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Carisoprodol: Update on Abuse Potential and Mechanism of Action

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Abstract

Carisoprodol is a centrally-acting skeletal muscle relaxant frequently prescribed for acute musculoskeletal conditions. Recreational use of carisoprodol is an increasing problem. Tolerance to carisoprodol develops quickly and abusers often take 10-20 times the normal dose, leading to intoxicating effects. Also, abrupt cessation of carisoprodol results in severe withdrawal syndrome including delusions, seizures and even death. Considering its alarming rate of abuse and subsequent consequences, carisoprodol was scheduled (schedule IV) at the federal level effective January 11, 2012. Until recently, it was widely accepted that the sedative and muscle relaxant effects of carisoprodol were due predominantly to its metabolite, meprobamate. However, it is now clear that carisoprodol itself modulates and directly gates γ-aminobutyric acid type A receptors ($GABA_A$Rs), the predominant inhibitory neurotransmitter receptors in mammalian brain. Recent work has provided additional insight into carisoprodol's interaction with $GABA_A$Rs. This may underlie the ability of carisoprodol in enhancing the sedative effects of CNS depressants, contributing to its potential for abuse. In this review, we discuss current understanding with regard to the abuse potential of carisoprodol, therapeutic and abuse-related actions of this drug, and possible molecular actions that underlie these effects.

Keywords: Substance abuse; $GABA_A$ receptors; Muscle relaxant; Carisoprodol; addiction; CYP2C19

Introduction

Carisoprodol is a centrally acting muscle relaxant, frequently prescribed to relieve skeletal muscle spasms and associated pain (1). Recent evidence confirms carisoprodol abuse leads to several adverse effects, such as psychomotor impairment and severe withdrawal that may predispose to hallucinations, seizures and death (2-5). Carisoprodol abuse has increased rapidly in recent years. Recreational users abuse carisoprodol for its muscle relaxing, anxiolytic and sedating effects, and often mix it with other CNS depressants to enhance its sedative or euphoric effects (6). The Drug Enforcement Agency (DEA) has reported cases of carisoprodol intoxication are also increasing. Seizures induced by carisoprodol misuse increased from fewer than 4000 in 2008 to more than 5000 in 2010, higher than other abused drugs like lorazepam and methylphenidate. Increasing popularity of carisoprodol among high school students is also a topic of concern. According to Monitoring the Future National Survey on Drug Use (2009), annual non-medical use of carisoprodol among all high school seniors was 1.3% and 1.4% in 2007 and 2008, respectively (7). These numbers are higher than other prescription abused drugs like chlordiazepoxide (0.2%) and lorazepam (0.4%) and comparable to clonazepam (1.3%) (7). Considering the danger posed by carisoprodol and its increasing abuse rate, an understanding of its mechanism of action is of interest. Its physiological effects have generally been attributed to actions of its primary metabolite meprobamate (8) at GABA type A receptors ($GABA_A$Rs), the predominant inhibitory neurotransmitter receptor in the brain (9). However, it is now known that carisoprodol can directly gate and allosterically modulate the $GABA_A$R, likely through a novel site(s) of action (10), and thus many actions may be attributable to the parent drug carisoprodol. In this review, we discuss current understanding with regard to the abuse potential of

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carisoprodol, therapeutic and abuse-related actions of this drug, and possible molecular actions that underlies these effects.

