Ibogaine Analogues: Drug Development for Addictive Disorders

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Center for Neuropharmocology and Neuroscience

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Stanley D. Glick, Ph.D., M.D.

Drug Abuse / Drug Dependence

- · Drug/substance abuse
 - Self-administered use of any drug/substance in a manner that deviates from the approved medical or social standards within a given culture
- · Addiction or psychological dependence
 - Repeated, compulsive seeking or use of a substance despite adverse social, psychological and/or physical consequences
 - * Chronic relopsing disorder
- Physical dependence
 - Adaptive, physiological state produced by repeated drug administration that is manifested as a withdrawal syndrome.

ADDICTION can occur without PHYSICAL DEPENDENCE PHYSICAL DEPENDENCE can occur without ADDICTION

Addicts are desperate for new therapies



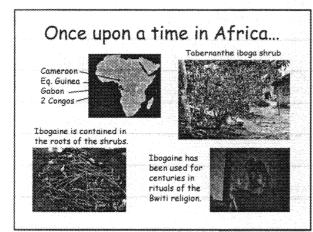
December 9, 1999
"...! am currently married and have a three year old daughter. I have used heroin on and off since I was 18 years old, more on than off...! have attended numerous substances abuse program and detoxes... I started a business and ought a house with my wife. Unfortunately, I am losing both due to my addiction. I crave heroin constantly, only heroin. I overdosed ten days ago and this wasn't the first time. If ity anything that might help me to stay clear and straight. Please consider me as a candidate for your research protocol..."

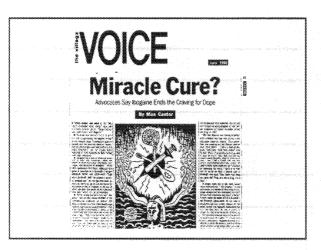


February 18, 2000 VTA

"...i am 83 years old and I have been using heroin for well over 25 years, never having the wilpower or success to kick the habit once and far all. At this point I know that I must stop and desperately want to. Sometines, I've marriaged to hold onto my county job for the past 13 years, and must continue to keep it for a feast 4 more years. We have recently field for bankuptor, and our condo is in foreclosure; yet it can become even worse if I don't get a grey on this habit. I have many reasons to stop, not least of all for the sake of my children, grandchildren and whe who is not at all that well herself. I invouid be so very grateful sir, if you could take the time to give me some idea, some direction as to how I might go about signing up or at least trying to participate in your research..."

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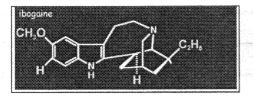




At very high concentrations, side effects are present... Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline, O'Hearn, E. and Molliver, M.E. Neuroscience 55:303-310 (1993).

The search for a better ibogaine...

- 1. It had to be as effective as ibogaine.
- 2. It had to lack all the side effects of ibogaine.



Is 18-MC a potential treatment for drug dependence?

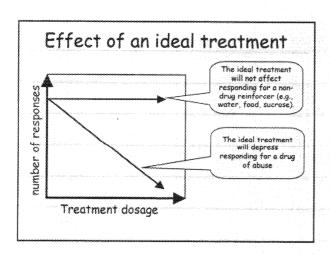
- 1. Is 18-MC effective in reducing drug self-administration?
- 2. Is 18-MC effective in reducing signs of drug withdrawal?

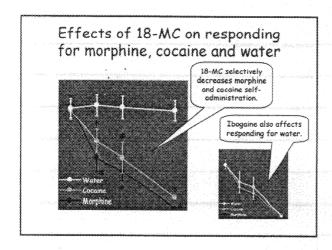
Drug self-administration

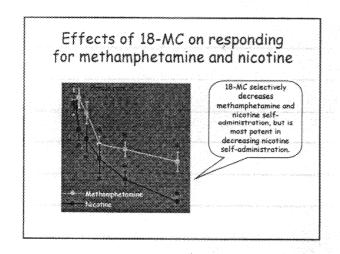


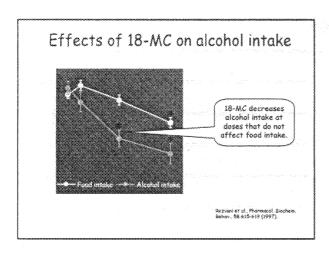
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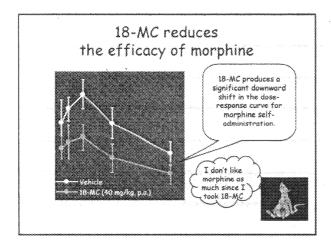
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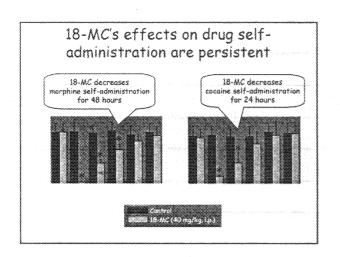


