Pharmacodynamics of Alcohol and Opioids: Pathways to Addiction and Euphoria

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NSERC CRSNG

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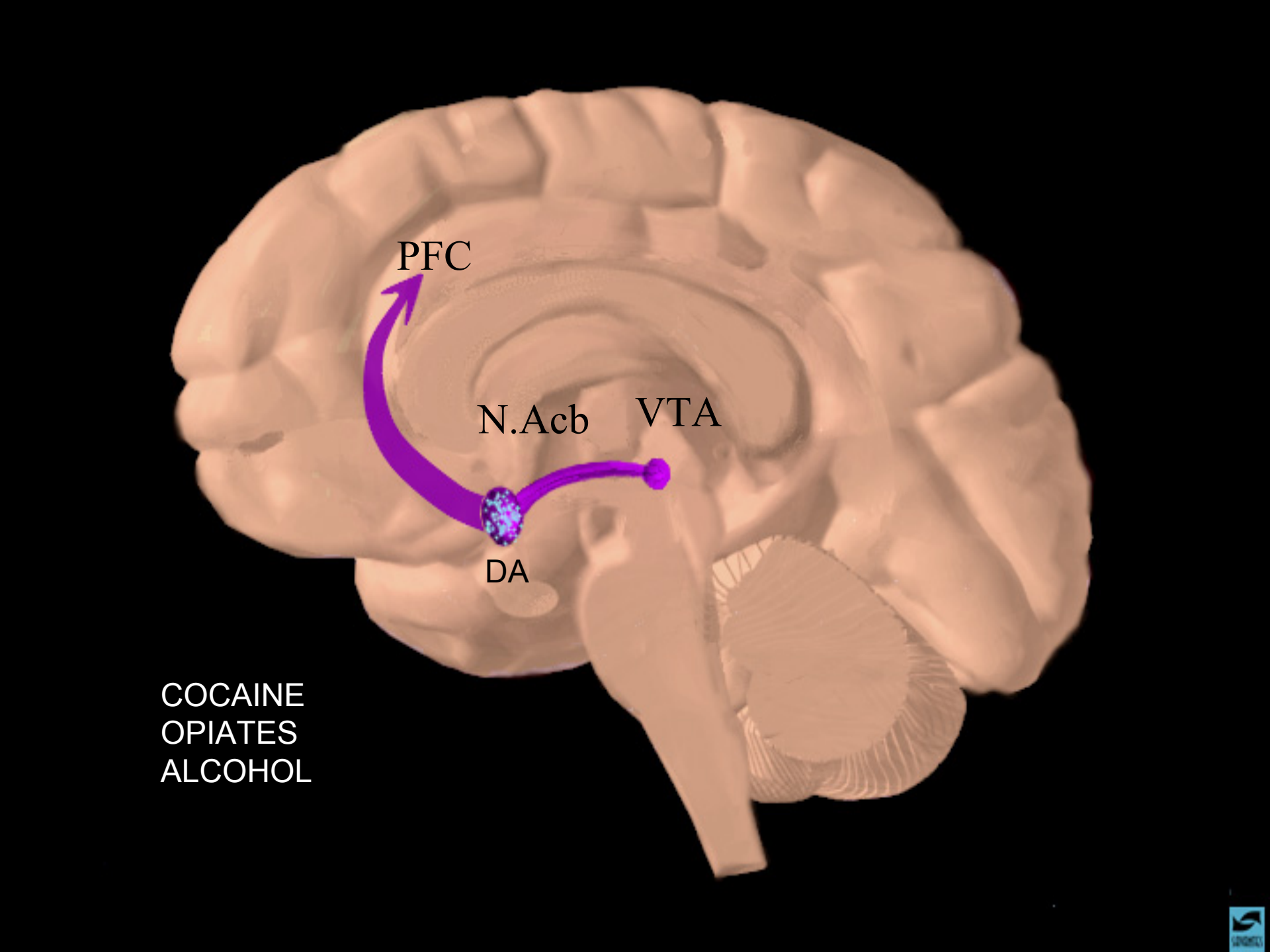
Which are the pathways to Euphoria and Addiction