Clinical Uses of Carisoprodol

Carisoprodol was first approved in 1959 by the Food and Drug Administration (FDA) for clinical use as a skeletal muscle relaxant (2). It is/has been marketed in the United States under the brand name Soma, Soridol and Rela in the United States, Carisoma in the United Kingdom, and under the names Sonoma, Somadril, Somacid, Scutamil C, Relacton-C, Mio Relax, and Relaxibys in other countries (7). Carisoprodol is commonly prescribed for acute musculoskeletal spasm and associated pain in adults. The analgesic, muscle relaxant and sedative effects of carisoprodol are the basis for its use in the alleviation of lower back pain and in the short-term treatment of painful, acute musculoskeletal conditions (1). Like other muscle relaxants, carisoprodol is often prescribed as an adjunct to rest or physical therapy and is also available in preparations with other analgesics such as aspirin or codeine (Soma® Compound or Soma® Compound with codeine) (11). The onset of action is rapid and effects last for 4-6 hours (12). It is available in 250 mg and 350 mg tablets, and is administered 3-4 times a day for a maximum duration of 2-3 weeks. Carisoprodol was the 2nd most prescribed muscle relaxant in the US in 2000, accounting for 21% of all skeletal muscle relaxant prescriptions. Together with cyclobenzaprine and metaxalone, these three drugs accounted for 45% of all skeletal muscle relaxant prescriptions dispensed in 2003 and 2004 (1, 13). A market intelligence corporation, IMS Health, reported 10.6 million prescriptions were dispensed in 2008 alone (14). The most common side effects of carisoprodol when taken medicinally are drowsiness, dizziness, and headaches (15). Other side effects include nausea, vomiting, hypotension, tachycardia, ataxia, vertigo, tremors and seizures. Adverse effects are generally observed after high dose administration or sudden cessation. Toxic doses of carisoprodol elicit agitation, myoclonus and bizarre movements (16, 17).

Abuse and Withdrawal Syndrome

Carisoprodol was developed as an analog of meprobamate, promoted as having less abuse liability and better muscle-relaxing properties (18). An early report suggested carisoprodol did not substitute for morphine or barbiturate and did not produce morphine- or barbiturate-like intoxication or withdrawal symptoms, and it was thus concluded carisoprodol does not pose abuse liability (12). However, more recent reports have confirmed its abuse potential, along with subjective and psychological impairment and severe withdrawal syndrome that may predispose to seizures and even death (2, 4, 7, 19-22). The American Association of Poison Control Centers reported 2632 cases of intentional carisoprodol ingestion requiring medical attention in 2008 (23).

Studies conducted in healthy individuals showed a single supra-therapeutic 700 mg dose of carisoprodol produced both subjective and psychomotor impairments, whereas a single therapeutic dose (350 mg) produced mainly psychomotor impairments and minimum subjective impairments (24). Administration of 10 mg oxycodone within 1 hour of 350 mg carisoprodol further affected the psychomotor impairments (4). In a study that assessed dose-dependent effects of carisoprodol, consumption of 1-3 tablets produced feelings of well-being and an energetic state, consumption of 4–10 tablets produced psychomotor excitement, cheerfulness, increased socialization and self-confidence, while consumption of a one-time dose of 10 tablets produced a state of disorientation and partial amnesia of the events occurring during intake (18). In a study conducted by Reeves and Burke (20), subjects consuming 12-30 tablets a day alone or in combination with other drugs like tramadol, benzodiazepines or alcohol reported euphoria and hallucinations. Misuse of carisoprodol has also been associated with suicide attempts (25).

In patients taking prescribed carisoprodol for extended use, the desire to continue its use is strong. Owens et al (26) found that in approximately 80% of reported cases, patients continued to purchase carisoprodol even after their insurance declined to cover the bills. Reeves et al. (8) reviewed use of carisoprodol in patients who had been taking carisoprodol for more than 3 months. A significant subset of individuals had been diagnosed with a substance abuse problem, and they were more likely to misuse carisoprodol than those without a history of drug abuse. Collectively, the evidence suggests that carisoprodol has addictive properties and abuse potential is high. Of additional concern is the fact that physician awareness of the potential dangers of carisoprodol may be inadequate. Reeves et al. also reported that whereas the great majority (95%) of physicians were aware that meprobamate is a controlled substance, fewer than 20% knew that carisoprodol is metabolized to meprobamate. Now

that carisoprodol is also scheduled, the recognition of dangers associated with its misuse should improve.

Carisoprodol is passed to nursing infants during breastfeeding. Serum concentrations of carisoprodol and meprobamate were measured from a nursing mother who took 3 times the normal dose of carisoprodol per day for severe back spasms before and after uncomplicated delivery, and during the first month of breast feeding (27). Significant amounts of carisoprodol and meprobamate were found in both the breast milk and the infant's serum, but no developmental toxicity was observed. Mild sedation in the baby while breast feeding was reported, however no signs of withdrawal were observed after feeding was stopped.