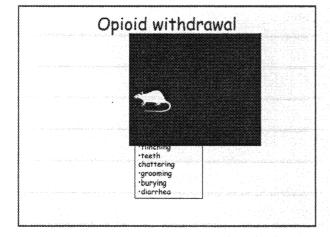


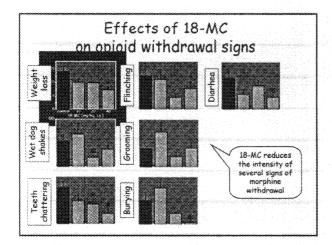












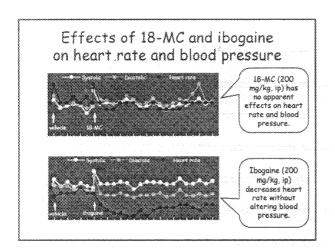
18-MC is a potentially effective anti-addictive treatment

- 1. 18-MC decreases the selfadministration of multiple drugs of abuse.
- 2. 18-MC alleviates several signs of morphine withdrawal.

Does 18-MC have side effects?

- 1. Nerve cell damage?
- 2. Cardiovascular toxicity?
- 3. Is 18-MC likely to cause hallucinations?
- 4. Is 18-MC addictive (i.e., reinforcing)?

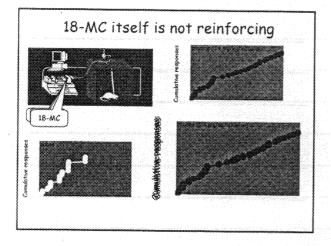
18-MC has no cerebellar toxicity Ibogaine 18-MC Che menth after 3x10Cmg/kg, i.p. 18-MC at very high doses does not produce any Purkinje cells.



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	Doministra de la composición

18-MC does not increase extracellular serotonin levels Thogoine 18-MC 18-MC, increases extracellular serotonin levels in the nucleus accumbens. So I won't hallucinate?

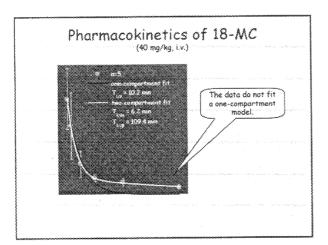


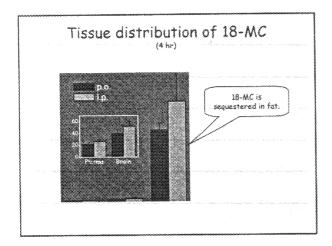
18-MC has no apparent side effects

- Unlike ibogaine, 18-MC does not induce tremors and does not damage the cerebellum.
- 2. Unlike ibogaine, 18-MC has no ill effect on the heart.
- 3. 18-MC may not be hallucinogenic.
- 4. 18-MC is not reinforcing and should not be liable to abuse.

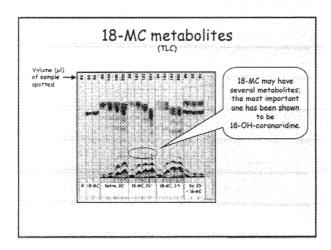
What are the pharmacokinetic properties of 18-MC?

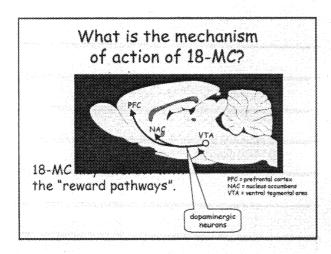
- 1. What is its half-life?
- 2. Is it uniformly distributed throughout the body?
- 3. Does it have any metabolites?