Which brain regions and which neurotransmitters are involved in Euphoria and Addiction


PFC
N.Acb
VTA
DA
COCAINE
OPIATES
ALCOHOL

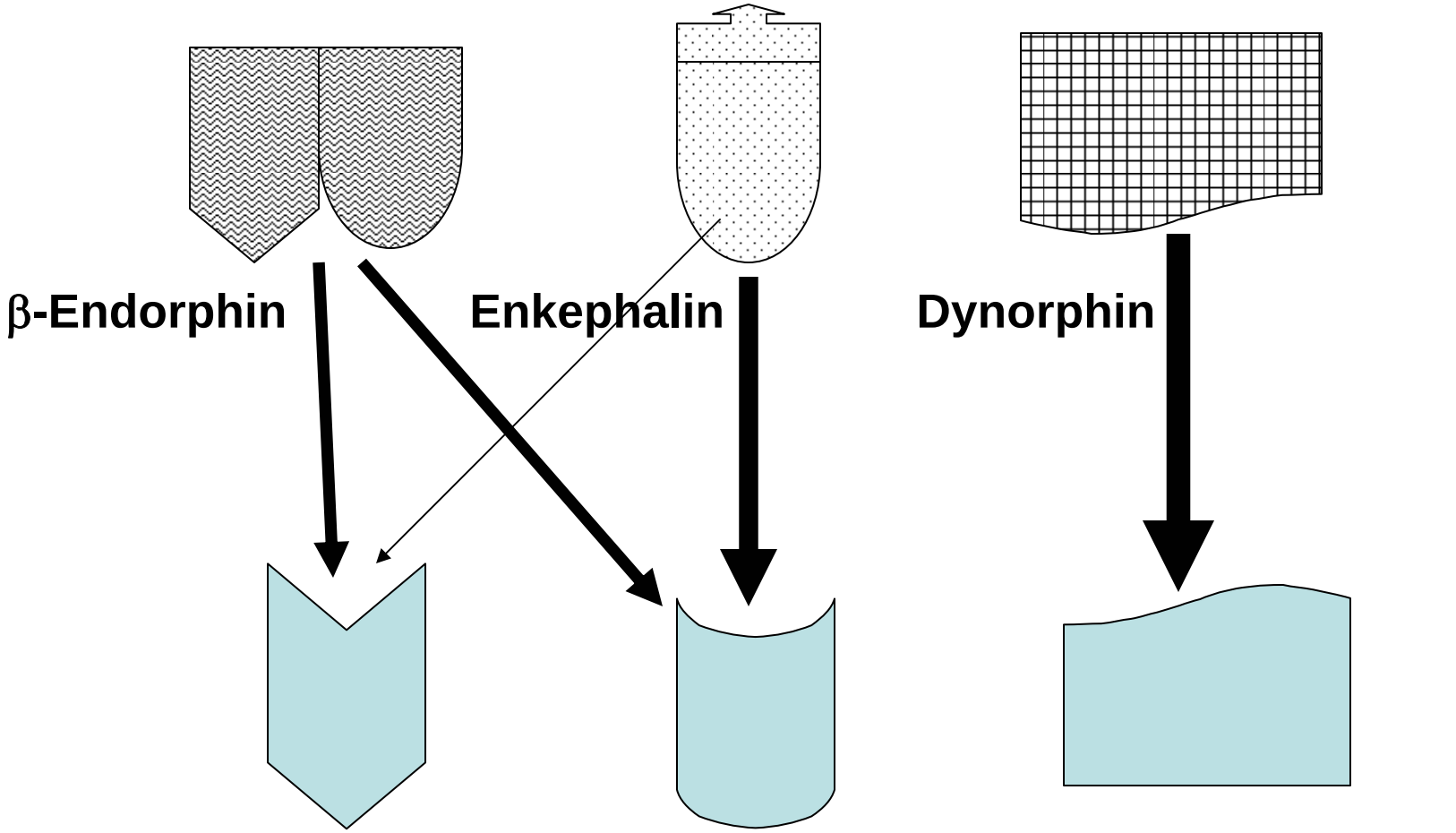
Dopamine in Drug Reinforcement

- **Increased Dopamine in the NAcb has been suggested to mediate the positive reinforcing properties of many drugs of abuse.**
- **If a drug increases Dopamine at the level of NAcb it is likely that the drug will be abused**
- **However, the reverse is not necessarily true. Drug reinforcement can occur in