18-Methoxycoronaridine: a putative anti-addictive agent

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Abstract

18-Methoxycoronaridine (18-MC) is a synthetic analog of ibogaine, an indole alkaloid found in the roots of *Tabernanthe iboga*. It has been reported that ibogaine possesses multiple effects, especially in treating drug addiction, but it can induce whole-body tremor, Purkinje cell loss in the cerebellum, bradycardia, and flaccid paralysis in rats. On the contrary, 18-MC produces none of the above-mentioned toxic effects. At a single dose (40 mg/kg, i.p.) 18-MC reduced self-administration of nicotine, morphine, cocaine, ethanol, and methamphetamine without any apparent toxicity in addicted rats. The mechanism of anti-addictive action of 18-MC is believed to mediate via blocking the alpha3beta4 nicotinic receptors in the habenulo-interpeduncular pathway modulating the dopaminergic mesolimbic pathway known to be involved in drug addiction. From a close observation on the information about 18-MC, it has been found that this compound is not available for clinical use at present because of its clinical trial in progress to be approved by the USFDA. Once 18-MC has been approved, it will be a useful drug for the treatment of polydrug abuse.

Keywords: *ibogaine, 18-methoxycoronaridine, anti-addiction*

บทคัดย่อ

18-Methoxycoronaridine (18-MC) เป็นสารสังเคราะห์ที่มีสูตรโครงสร้างคล้ายกับ ibogaine ซึ่งเป็นอัลคาลอยด์ที่สกัดได้จากรากของต้น *Tabernanthe iboga* มีรายงานว่า ibogaine มีผลหลายอย่างที่สำคัญ เช่น ผลในการรักษาการติดยาเสพติด แต่สารนี้ทำให้เกิดอาการพิษในหนูขาวใหญ่ เช่น อาการสั่นตลอดตัว การสูญเสีย Purkinje cell ในสมอง หัวใจเต้นช้า และอัมพาต ในทางตรงกันข้าม 18-MC เป็นสารที่ปราศจากอาการพิษดังกล่าว การให้ 18-MC ครั้งเดียวด้วยขนาด 40 มก/กก ทางช่องท้องของหนูขาวใหญ่สามารถลดการเสพยาเสพติด เช่น นิโคติน มอร์ฟีน โคเคน เอทานอล และเมทแอมเฟตามีน ในหนูที่ติดสารเหล่านี้ได้ เชื่อว่า 18-MC ออกฤทธิ์โดยขับยั้งตัวรับของนิโคตินชนิดอัลฟา3เบตา4 ใน habenulo-interpeduncular pathway ซึ่งควบคุม dopaminergic mesolimbic pathway ที่เกี่ยวข้องกับการเสพติดยา จากการติดตามข้อมูลด้านนี้อย่างใกล้ชิดพบว่า ปัจจุบันยังไม่มีการใช้ 18-MC ในสถานพยาบาลเพราะยังไม่ได้รับการรับรองจากสำนักงานคณะกรรมการอาหารและยาแห่งประเทศสหรัฐอเมริกา ในอนาคตเมื่อได้รับการรับรองแล้วสาร 18-MC นี้จะมีประโยชน์ในการรักษาการติดยาเสพติดหลายประเภท

คำสำคัญ*: ibogaine, 18-methoxycoronaridine, anti-addiction*

1. Introduction

Although addictive drugs produce their own characteristic acute effects, all share one common feature that they induce strong feelings of euphoria and reward. Once the abused drug is absent, signs of withdrawal become apparent (Lüscher, 2007). Commonly used addictive drugs include opioids (morphine, heroin), CNS stimulants (methamphetamine, cocaine), CNS depressants (ethanol), psychedelic agents (LSD, ecstasy), cannabinoids (marijuana), inhalants (toluene, hydrocarbons), and nicotine (O'Brien, 2001).