Carisoprodol abuse has increased rapidly in recent years. Low cost and easy accessibility compared to other illegal drugs make it an ideal choice for substance abusers. Abusers often combine carisoprodol with other psychoactive drugs to augment or alter their effects. For example, it may be combined with alcohol or benzodiazepines to increase their sedative effects, with cocaine to attenuate jitteriness associated with its use, and with other drugs to get synergistic relaxation and euphoria (20, 28). Individuals may substitute carisoprodol for opiates or benzodiazepines if these drugs are not accessible (29). As per the National Survey on Drug Use and Health in 2009, an estimated 2.9 million people in the United States admitted lifetime consumption of carisoprodol for non-medical purposes. In 2008, the National Forensic Laboratory information system reported carisoprodol as 1 of the 25 most frequently abused drugs (2). In 1996, the DEA proposed scheduling of carisoprodol, but the FDA and drug advisory committee did not take this action, feeling the evidence regarding abuse potential of carisoprodol was insufficient (2). Following additional hearings on the possible scheduling of carisoprodol in 2010, carisoprodol was placed in schedule IV of the Controlled Substance Act of 1970 (30), effective January 11, 2012. Since the earlier review, a better understanding of the potential mechanism underlying its actions had been developed, and abuse of carisoprodol had risen significantly. For example, in 2009, out of roughly 50,000 emergency department visits related to abuse of musculoskeletal relaxants, 30,000 visits were due to misuse of carisoprodol; this is double the number of visits related to carisoprodol abuse reported just five years earlier (7). Considering the subjective, psychomotor impairment and CNS depressant effects of carisoprodol, it is not surprising that carisoprodol use increases risk of traffic accidents and accidents while operating heavy machine (24). Indeed, carisoprodol and meprobamate have been ranked 7th out of the top 10 classes of drugs associated with driving under the influence of drugs, and this activity may in fact result in a charge of driving while intoxicated (DWI) (31).

Carisoprodol abuse is not only an issue in the United States; its abuse has been documented in many other countries (6, 15, 18, 31). In 2007, Norway scheduled Carisoprodol as class "A" drug, which is the highest scheduling level in Norway and a category that includes narcotics and hypnotics (32). Recently, the Committee for Medicinal Products for Human Use (CHMP) concluded the abuse potential associated with carisoprodol outweighs its benefits as a therapeutic drug; carisoprodol was removed from the market by the European Medicines Agency in 2008 and is only available to those for whom there are no other alternatives (32). In South Sulawesi, sex workers spend nearly all their earnings to buy carisoprodol (6). They take up to 10 pills a day, often along with alcohol and other psychoactive prescription drugs. These individuals consistently report beneficial effects of taking carisoprodol, including enhanced confidence and reduced shyness, both of which facilitate attracting customers. As education about the adverse effects of carisoprodol is not readily available to them, its use is very common (6). Carisoprodol has become a cross-border problem as well. Several thousands of pills can easily be purchased at a time in Mexico to be smuggled into United States for illegal distribution (33). Correspondingly, the Los Angeles police department reported carisoprodol is one of the prescribed drugs they encounter most frequently at the US-Mexico border crossing (20).

A significant problem with carisoprodol is that tolerance to its effects develops rapidly, and increased consumption of tablets often follows. Subsequent abrupt cessation results in withdrawal syndrome (34). Abrupt cessation of carisoprodol administration in humans (100 mg/kg/day, 5 times the normal daily dosage) results in insomnia, abdominal cramps, headache, chills and nausea (35). Hallucinations, delusions, tremors, seizures and even death have also been reported (20, 21, 36). Prisoners in Norway who had been taking 700 - 2100 mg/day of carisoprodol for at least 9 months showed withdrawal symptoms including insomnia, anxiety, irritability and muscular pain upon sudden