the absence of Dopamine in the NAcb. The NAcb can be lesioned and drugs can still be abused.**
- **Additional systems may be involved in reinforcement.**

Neurotransmitters	
Amino Acids	
Glutamate	GABA
Biogenic Amines	
Dopamine	Norepinepherine
Serotonin	
Neuropeptides	
Opioid Peptides	CRH
NPY	Substance P
Other	
Endocannabinoids	

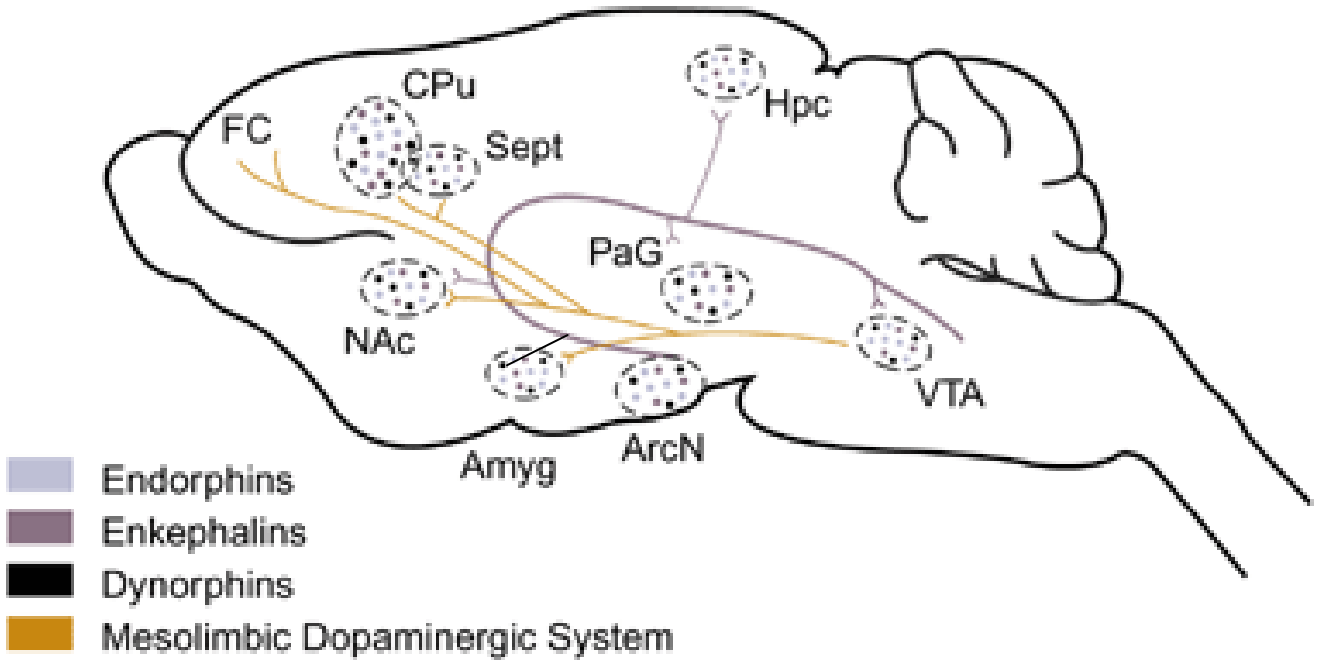
The endogenous opioid system and the mesolimbic Dopamine system have been shown to interact in inducing drug reinforcement and addiction.