In spite of many years of intensive research, a safe, reliable and cost-effective treatment for addiction has not been developed (Meltzer, 1987). Despite the apparent similarities among the psychological symptoms produced by many addictive drugs, the primary goal of pharmacotherapy is to target specific receptors at which the abused drugs act. For example, opioid antagonists (Colchin & Mushlin, 1976; Resnick, Schuyten-Resnick, & Washton, 1980; Meltzer, 1987; Buie, 1994), the acylating mu-opioid receptor ligand beta-funaltrexamine (Delander, Portoghese, & Takemori, 1984), and particularly the mixed mu receptor agonist/kappa receptor antagonist buprenorphine (Frischer, 1992; Forsyth, Farquhar, Gemmel, Shewan, & Davies, 1993; Torrens, San, & Cami, 1993; Buie, 1994) have been proposed to treat opiate dependence. However, their efficacy is questionable.

Traditional methadone replacement therapy for opioid addiction, though effective while the

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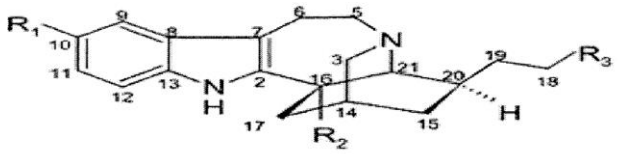
treatment is maintained, has a relapse rate of more than 80% when the drug is discontinued (Ball & Ross, 1991). Furthermore, the agents that block dopamine reuptake that have been suggested to be effective in the treatment of stimulant (e.g., cocaine) abuse yield unsatisfactory results (Berger, Gawin, & Kosten, 1989; Preston, Sullivan, Berger, & Bigelow, 1993).

An indole alkaloid, ibogaine, was first isolated and crystallized from the roots of *Tabernanthe iboga* in 1901 (Alper, 2001). Anecdotal reports indicated that a single dose of ibogaine eliminates withdrawal symptoms and reduces drug craving for extended periods of time (Mash, Kovera, Buck, Norenberg, Shapshak, Hearn, & Sanchez-Ramos, 1998). However, there are limited clinical data regarding the outcomes in patients treated with ibogaine. Mash, Kovera, Pablo, Tyndale, Ervin, Kamlet, & Hearn (2001) report having treated 32 patients with a fixed dose of 800 mg of ibogaine HCl for heroin withdrawal in a clinic in St.Kitts, West Indies. Resolution of withdrawal symptoms occurred at 12 hours following ibogaine administration and 24 hours after the last use of the opiate. The resolution of withdrawal symptoms was sustained during subsequent observations over an interval of approximately one week after ibogaine treatment. No episodes of psychosis or major affective disorder were detected in the patients.

Noribogaine is an active metabolite of ibogaine as shown in Figure 1 (Mash, Staley, Baumann, Rothman, & Hearn, 1995). Ibogaine has multiple actions and is capable of treating diverse addictions, including opioid and stimulant abuse, alcoholism, and smoking (Glick, Maisonneuve, & Szumlinski, 2001). However, ibogaine can induce whole-body tremor, Purkinje cell loss in the cerebellum, bradycardia, and flaccid paralysis in rats. Whereas a novel iboga alkaloid congener, 18-methoxycoronaridine (18-MC) (Figure 1), has been developed without the aforementioned toxic effects of ibogaine (O' Hearn & Molliver, 1993; Glick, Kuehne, Maisonneuve, Bandarage, & Molinari, 1996; Glick & Maisonneuve, 2000).

Furthermore, high oral doses of iboga extracts which are likely to contain additional alkaloids, may lead to convulsions, paralysis, and respiratory arrest in humans (Evans-Schultes & Hofmann, 1980).



Alkaloid	R_1	R_2	R_3
Ibogaine	OCH_3	H	H
Noribogaine	OH	H	H
(+) -18- Methoxycoronaridine	H	CO_2CH_3	OCH_3

Figure 1 Chemical structures of ibogaine, noribogaine, and 18-methoxycoronaridine (Alper, 2001).

It was found that intracerebral injections of several iboga alkaloids induced tremors in mice. Tremorigenic activity was increased by the addition of a methoxy group at position 10 or 11 and was reduced or abolished by the introduction of a carbomethoxy group at position 16 as illustrated in Figure 1 (Singbartl, Zetler, & Schlosser, 1973). 18-MC possesses both of these nontremorigenic features.