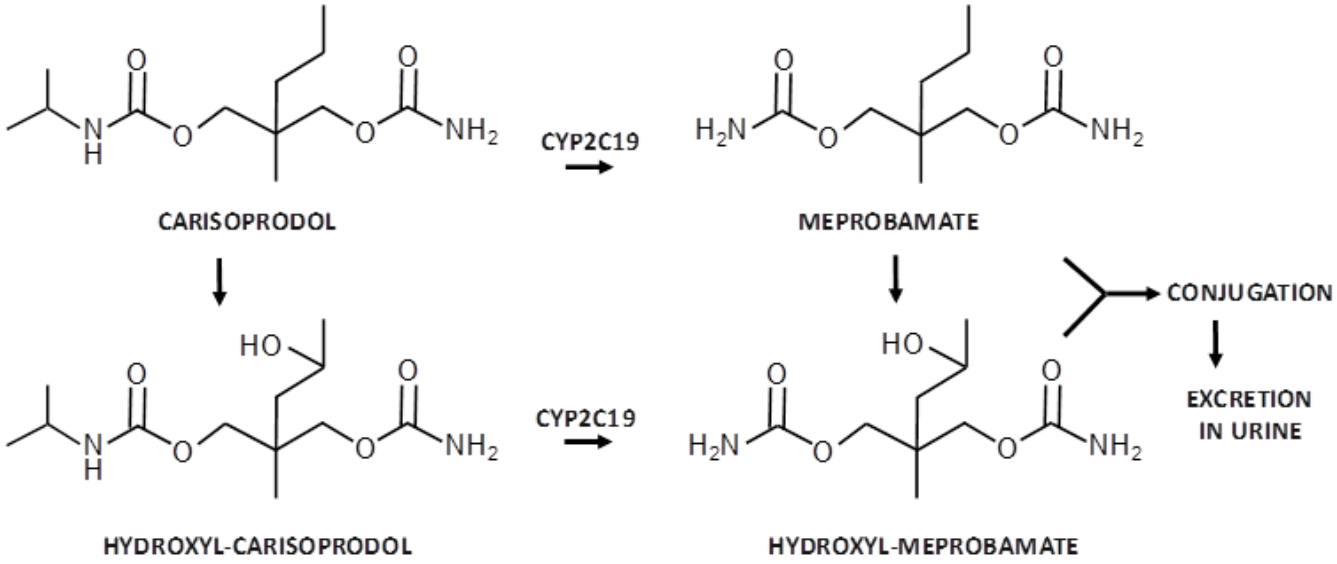


Figure 1. Metabolism of carisoprodol via cytochrome CYP2C19 enzyme. Carisoprodol is metabolized by cytochrome CYP2C19 enzyme via N-dealkylation of its isopropyl group, to form its active metabolite meprobamate. Carisoprodol is also metabolized to a small extent to an inactive metabolite, hydroxyl-carisoprodol, by an unknown enzyme. Meprobamate and hydroxyl-carisoprodol further metabolized to hydroxyl-meprobamate and conjugate and excreted by kidney in urine.

discontinuation of drug intake (37). Whereas withdrawal symptoms are generally associated with cessation of large doses of carisoprodol, they have been observed with cessation of as few as 4 to 8 tablets of carisoprodol per day (38). Whereas toxic and withdrawal symptoms have a notable GABAergic component (below), other systems may be affected. Bramness et al (17) reported 4 cases where subject had consumed up to 65 pills of carisoprodol alone or along with other sedative/hypnotics; these subjects showed characteristic effects that might be associated with serotonergic activation, such as tachycardia, hypertension, involuntary, robot-like, choreiform movements, tremors and shivering (5, 16). In that study, however, signs and symptoms included in the classification of serotonergic syndrome were nonspecific; because a complete drug screening was not performed, one cannot rule out the possibility that other drugs present were eliciting the serotonergic effects. Behavior studies suggest possible involvement of the NMDA receptor in the actions of carisoprodol, as the NMDA receptor antagonist MK-801 partially substituted for the discriminative stimulus effects of carisoprodol (39). Currently, a suitable and efficient treatment for carisoprodol intoxication and withdrawal is not available. Withdrawal syndromes are treated with barbiturates and benzodiazepines to suppress anxiety and agitation (40). Treating carisoprodol overdose is more complicated because of the presence of serotonergic-like symptoms noted above. A benzodiazepine antagonist is generally given in cases of carisoprodol intoxication, but considering carisoprodol does not act at the benzodiazepine site (below), this is not an entirely appropriate approach.