The Endogenous Opioid Peptide Family and Receptors



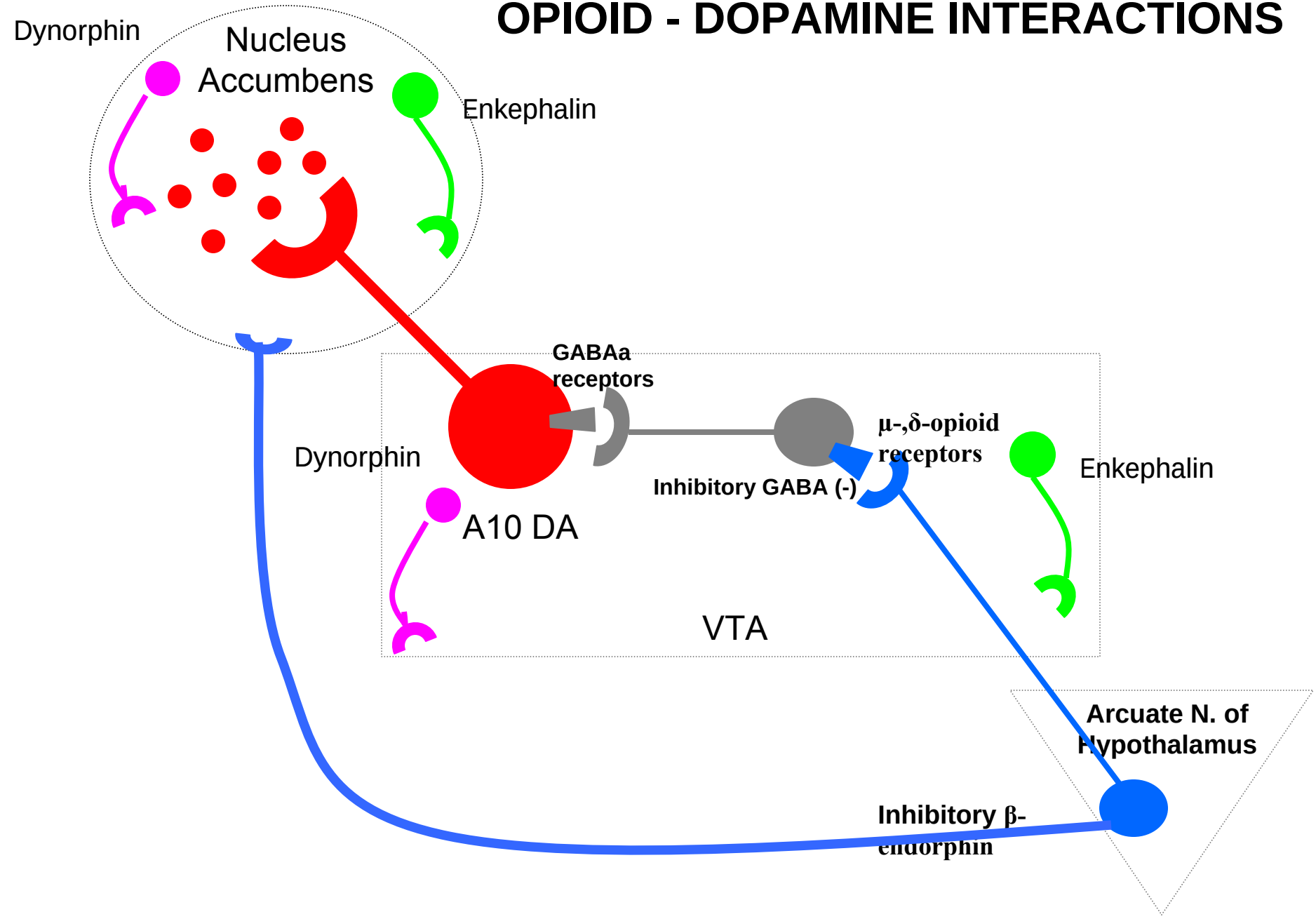
* Size of arrows indicates the affinity of the opioid peptides to receptors.