In addition, 18-MC has a much lower affinity than ibogaine for sigma-2 receptors since an agonist of these receptors is believed to be responsible for neurotoxicity in rats (Glick, Maisonneuve, & Szumlinski, 2001). 18-MC has no effect on either heart rate or blood pressure according to animal studies (Glick, Maisonneuve, Hough, Kuehne, & Bandarage, 1999). Maisonneuve & Glick (2003) also pointed out that 18-MC is a selective alpha3beta4 nicotinic receptor antagonist.

2. Anti-addictive effects of 18-MC

2.1 Effect on nicotine self-administration

In animal studies, 18-MC has been proved to be effective at reducing self-administration of several drugs of abuse. At a single dose of 40 mg/kg, i.p., it significantly attenuated nicotine-induced dopamine release in the nucleus accumbens of awake and freely moving rats. In an oral model of

nicotine self-administration, 18-MC decreased rats' preferences for nicotine for at least 24 hours (Glick, Maisonneuve, Visker, Fritz, Bandarage & Kuehne, 1998). This may be due to the blockade of alpha3beta4 nicotinic receptors in diencephalic pathways that modulate mesocortical limbic pathways which are more directly involved in drug reinforcement. Because diencephalic pathways have high densities of the receptors, antagonists of alpha3beta4 nicotinic receptors seem to be a totally novel mechanism for treating polydrug abuse (Glick, Maisonneuve, & Kitchen, 2002).

The above-mentioned hypothesis has been confirmed by the findings that local administration of 18-MC into the medial habenula which has high densities of alpha3beta4 nicotinic receptors, decreased nicotine self-administration in rats. Similar treatment was performed in three brain areas containing moderate densities of the receptors, namely, the basolateral amygdala, dorsolateral tegmentum, and ventral tegmentum. It has been shown that local injection of 18-MC into the first two brain areas reduced nicotine self-administration. No response was observed when the agent was administered into the ventral tegmentum (Glick, Sell, McCallum, & Maisonneuve, 2011).

2.2 Effect on morphine self-administration

In the attenuation of the reinforcing efficacy of opioids by 18-MC, it was demonstrated that the compound selectively interfered with morphine-induced dopamine release, without altering stimulation of dopamine synthesis by morphine (Maisonneuve & Glick, 1999). Reduction of the rewarding effects of morphine by 18-MC is mediated via the blocking of alpha3beta4 nicotinic receptors in brain areas with high densities of the receptors such as the medial habenula and interpeduncular nucleus. 18-MC was administered directly into these brain areas of morphine-dependent rats and then followed by administration of naltrexone to precipitate a withdrawal symptom. The result was significant amelioration of symptoms such as teeth chattering, wet-dog shakes, burying, and diarrhea (Panchal, Taraschenko, Maisonneuve, & Glick, 2005).

While there are very low densities of alpha3beta4 nicotinic receptors in the mesolimbic pathway, these receptors are prominently localized in the medial habenula and in the interpeduncular nucleus (Panchal et al., 2005). These nuclei and the habenulo-interpeduncular pathway connecting them are believed to function as part of an alternate pathway modulating the dopaminergic mesolimbic pathway known to be involved in drug addiction. Pretreatment with a single dose of 18-MC, 40 mg/kg, i.p. or local infusion of 18-MC into either the medial habenula or interpeduncular nucleus blocked the sensitized dopamine response to repeated intraperitoneal injection of morphine in the rat nucleus accumbens; 18-MC had no effect on the dopamine response to acute morphine administration. The results suggest that the potential anti-addictive efficacy of 18-MC might be related to an ability to restore normal functioning to a hypersensitive mesolimbic dopamine system produced by previous repeated morphine injection by acting in the habenulo-interpeduncular pathway (Szumlinski, Maisonneuve & Glick, 2000; Taraschenko, Shulan, Maisonneuve, & Glick, 2007). 18-MC has a significantly low affinity for sigma while it retains modest affinity for mu and kappa opioid receptors. It has no affinity at the alpha4beta2 subtype nor at NMDA channels nor at the serotonin transporter (Glick et al., 1999; Maisonneuve & Glick, 2003).

