuronal activity of the DRN may result in a disinhibition of the hippocampal synaptic function [50, 54, 120], thereby facilitating the plastic phenomenon underlying the behavioral expression of chronic DZ administration.

Neuronal Circuitry Activated During Development of Tolerance, Dependence and Withdrawal to DZ

Considering all the results discussed here, we can assume that the same neuronal circuitry is activated during the development of tolerance and dependence to DZ as a consequence of the learning associative processes. The hippocampal synaptic plasticity may be the biological substrate underlying, at least partially, both phenomenons. The facilitation of the hippocampal synaptic transmission may be due to an increased glutamatergic input, as a consequence of the over expression of the NMDA receptors and the facilitated NE activity in this area. The behavioral alteration observed during DZ withdrawal might be explained by the increased activity of DRN 5-HT serotonergic containing neuron, see Fig. (**3**). However, bearing in mind the complexity of the biological changes due to the chronic administration of psychotro-

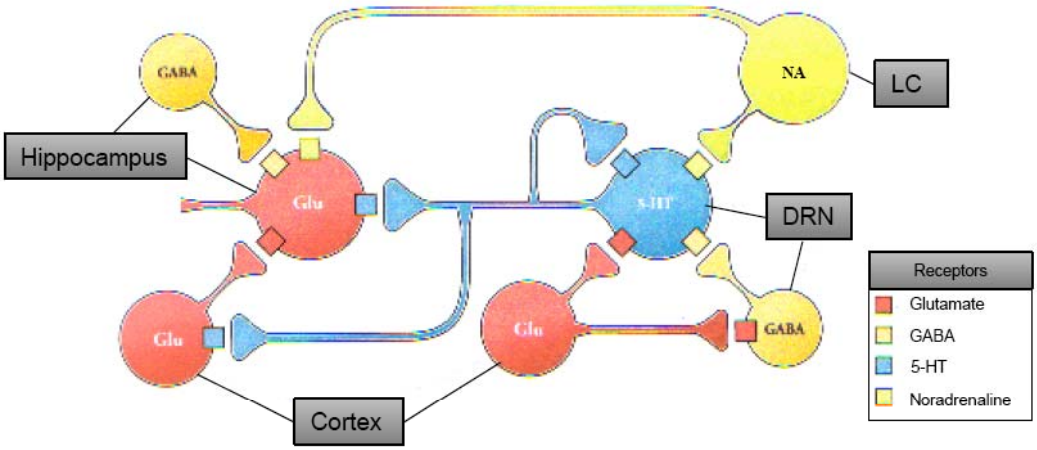

Fig. (3). Brain circuitry associated to Benzodiazepine withdrawal.

Schematic representation of some brain areas involved in dependence and withdrawal to benzodiacepines. Noradrenergic (NA) projections are sent from the Locus Coeruleus (LC) to Dorsal Raphe Nucleus (DRN) and hippocampus (H). Serotoninergic projections are sent from DRN to H and Cortex (C). Cortical projections inervate H and DRN. GABAergic interneurons are present in H and DRN.

pic drugs, we can not rule out the participation of other brain areas not considered in this review.

Cocaine and Dentate Gyrus Hippocampal LTP

The environmental context of the psychotropic experience is determinant for the cocaine seeking-behaviour in humans which also can be extended to rodent. These conditioned aspects of addiction have led many authors to propose a common neurobiological mechanism mediating drug addiction and memory. In this aspect, a pivotal role has been attributed to the synaptic plasticity at glutamate synapses in different areas of the brain, such as the hippocampus, frontal cortex, ventral tegmental area (VTA) and nucleus accumbens (NAcc). A lasting increase in the efficacy of glutamatergic synaptic transmission (LTP) is accepted as a molecular mechanism for memory storage in the brain [64, 95]. Related to this, the hippocampal LTP is the neurobiological substrate for learning and memory in which contextual cues are relevant [69]. It is thought that the reward pathway, involving the ventral midbrain NAcc and frontal cortex, is the main neuronal circuitry in the neurobiology of addiction. However, other brain areas, such as the hippocampal formation, have been implicated as beeing potential responsible for the initiation and maintenance of drug addiction [23]. Recently, Perrotti *et al.* [82] have pointed out that different addictive drugs, such as cocaine, morphine, and Δ9 Tetra-hydrocannabinoide (Δ9 THC) but not alcohol, have the capacity to increase the expression of ΔFosB on the *dentate gyrus* of the hippocampal formation. Working with rodent, several chronic cocaine treatments have demonstrated a modulator effect on the CA_1 hippocampal synaptic plasticity [17, 106]. Moreover, reinstatement of cocaine seeking behavior in the rat was observed after a hippocampal theta burst stimulation [114].

The molecular basis of LTP generation is currently under investigation. Generally, it is accepted that an NMDA receptor-mediated increase in postsynaptic calcium concentration is required for the development of LTP. Cocaine impairs the reuptake of different monoamines, such as NA, DA and 5-HT, in the pre-synaptic terminal. These monoamine increases on the synaptic gap can influence the synaptic mechanisms underlying the LTP phenomenon on hippocampal formation, synaptic remodeling on the post-synaptic membrane and also the structure of the dendrite spines [55, 57].

Repeated administration of psychostimulants such as amphetamine and cocaine causes increases in some behavioral responses to the drug; with this effect being called behavioral sensitization [49, 112]. Repeated cocaine administration was found to have a good correlation with the increased EAA transmission in the nucleus accumbens and other brain areas of the reward system [5, 84, 110, 123].

It has been demonstrated that inhibitory avoidance (IA) creates a stable memory trace in a single trial and causes a substantial changes in the gene expression of hippocampus, suggesting that this is an area of grate synaptic plasticity [116]. In agreement with this, we have recently demonstrated that only sensitized rats after chronic cocaine administration (15 mg/kg/day) for 5 days, showed an increase in the dentate gyrus hippocampal synaptic plasticity and improved the retention of IA in the step-down paradigm (unpublished observation). Furthermore, Del Olmo *et al.* have recently published that cocaine self-administration improves behavioral performance in a high demanding water task [16] and also increases the synaptic plasticity on the CA1 area of hippocampal formation [17].

CONCLUSION

In the present review, we have emphasized that the contextual clues associated to drug administration are relevant in the development of addiction to DZ and other psychostimulants. Also, we have pointed out that the increased plasticity observed in the hippocampus, concomitant to the development of tolerance, dependence and withdrawal may be the neurobiological substrate underlying the behavioral alterations observed as a consequence of chronic DZ administration. The hippocampal glutamatergic transmission seems to be relevant for the development of these adaptive processes, together with the modulator effects of the noradrenergic and

serotonergic systems. Moreover, a conspicuous role for LC NE activity in the withdrawal to opiates drugs [6] and cocaine has been described (unpublished observation). If we extend these findings concerning the mechanisms of craving and relapse to other psychostimulant drugs, we can conclude that an associative process of learning is very important, irrespective of the particular chemical nature and mechanisms of action of the drug under study.

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