Pharmacology of Carisoprodol

Pharmacokinetics

Carisoprodol is a white crystalline powder with mild characteristic odor and a bitter taste. It is a racemic mixture of two stereoisomers, (*RS*)-2-{[(aminocarbonyl)oxy]methyl}-2-methylpentyl isopropylcarbamate. Its molecular weight is 260.33 Da and its octanol\water partition coefficient is 2.36. Carisoprodol solubility is independent of pH. It is freely soluble in organic solvents like DMSO, chloroform, acetone and alcohol and moderately soluble in water (30 mg/100 mL at 25 °C) (12). The structure of carisoprodol is closely related to meprobamate, differing only by a hydrogen atom substituting for the isopropyl group on one of the carbamyl nitrogens (Figure 1).

Carisoprodol is rapidly absorbed from the gastrointestinal tract, crosses the blood brain barrier and distributes throughout the CNS. With a single dose of 350 mg, effects of carisoprodol begin within 30 minutes of administration and peak plasma concentrations reach 4-7 μg/mL in 2 to 4 hours (12). Carisoprodol is metabolized to

meprobamate in the liver through N-dealkylation by the cytochrome P450 enzyme CYP2C19 (41, 42). Carisoprodol is also metabolized to a small extent by an unknown enzyme to an inactive metabolite, hydroxyl-carisoprodol. Both meprobamate and hydroxyl-carisoprodol are further metabolized to hydroxyl-meprobamate, conjugated and excreted by the kidney (43). With a single dose of 350 mg of carisoprodol, less than 1% is excreted unchanged whereas approximately 4.7% is excreted as meprobamate in urine within 24 hours (44).

The half-life of carisoprodol metabolism is approximately 1.5 hours, but it may be altered significantly, depending on the CYP2C19 enzyme allele (45). Cytochrome P450 2C19 (CYP2C19) is a genetic polymorphic enzyme comprising different alleles. CYP2C19*1 allele encodes normal activity, whereas *2, 3 and 4 alleles encode no activity. CYP2C19*17 has been reported as a CYP2C19 allele with superior enzymatic activity (46). People with one normal, two normal or one CYP2C19*17 allele, and two abnormal CYP2C19 alleles with no activity are categorized as “intermediate” (IM), “extensive” (EM) and “poor” (PM) metabolizers of carisoprodol, respectively (45). The CYP2C19 genotype influences the pharmacokinetics of carisoprodol, and thus carisoprodol and meprobamate blood concentrations. EMs and IMs metabolize carisoprodol with a half-life of 1.5 hours (41, 42). Roughly 2-3% of Caucasians are PMs; they eliminate carisoprodol with a half-life of more than 6 hours and generate meprobamate to a small extent (47). Carriers of deficient CYP2C19 alleles accumulate higher concentrations of carisoprodol that may lead to intoxication, while potentially high levels of the active metabolite meprobamate can accumulate in CYP2C19*17 carriers. However, CYP2C19 genetics alone do not appear to play a significant role in carisoprodol-related mortality (48). Instead, interaction with other drugs likely plays a key role in carisoprodol-related fatalities (22). Postmortem evaluation of carisoprodol concentration in blood and liver has shown carisoprodol concentrations as low as 15 mg\L in blood and 50mg\kg in liver can be fatal in the presence of other sedative/hypnotics like alcohol, diazepam, alprazolam and temazapam (22).

Age, sex and co-administration of other drugs that interact with the CYP2C19 enzyme also affect carisoprodol metabolism and thus blood concentrations (49). A retrospective study conducted on 14,965 subjects assessed effects of age, sex and drugs that inhibit CYP2C19 enzymes (esomeprazole, fluoxetine or omeprazole). Metabolic rates were twice as high in young subjects compared to elderly, and were approximately 20% higher in females than males (49). Also, esomeprazole and fluoxetine, but not omeprazole, significantly decreased the metabolic rate of carisoprodol. Use of oral contraceptives inhibits the metabolism of carisoprodol in a CYP2C19 genotype-dependent manner; IMs using oral contraceptives accumulate more carisoprodol than EMs using them (50). As more than 25% of women aged 20-40 use oral contraceptives (51), it is important for clinicians to be aware of the potential effects on carisoprodol concentration in those taking oral contraceptives.