2.3 Effect on cocaine self-administration

In the studies of the effects of 18-MC on cocaine addiction, it was found that a single injection of 40 mg/kg, i.p. significantly decreased cocaine self-administration in rats. Some of them did not intake cocaine for several days or weeks, and it was concluded that 18-MC decreased extracellular level of dopamine in the nucleus accumbens (Glick, et al., 1996). Szumlinski, McCafferty, Maisonneuve, & Glick (2000) suggested that the anti-addictive efficacy of 18-MC might be related to an ability to selectively block the expression of sensitized extracellular levels of dopamine in the nucleus accumbens in rats with previous cocaine experience.

2.4 Effect on methamphetamine self-administration

A single intraperitoneal injection of 40 mg/kg 18-MC reduced methamphetamine self-administration for 24 hours or longer in rats (Glick, Maisonneuve, & Dickinson, 2000). This finding was confirmed by Glick, Sell, & Maisonneuve (2008) who found that local administration of 18-MC into either the medial habenula or interpeduncular area decreased methamphetamine self-administration in rats. Similar results were obtained by local infusion of two other nicotinic antagonists, mecamylamine and alpha-conotoxin, into the same brain areas.

These findings are consistent with the hypothesis that 18-MC reduces methamphetamine self-administration by indirectly modulating mesolimbic pathway via the blockade of alpha3beta4 nicotinic receptors in the habenulo-interpeduncular pathway.

The data concerning the efficacy of 18-MC in reducing self-administration of the aforementioned four drugs of abuse in rats indicate that 18-MC is most potent against nicotine abuse but least potent for methamphetamine addiction. The results suggest that a nicotinic antagonist action of 18-MC is likely to contribute to its putative anti-addictive efficacy (Glick, Maisonneuve, & Dickinson, 2000). The single effective dose of 18-MC, 40 mg/kg, i.p., produces no apparent toxic effects in rats (Glick et al., 1996).

2.5 Effect on ethanol self-administration

Ibogaine, noribogaine, and 18-MC were found to have an anti-addictive effect against ethanol consumption in rats (Rezvani, Overstreet, Yang, Maisonneuve, Bandarage, Kuehne, & Glick, 1997; Maisonneuve & Glick, 2003; He, McGough, Ravindranathan, Jeanblanc, Logrip, Phamluong, Janak, & Ron, 2005; Carnicellar, He, Yowell, Glick, & Ron, 2010). Single intraperitoneal injection of 5, 20, and 40 mg/kg of 18-MC significantly and dose dependently attenuated alcohol consumption and preference in alcohol-preferring rats (Rezvani et al., 1997).

Increased glial cell line-derived neurotrophic factor (GDNF) in the ventral tegmental area (VTA) has been suggested to cause a decrease in ethanol consumption following the administration of ibogaine to rats (He et al., 2005; He & Ron, 2006). GDNF has been proposed to enhance the regeneration of dopaminergic function (Ron & Janak, 2005). Using SH-SY5Y cell culture, it was found that noribogaine, like ibogaine not 18-MC, induces a robust increase in GDNF mRNA levels. In addition, intra-VTA infusion of noribogaine and 18-MC on rat operant alcohol self-administration indicated that noribogaine, but not 18-MC, decreases alcohol consumption. The results suggest that noribogaine and 18-MC have different mechanisms and sites of action (Carnicella et al., 2010).

The hypothesis that GDNF may be responsible for the improvement in euphoria and mood in chronic withdrawal from abused substances is appealing and is unlikely to explain efficacy in acute opiate withdrawal (Alper, Lotsof, & Kaplan, 2008).