Endogenous Opioid and Dopamine System Interactions



Gianoulakis, Alcohol Health & Research World 22(3):202–210, 1998

OPIOID - DOPAMINE INTERACTIONS



Ethanol and Opioids

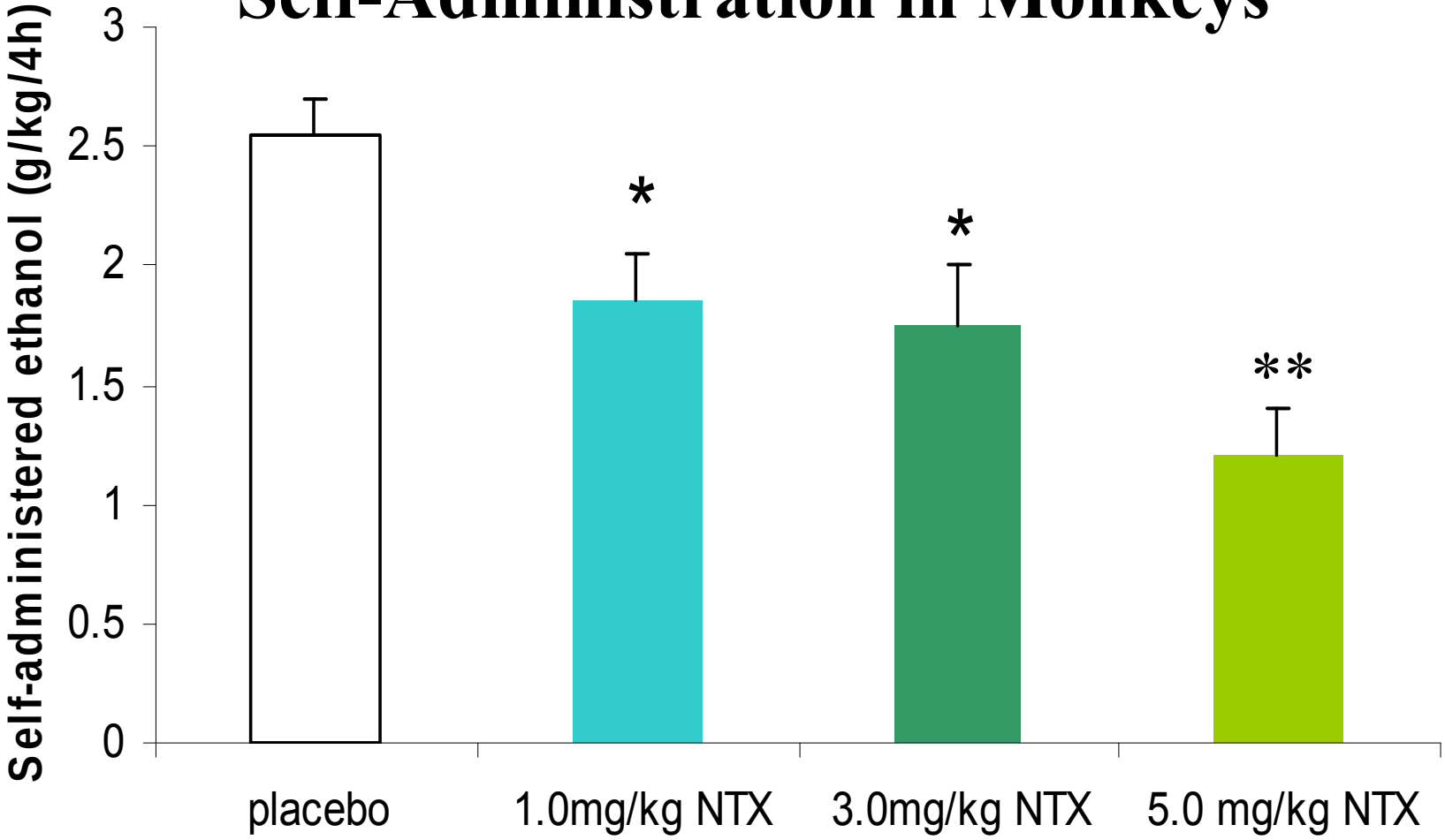
Ethanol lacks specific binding sites (receptors) yet it has numerous effects in the central nervous system (CNS).