Pharmacodynamics

Carisoprodol mediates its effects centrally rather than through direct skeletal muscle relaxation (10). Inhibition of inter-neuronal transmission in the descending reticular formation and spinal cord is one of the mechanisms proposed for its muscle relaxant properties. Whereas the precise mechanism of action of carisoprodol is not fully understood, it has been thought that carisoprodol exerts its effects via its metabolite, meprobamate. Meprobamate is a sedative-hypnotic that was commonly used in the treatment of anxiety. It is currently classified as a schedule IV controlled substance at the federal level, with abuse potential comparable to that of benzodiazepines (52, 53). Meprobamate was introduced in 1955 under the brand names Miltown and Equinil, but within a few years was replaced by benzodiazepines because of high abuse liability (7). Although the central mechanism of action of meprobamate has also not been fully elucidated, $GABA_A$ receptors are a key target. Meprobamate allosterically potentiates $GABA_A$ receptors and directly gates the receptor at millimolar concentrations (54). Meprobamate intoxication causes cardiogenic hypotension, CNS depression, flaccid muscles and loss of tendon reflexes (55). As noted, it was assumed therapeutic effects and abuse potential of carisoprodol are due to its metabolism to meprobamate (56). Following a single 700 mg dose of carisoprodol, serum levels of meprobamate surpass those of carisoprodol in 2.5 hours, and approximately 90% of carisoprodol is metabolized to meprobamate in 6 hours (42). Despite the likely contribution of meprobamate to the therapeutic and adverse effects of carisoprodol, the pharmacological and physiological effects of carisoprodol are somewhat distinct, suggesting carisoprodol has its own actions (19). For example, supratherapeutic doses of carisoprodol mainly result in CNS

depressant effects such as dizziness, drowsiness, ataxia, tremors, blurred vision and headache, whereas agitation and bizarre movements occur with toxic levels of meprobamate (7, 17, 19). Moreover, signs of toxicity are observed within 30 minutes of overdose of carisoprodol (t ½ 1.5 hours), before it is metabolized to meprobamate (t ½ 11 hours) (12).

Gonzalez et al., using whole cell patch electrophysiology in HEK cells, showed carisoprodol itself allosterically modulates and directly activates $GABA_A$Rs (10). Carisoprodol inhibits the receptor at high concentration, eliciting rebound currents upon termination of drug application, as observed with barbiturates. In vivo studies showed maximal depression of motor activity was observed within 10 minutes of carisoprodol administration, a timeframe inconsistent with effects being due to conversion to meprobamate (10, 34). In addition, in rats trained to discriminate carisoprodol from saline, the GABAergic ligands pentobarbital, chlordiazepoxide and meprobamate substituted for carisoprodol (10). These results suggest $GABA_A$ receptors as potential targets of carisoprodol, and demonstrate its capacity to enhance the sedative effects of CNS depressants, contributing to its potential for abuse. Discriminative stimulus effects of carisoprodol were blocked by the barbiturate antagonist bemegride, but not by the benzodiazepine antagonist flumazenil. Similarly, carisoprodol-gated currents were blocked by bemegride but not by flumazenil(19). These results rule out the involvement of the benzodiazepine binding in carisoprodol modulation of $GABA_A$ receptors. Recently, Gatch et al. (34) characterized tolerance and dependence potential in mice. Tolerance (measured as loss of righting reflex) developed quickly, as mice showed a decrease in the loss of righting reflex following just 4 doses of carisoprodol. Whereas spontaneous withdrawal symptoms were not produced within 24 hours following withdrawal from carisoprodol, precipitated withdrawal signs were observed with administration of either the benzodiazepine antagonist flumazenil or the barbiturate antagonist bemegride (34).