3. Pharmacokinetics of 18-MC

Plasma and tissue levels of 18-MC have been measured in rats using gas chromatography-mass spectrometry. It has short initial half-life of 5 to 10 min and terminal half-life of over 100 min. Consistent with a two-compartment model of its elimination 18-MC, like ibogaine, is highly sequestered in adipose tissue (Hough, Pearl, & Glick, 1996; Glick et al., 1999). In absolute terms, however, 18-MC levels in fat account for only a small fraction of the administered dose (approximately 10%), suggesting that the compound is rapidly metabolized. Studies of human liver microsomes indicated that 18-MC was metabolized to 18-hydroxycoronaridine (18-HC), the major metabolite, by the polymorphic CYP2C19 (Zhang, Ramamoorthy, Tyndale, Glick, Maisonneuve, Kuehne, & Seller, 2002). It remains to be determined whether 18-HC is active and whether it contributes to the protracted behavioral effects of 18-MC (Glick, Maisonneuve, & Szumlinski, 2001).

4. Future studies on 18-MC

Despite the fact that 18-MC was synthesized in 1996, it has not yet been tested in humans. Recently, Obiter Research Company in Illinois, which has a patent license to synthesize and market 18-MC, has decided not to carry out the study of this compound any further, because it is already a one-time-use agent. Instead, Obiter Research has established a company called Savant, which will see 18-MC through clinical trials, get USFDA approval, and then open clinics where abusers can receive a holistic treatment for addiction. Moreover, Obiter Research is still trying to reduce the 18-MC production cost (Heckel, 2011).

5. Conclusion

It has been shown in the animal studies that 18-MC is effective in reducing self-administration of some drugs of abuse such as nicotine, morphine, methamphetamine, cocaine, and ethanol. This agent is most potent against nicotine addiction. 18-MC exerts its anti-addictive effect by blocking alpha3beta4 nicotinic receptors in certain brain areas, including the medial habenula, interpeduncular nucleus, basolateral amygdala, and dorsolateral tegmentum. The habenulo-interpeduncular pathway is believed to play a role in modulating the dopaminergic mesolimbic pathway involved in drug addiction.

The role of GDNF in the behavioral effects of abused drugs and in the neuroadaptations induced by repeated exposure to drugs in the mesolimbic dopamine system has been studied since the mid 1990s (Ghitza, Zhai, Wu, Airavaara, Shaham, & Lu, 2010). Experimental manipulations that increase GDNF expression in the dorsal striatrum, ventral tegmentum, and nucleus accumbens decrease self-administration of cocaine (Green-Sadan, Kinor, Roth-Deri, Geffen-Aricha, Schindler, & Yadid, 2003) and alcohol in rats (Carnicellar et al., 2010).

Ibogaine, noribogaine, and 18-MC have been demonstrated to attenuate ethanol consumption in alcohol-preferring rats (Rezvani et al., 1997; Maisonneuve & Glick, 2003; He et al., 2005; Carnicellar et al., 2010). Unlike noribogaine, 18-MC produces no change in the levels of GDNF in the VTA and fails to decrease self-administration of the alcohol. It has been suggested that noribogaine and 18-MC have different mechanisms and sites of action (Carnicellar et al., 2010). These findings support the hypothesis that anti-addictive effect of 18-MC is mediated via the blockade of alpha3beta4 nicotinic receptors located mainly in the medial habenula and interpeduncular nucleus.

Pharmacokinetic data of 18-MC in rats indicated that this agent fits a two-compartment model. In vitro studies also revealed that 18-MC is metabolized to 18-HC, which is the main metabolite, by the human polymorphic CYP2C19 (Zhang et al., 2002). Further investigations are required to determine whether it is an active metabolite of 18-MC or not.