Ethanol's effects in the CNS may be mediated by its effects on other neurotransmitters.

The Endogenous opioid system may mediate some of ethanol's effects, such as those of reward and reinforcement.

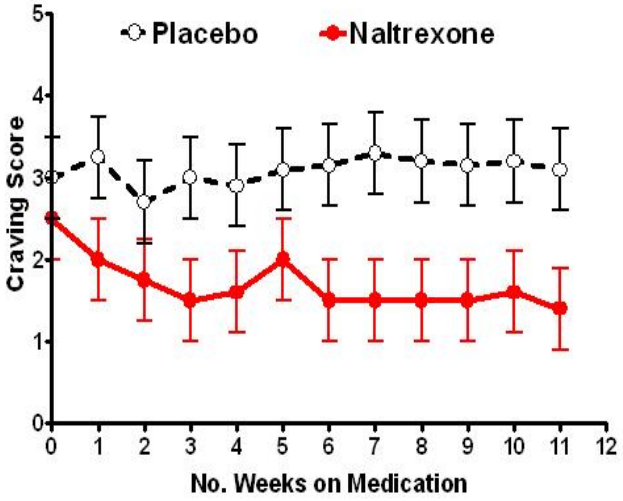
Evidence of Ethanol-Opioid Interactions

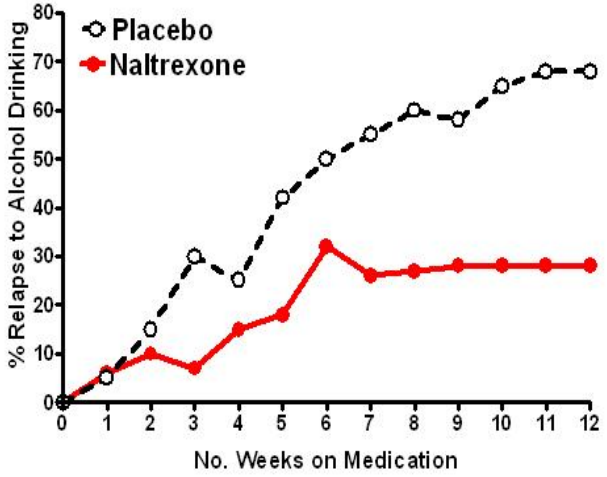
Effect of Naltrexone on Alcohol Self-Administration in Monkeys