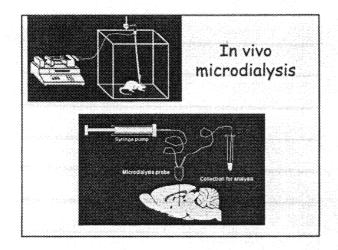


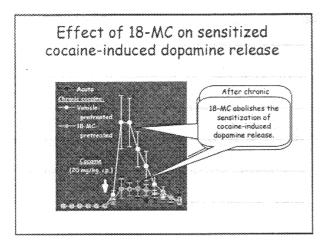


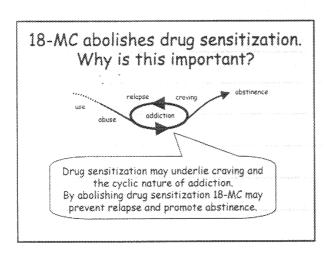
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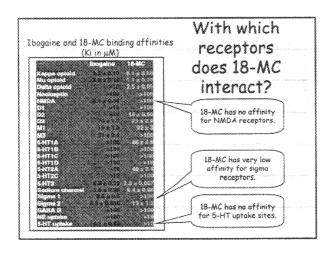


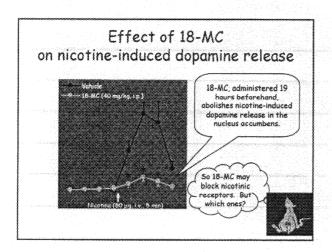


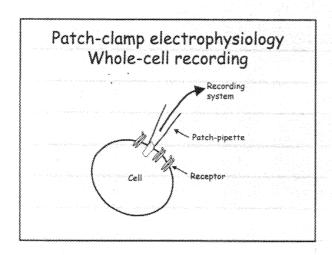


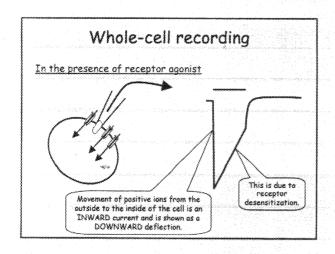


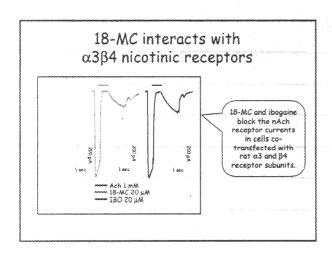


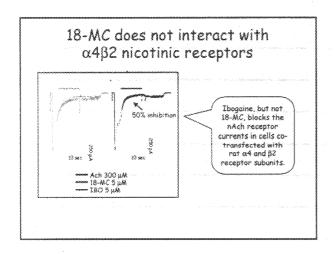


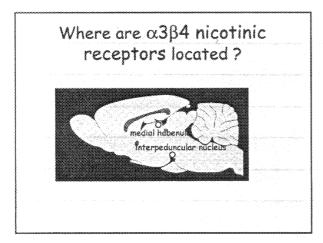












Connections between habenulointerpeduncular and mesolimbic systems







mHb = medial haberula
IP = interpeduncular nucleus
VTA = ventral tegmental area
NAC = nucleus accumbens
R = raphe nuclei
PFC = prefrontal cortex
MD = medial dorsal thalamic nucleus

Is 18-MC blockade of α3β4 nicotinic receptors relevant to its anti-addictive effects?

- Effects of combination of low doses of nonspecific a3β4 nicotinic receptors on drug selfadministration
- 2. Effects of interpeduncular administration of 18–MC on drug self-administration
- Correlations between potencies of 18-MC congeners to block α3β4 nicotinic receptors and their effects on drug self-administration

Non-specific $\alpha 3\beta 4$ nicotinic antagonists

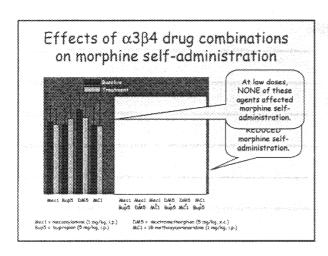
DRU6	IC50 (µM)
mecamylamine	0.09-10 (Papke et al., 200); Hermandez et al., 2000)
bupropion	1.4 (Fryer and Lukas, 1999)
dextromethorphan	8.9 (Hernandez et al., 2000)

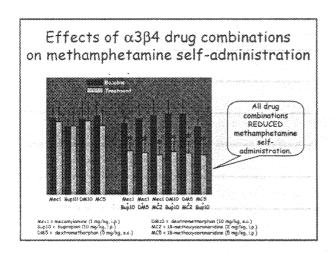
Mecamylamine, an antihypertensive agent (Inversine Φ), is a non-specific nicotinic receptor antagonist.