If 18-MC is approved by the USFDA, it will be a life-saving drug for addicts, tobacco smokers in particular. According to the World Health Organization (2011), tobacco smoking kills nearly 6 million people each year. This number includes more than 600,000 passive smokers. The number is predicted to increase beyond 8 million per year by 2030. They die from cancer, heart disease, asthma and other illnesses as a consequence of chronic exposure to toxic substances in tobacco smoke such as polycyclic aromatic hydrocarbons, nitrosamines, aldehydes, active oxygen species, free radicals, and nicotine (Hecht, 1999 ; Klaassen, 2001). Moreover, nicotine produces pleasant feelings leading to the development of addiction in smokers. Nicotine replacement therapy is available in various dosage forms. It is effective during the initial phase of treatment but most smokers resume smoking over the ensuing weeks or months (O'Brien, 2001). 18-MC may also be used to treat heroin, ethanol, and cocaine dependence. After USFDA approval, Savant Company must conduct careful postmarketing surveillance to monitor the safety of 18-MC in a large number of patients. Despite not yet approved by the FDA for treatment, this novel approach in treating polydrug abuse has already had a strong impact on the area of pharmacotherapy of drug addiction. Ideally, in the end, the cost of treatment should be affordable by the majority of drug abuse patients.

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7. References

Alper, K. R. (2001). Ibogaine: A review. *The Alkaloids*: *Chem. Biol*, *56*, 1-38.

Alper, K.R., Lotsof, H. S., & Kaplan, C. D. (2008). The ibogaine medical subculture. *J. Ethnopharmacol*, *115*, 9-24.

Ball, J. C., & Ross, A. (1991). *The effectiveness of methadone maintenance treatment: patients, programs, services, and outcome*. New York, USA: Springer-Verlag.

Berger, P., Gawin, F., & Kosten, T. R. (1989). Treatment of cocaine abuse with mazindol. *Lancet*, *1*, 283.

Buie, J. (1994). 46 new drugs for mental illness could reach market within 3 to 6 years. *Psychiatric Times*, *XI*, 44.

Carnicella, S., He, D. Y.,Yowell, Q. V., Glick, S. D., & Ron, D. (2010). Noribogaine, but not 18-MC, exhibits similar actions as ibogaine on GDNF expression and ethanol self-administation. *Addict. Biol*, *15*, 424-433.

Colchin, J., & Mushlin, B. E. (1976). Effect of agonist-antagonist interaction on the development of tolerance and dependence. *Ann. N.Y.Acad. Sci*, *281*, 224-251.

Delander, G. E., Portoghese, P. S., & Takemori, A. E. (1984). Role of spinal mu opioid receptors in the development of morphine tolerance and dependence. *J. Pharmacol. Exp*. *Ther*, *231*, 91-96.

Evans-Schultes, R., & Hofmann, A. (1980). Tabernanthe Iboga. *The botany and chemistry of hallucinogens* (pp. 235-239). Illinois, USA: Charles C. Thomas Publisher.

Forsyth, A. J., Farquhar, D., Gemmell, M., Shewan, D., & Davies, J. E. (1993). The dual use of opioids and temazepam by drug injectors in Glasgow (Scotland). *Drug Alcohol Depend, 32*, 277-280.

Frischer, M. (1992). Estimated prevalence of injecting drug use in Glasgow. *Br. J. Addict, 87*, 235-243.

Ghitza, U.E., Zhai, H., Wu, P., Airavaara, M., Shaham, Y., & Lu, L. (2010). Role of BDNF and GDNF in drug reward and relapse : a review. *Neurosci. Biobehav. Rev, 35*, 157-171.

Glick, S. D., Kuehne, M. E., Maisonneuve, I. M., Bandarage, U. K., & Molinari, H. H. (1996). 18-Methoxycoronaridine, a non-toxic iboga alkaloid congener: effects on morphine and cocaine self-administration and on mesolimbic dopamine release in rats. *Brain Res, 719*, 29-35.

Glick, S. D., Maisonneuve, I. M., Visker, K. E., Fritz, K. A., Bandarage, U. K., & Kuehne, M. E. (1998). 18-Methoxycoronaridine attenuates nicotine-induced dopamine release and nicotine preferences in rats. *Psychopharmacology, 139*, 274-280.

Glick, S. D., Maisonneuve, I. M., Hough, L. B., Kuehne, M. E., & Bandarage, U. K. (1999). (±) 18-Methoxycoronaridine : A novel iboga alkaloid congener having anti-addictive efficacy. *CNS Drug Reviews, 5*, 27-42.