Altshuler et al. (1980) LifeSci 26:679

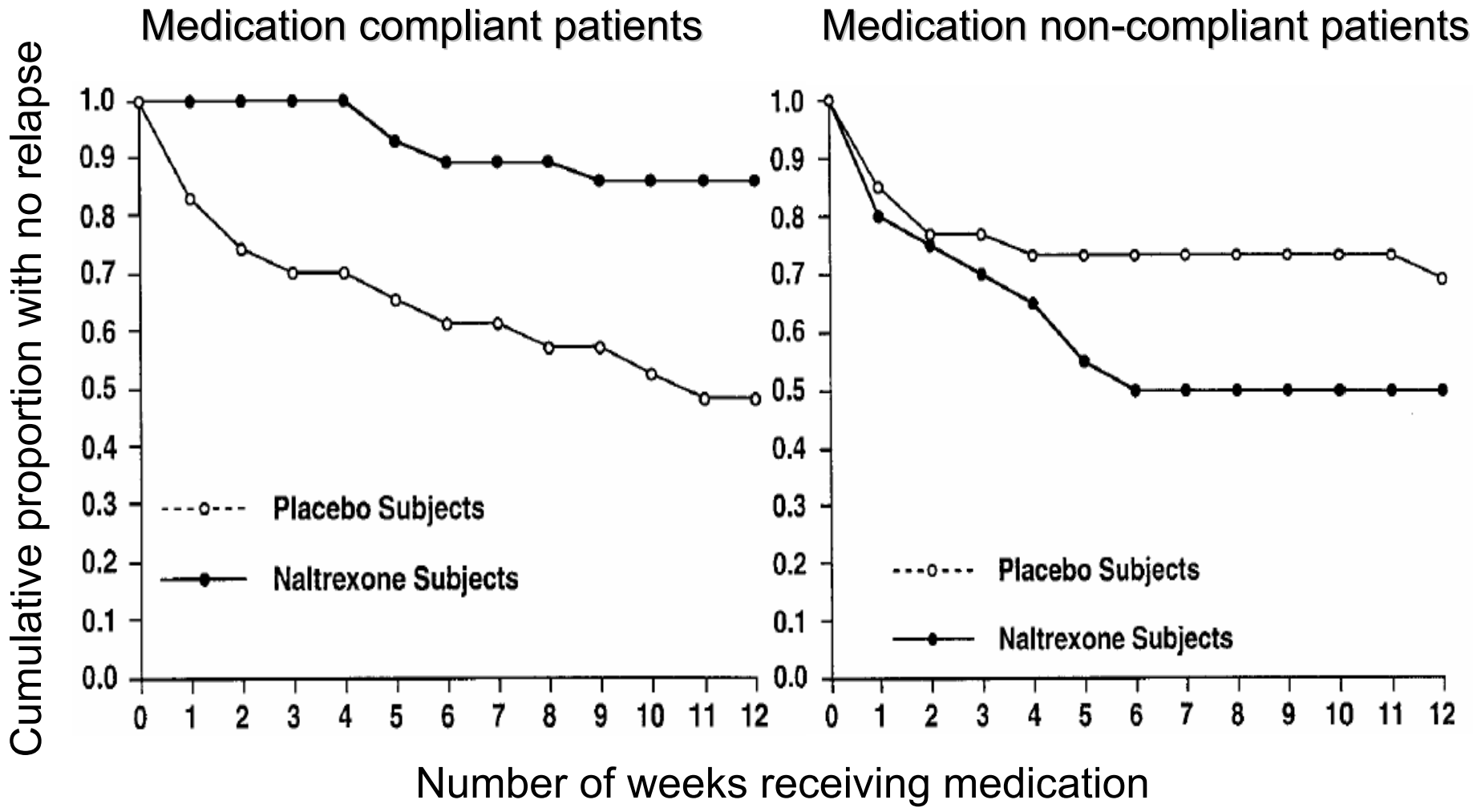
Effect of Naltrexone on Craving and Drinking in Alcohol-Dependent Human Subjects