Molecular Mechanism of Carisoprodol Actions

$GABA_A$ receptors are composed of α, β and γ subunits, each of which has multiple isoforms (57). Recent studies have shown that whereas carisoprodol allosterically modulates and directly gates a spectrum of receptors comprising multiple subunit isoforms, potency and efficacy of effect do vary in a subunit-dependent manner (58). Unlike benzodiazepines, carisoprodol is capable of direct gating and allosteric modulating $GABA_A$ receptors in the absence of the γ2 subunit (58). When evaluated in αxβyγ2 receptors, with x = 1-6 and y = 1-2, the allosteric modulatory effects of carisoprodol were found to be most efficacious in α1ß2γ2 receptors. Regarding direct gating actions, carisoprodol was observed to be most efficacious in ß1-expressing receptors, and least potent and efficacious in α3-expressing receptors in αxβyγ2 configurations (58). For extra-synaptic, δ-containing $GABA_A$ receptor, carisoprodol was more efficacious as a direct gating agonist than GABA. Moreover, like barbiturates, neurosteroids and general anesthetics, non-direct gating concentrations of carisoprodol potentiated saturated GABA currents (58). Although drug discrimination and electrophysiological studies suggest possible overlap of the mechanism of action of carisoprodol and barbiturate effects, site-directed mutagenesis on homomeric ρ1 GABA receptors have shown functional domains are not equivalent (10, 19). Specifically, mutation of tryptophan to methionine at position 328 of the ρ1 subunit (ρ1W328M) confers pentobarbital direct gating sensitivity to insensitive wild type ρ1 GABA receptors, whereas this mutation does not confer sensitivity to carisoprodol (10). Thus whereas carisoprodol shares several properties with barbiturates and a barbiturate antagonist can attenuate some of its effects, the two molecules interact at distinct sites on the $GABA_A$ receptors.

Molecular Actions of Carisoprodol Coincide with Reward Signaling

The mesolimbic system is well documented for its involvement in the mechanism of addiction of opioids, ethanol, psychostimulants and nicotine (59). These drugs increase dopaminergic transmission in the mesolimbic system, increasing the levels of dopamine in the nucleus accumbens (60). Recently, Tan et al. showed α1-containing $GABA_A$ receptors are involved in addictive properties of benzodiazepines, and their activation elicits an increase in nucleus accumbens dopamine levels (61). GABAergic neurons in ventral tegmental area (VTA) specifically express α1-containing $GABA_A$ receptors, while dopaminergic neurons transmitting to nucleus accumbens from VTA express α2, α3 and α4-containing $GABA_A$ receptors, but not α1-containing receptors (62) (Figure. 2). Potentiation of α1-containing $GABA_A$ receptors on GABAergic neurons by benzodiazepines inhibits the neuron and decreases the release of GABA at dopaminergic neuron synapses. This