Glick, S. D., & Maisonneuve, I. M. (2000). Development of novel medications of drug addiction. The legacy of an African shrub. *Ann. N.Y. Acad. Sci, 909*, 88-103.

Glick, S. D., Maisonneuve, I. M., & Dickinson, H. A. (2000). 18-MC reduces amphetamine and nicotine self-administration in rats. *Neuroreport, 11*, 2013-2015.

Glick, S. D., Maisonneuve, I. M., & Szumlinski, K. K. (2001). Mechanisms of action of ibogaine: relevance to putative therapeutic effects and development of a safer iboga alkaloid congener. *The Alkaloids*: *Chem. Biol, 56*, 39-53.

Glick, S. D., Maisonneuve, I. M., & Kitchen, B. A. (2002). Modulation of nicotine self-administration in rats by combination therapy with agents blocking alpha3beta4 nicotinic receptors. *Eur. J. Pharmacol, 448*, 185-191.

Glick, S. D., Sell, E. M., & Maisonneuve, I. M. (2008). Brain regions mediating alpha3beta4 nicotinic antagonist effects of 18-MC on methamphetamine and sucrose self-administration. *Eur. J. Pharmacol, 599*, 91-95.

Glick, S. D., Sell, E. M., McCallum, S. E., & Maisonneuve, I. M. (2011). Brain areas mediating $\alpha 3\beta 4$ nicotinic antagonist effects of 18-MC on nicotine self-administration. *Eur. J. Pharmacol, 669*, 71-75.

Green-Sadan, T., Kinor, N., Roth-Deri, I., Geffen-Aricha, R., Schindler, C.J., & Yadid, G. (2003). Transplantation of glial cell line-derived neurotrophic factor-expressing cells into the striatum and nucleus accumbens attenuates acquisition of cocaine self-administration in rats. *Eur. J. Neurosci, 18*, 2093-2098.

He, D. Y., McGough, N. H., Ravindranathan, A., Jeanblanc, J., Logrip, M. L., Phamluong, K., Janak, P. H., & Ron, D. (2005). Glial cell line-derived neurotrophic factor mediates the desirable actions of the anti-addiction drug ibogaine against alcohol consumption. *J. Neurosci, 25*, 619-628.

He, D. Y., & Ron, D. (2006). Autoregulation of glial cell line-derived neurotrophic factor expression: implications for the long-lasting action of the antiaddiction drug, Ibogaine. *FASEB J, 20*, 2420-2422.

Hecht, S. S. (1999). Tobacco smoke carcinogens and lung cancer. *J. Natl. Cancer Inst, 91*, 1194-1210.

Heckel, J. (2011). Editor's Note. *Central Illinois Business Magazine*, January.

Hough, L. B., Pearl, S.M., & Glick, S. D. (1996). Tissue distribution of ibogaine after intraperitoneal and subcutaneous administration. *Life Sci, 58*, 119-122.

Klaassen, C. D. (2001). *Casarett & Doull's toxicology*. 6th ed. New York, USA: McGraw-Hill.

Lüscher, C. (2007). Drugs of abuse. *Basic and clinical pharmacology* (pp. 511-525). 10th ed. Singapore: McGraw-Hill.

Maisonneuve, I. M., & Glick, S. D. (1999). Attenuation of the reinforcing efficacy of morphine by 18-methoxycoronaridine. *Eur. J. Pharmacol, 383*, 15-21.

Maisonneuve, I. M., & Glick, S. D. (2003). Anti-addictive actions of an iboga alkaloid congener : a novel mechanism for a novel treatment. *Pharmacol. Biochem. Behav*, *75*, 607-618.

Mash, D. C., Staley, J. K., Baumann, M. H., Rothman, R. B., & Hearn, W. L. (1995). Identification of a primary metabolite of ibogaine that targets serotonin transporters and elevates serotonin. *Life Sci*, *57*, PL 45-50.