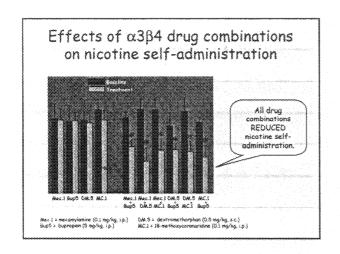
Bupropion, an antidepressant (Wellbutrin®) and an anti-smoking aid (Zyban®), is also a dopamine uptake blocker.

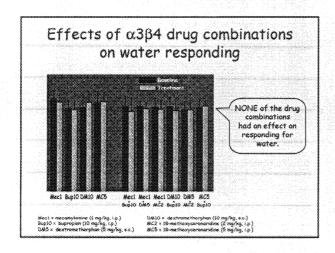
Dextromethorphan, an antitussive in many OTC cough medicines (Benylin®, Deisym®, DexAlone™, Pertussin®, Robitussin®, Sucrets®), is also a NMDA receptor antagonist.

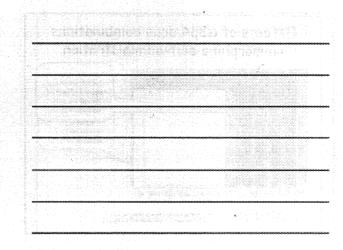
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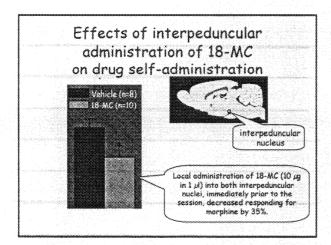


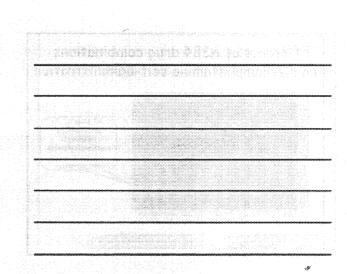


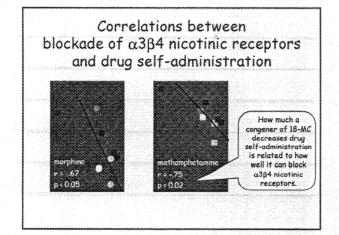


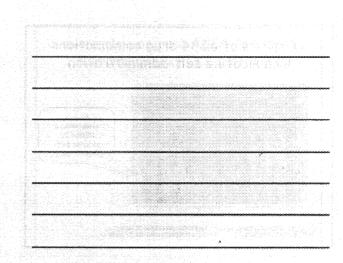












## Is 18-MC blockade of α3β4 nicotinic receptors relevant to its anti-addictive effects?

- Combinations of low doses of non-specific α3β4
  nicotinic receptor antagonists decrease drug
  self-administration.
- Interpeduncular administration of 18-MC decreases morphine self-administration.
- 3. There are significant correlations between potencies of 18-MC congeners to block  $\alpha3\beta4$  nicotinic receptors and their effects on drug self-administration.

#### Conclusions

- 1. 18-MC may be useful in treating many forms of drug addiction, including opioid (e.g., heroin) and stimulant (e.g., cocaine, methamphetamine) abuse, alcoholism and smoking.
- 2. 18-MC should lack all of ibogaine's prominent side effects.
- 3. 18-MC abolishes the dopamine sensitization that occurs with chronic drug administration and that may underlie craving and relapse.
- 4. An antagonist action at  $\alpha 3\beta 4$  nicotinic receptors appears to be 18-MC's most important action. 18-MC has greater selectivity for this site than either ibogaine or other existing agents.

### Clinical application

Antagonism of acetylcholine's actions at  $\alpha3\beta4$  nicotinic receptors may constitute a novel mechanism and strategy for reducing addiction to multiple drugs.

Low dose combinations of existing agents (i.e., dextromethorphan, mecamylamine and bupropion) may be viable therapies, and readily testable, in lieu of single agents acting specifically at this site.

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