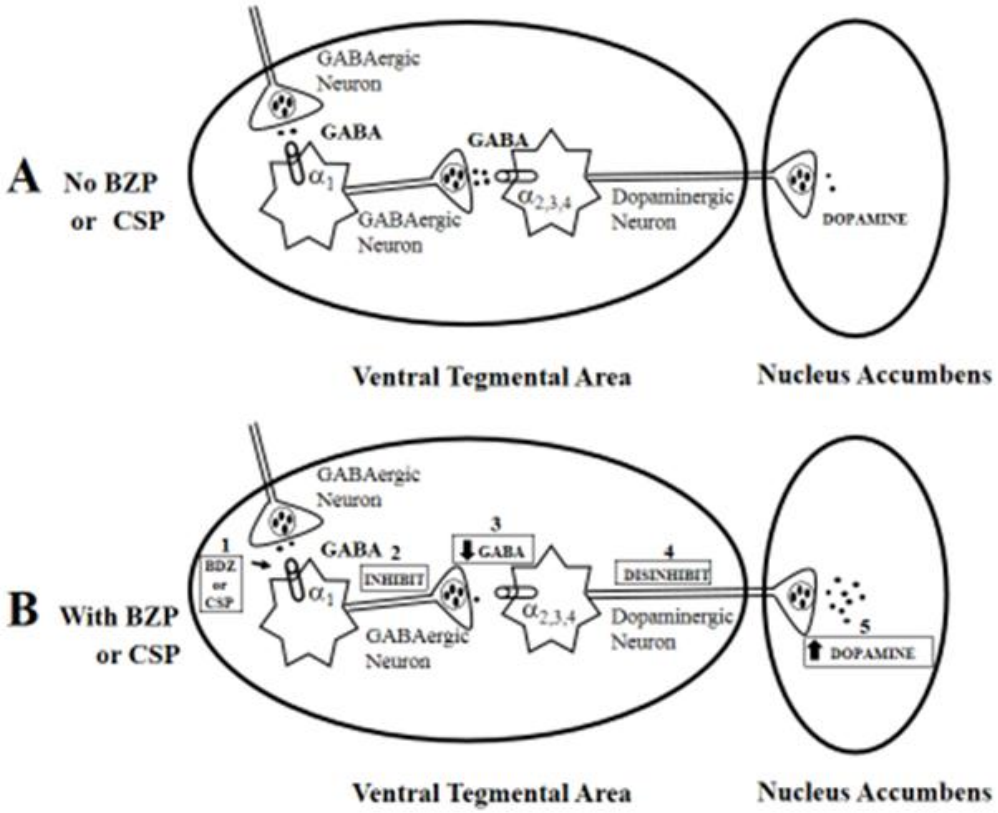


Figure 2. Involvement of $GABA_A$ receptors in drug addiction pathways. A, Dopaminergic and GABAergic pathways of the mesolimbic system. GABAergic neurons of ventral tegmental area (VTA) specifically express α1 containing $GABA_A$ receptors whereas dopaminergic neurons express non α1-containing $GABA_A$ receptors (namely α2, α3 and α4-expressing receptors). Dopaminergic neurons project to nucleus accumbens and release dopamine. All addictive drugs increase the dopamine levels in nucleus accumbens via mesolimbic pathways. **B,** Benzodiazepine (BZP) mechanism of addiction and likely path utilized by carisoprodol (CSP). Potentiation of α1-expressing $GABA_A$ receptors on GABAergic neurons by benzodiazepines or carisoprodol (likely) inhibit the postsynaptic potential and decrease the release of GABA at dopaminergic neuron synapses. Decreased GABA levels at the synapse leads to disinhibition of dopaminergic neurons and increases in dopamine release at nucleus accumbens. Technically BZP (or CSP) should cancel its effects via potentiation $GABA_A$ receptors on dopaminergic neurons, but the effects of both BZP and CSP predominant on α1-containing $GABA_A$ receptors. Figure 2 is adapted from (60).

inhibition leads to disinhibition of dopaminergic neurons expressing non α1-containing $GABA_A$ receptors, resulting in more release of dopamine at nucleus accumbens (61). Theoretically the effects of benzodiazepines at these two sites would effectively cancel each other out, and thus have nominal effects on dopamine levels. However, the actions of benzodiazepines are more predominant on α1-containing receptors (63), thus dopamine levels are increased. Our subunit-dependent studies have shown that carisoprodol is considerably more efficacious at α1-containing receptors compared to those expressing other α subunit isoforms (58). Thus the molecular pharmacologic profile of carisoprodol corresponds well to current understanding of involvement of specific $GABA_AR$ subunit isoforms in abuse potential.

An understanding of subunit isoform association with physiologic effects of GABAergic signaling has also developed over the past several years (57). In an early study using knock-in technology to study roles of a specific amino acid in the α1 receptor (histidine at position 101) (60), mutant mice expressing α1(H101R) $GABA_A$ receptors showed no sedative and anterograde amnestic effects of diazepam, and anticonvulsant effects were significantly reduced. Equivalent knock-in mutations of the conserved histidine were subsequently studied in α2 and α3 receptors (64). In α2(H101R) mice, anxiolytic and myorelaxant effects of diazepam were completely abolished, while sedative effects were present. In α3(H126R) mutant mice, myorelaxant properties of diazepam were reduced (present at high diazepam doses) while sedative and anxiolytic properties were intact. These results demonstrated diazepam mediate its muscle relaxant effects mainly through α2 containing $GABA_A$ receptors, and also through α3 $GABA_A$ receptors at high concentrations.

Carisoprodol's pharmacological actions at $GABA_ARs$ are consistent with the therapeutic effects of the drug. The quest to develop GABAergic ligands with better delineation of therapeutic and adverse actions has begun to show considerable promise in recent years, and a number of agents with unique subunit-selective profiles are in development for the treatment of anxiety, sleep disorder, down syndrome, autism, schizophrenia and epilepsy (65, 66). With regard to muscle relaxants, a drug selective primarily for α2-expressing $GABA_A$ receptors would likely have less abuse potential and fewer sedative effects (60). It would be desirable to understand $GABA_A$ receptor subunit amino acid domains that confer carisoprodol sensitivity and subunit-dependence. Finding the molecular action of carisoprodol should help in understating the mechanism underlying its abuse potential and muscle-relaxing properties. This information would help in treatment of tolerance and withdrawal effects of carisoprodol, and in development of a new drug with better muscle-relaxing properties and reduced abuse potential.

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Conflict of Interest

No potential conflicts of interest to disclose.

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