Mash, D. C., Kovera, C. A., Buck, B. E., Norenberg, M. D., Shapshak, P., Hearn, W. L., & Sanchez-Ramos, J. (1998). Medication development of ibogaine as a pharmacotherapy for drug dependence. *Ann.N.Y.Acad. Sci*, *844*, 274-292.

Mash, D. C., Kovera, C. A., Pablo, J.,Tyndale, R., Ervin, F. R., Kamlet, J. D., & Hearn, W. L. (2001). Ibogaine in the treatment of heroin withdrawal. *The Alkaloids : Chem. Biol*, *56*, 155-171.

Meltzer, H. Y. (1987). *Psychopharmacology : The third generation of progress*. New York, USA: Raven Press.

O'Brien, C. P. (2001). Drug addiction and drug abuse. *Goodman & Gilman's the pharmacological basis of therapeutics* (pp. 621-642). 10th ed. New York, USA: McGraw-Hill.

O'Hearn, E., & Molliver, M.E. (1993). Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline. *Neuroscience*, *55*, 303-310.

Panchal, V., Taraschenko, O. D., Maisonneuve, I. M., & Glick, S. D. (2005). Attenuation of morphine withdrawal signs by intracerebral administration of 18-methoxycoronaridine. *Eur. J. Pharmacol*, *525*, 98-104.

Preston, K. L., Sullivan, J. T., Berger, P., & Bigelow, G. E. (1993). Effects of cocaine abuse and in combination with mazindol in human cocaine abusers. *J. Pharmacol. Exp. Ther*, *267*, 296-307.

Resnick, R. B., Schuyten-Resnick, E., & Washton, A. M. (1980). Assessment of narcotic antagonists in the treatment of opioid dependence. *Annu. Rev. Pharmacol. Toxicol*, *20*, 463-474.

Rezvani, A. H., Overstreet, D. H., Yang,Y., Maisonneuve, I. M., Bandarage, U. K., Kuehne, M. E., & Glick, S. D. (1997). Attenuation of alcohol consumption by a novel nontoxic ibogaine analogue (18-methoxycoronaridine) in alcohol-preferring rats. *Pharmacol. Biochem. Behav*, *58*, 615-619.

Ron, D., & Janak, P. H. (2005). GDNF and addiction. *Rev. Neurosci*, *16*, 277-285.

Singbartl, G., Zetler, G., & Schlosser, L. (1973). Structure-activity relationships of intracerebrally injected tremorigenic indole alkaloids. *Neuropharmacology*, *12*, 239-244.

Szumlinski, K. K., Maisonneuve, I. M., & Glick, S. D. (2000). The potential anti-addictive agent, 18-methoxycoronaridine, blocks the sensitized locomotor and dopamine responses produced by repeated morphine treatment. *Brain Res*, *864*, 13-23.

Szumlinski, K. K., McCafferty, C. A., Maisonneuve, I. M., & Glick, S. D. (2000). Interaction between 18- methoxy-coronaridine (18-MC) and cocaine: dissociation of behavioural and neuro-chemical sensitization. *Brain Res*, *871*, 245-258.

Taraschenko, O. D., Shulan, J. M., Maisonneuve, I. M., & Glick, S. D. (2007). 18-MC acts in the medial habenula and interpeduncular nucleus to attenuate dopamine sensitization to morphine in the nucleus accumbens. *Synapse*, *61*, 547-560.

Torrens, M., San, L., & Cami, J. (1993). Buprenorphine versus heroin dependence: comparison of toxicologic and psychopathologic characteristics. *Am. J. Psychiatry*, *150*, 822-824.

World Health Organization. (2011). 10 Facts on the tobacco epidemic and its control. Retrieved April 18, 2012, from http://www.who.int/features/factfiles/tobacco_epidemic/en/index.html

Zhang, W., Ramamoorthy, Y., Tyndale, R. F., Glick, S. D., Maisonneuve, I. M., Kuehne, M. E., & Sellers, E. M. (2002). Metabolism of 18-methoxycoronaridine, an ibogaine analog, to 18-hydroxycoronaridine by genetically variable CYP2C19. *Drug Metab. Dispos*, *30*, 663-669.