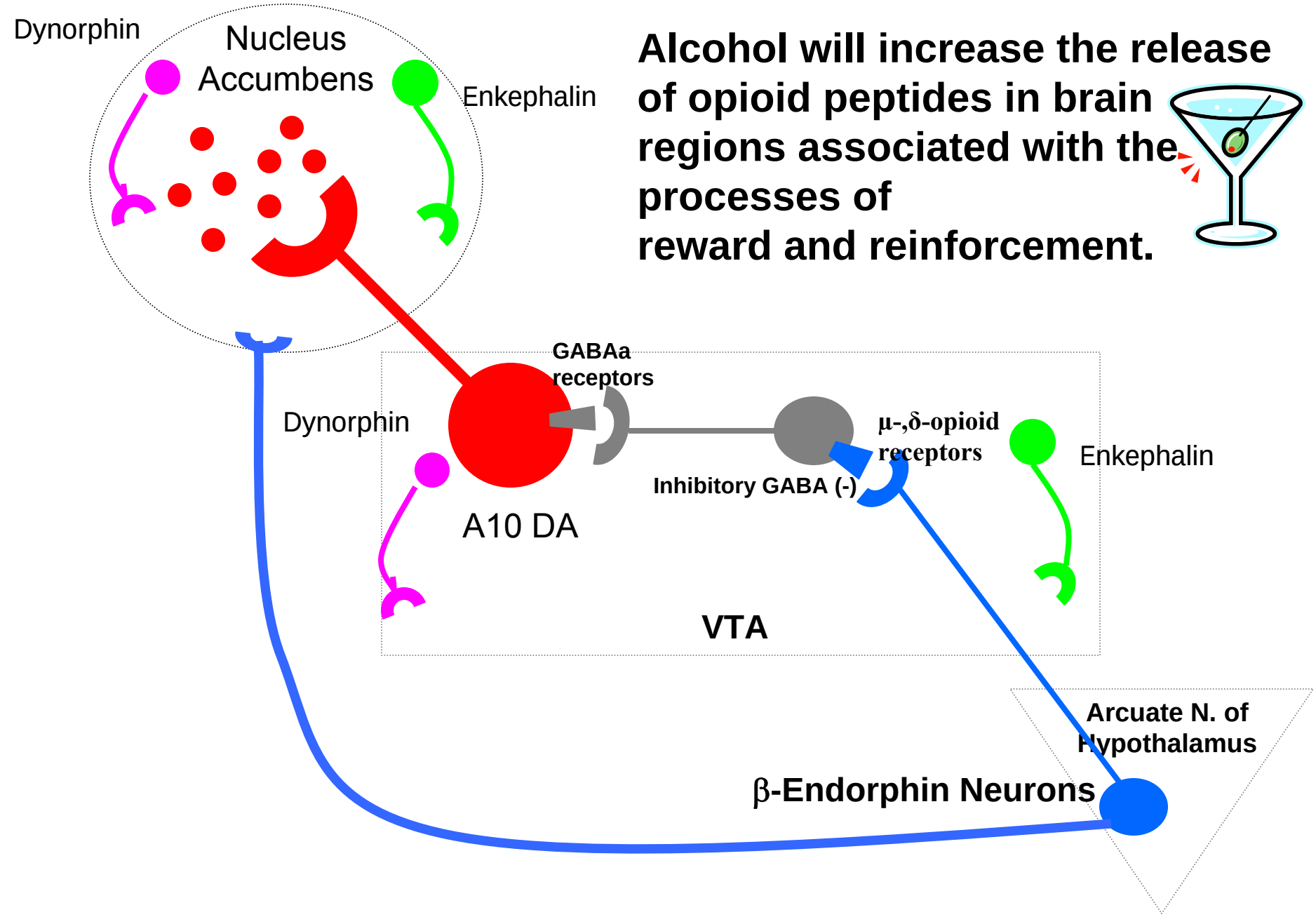


Volpicelli et al., (1992). Archives of General Psychiatry. 49:876-880.

Effect of Naltrexone on Maintenance of Abstinence to Alcohol in Humans



Weinrieb & O'Brien (1997) AnnRevMed 48:477


Dynorphin
Nucleus Accumbens
Enkephalin
Alcohol will increase the release of opioid peptides in brain regions associated with the processes of reward and reinforcement.
GABAa receptors
Dynorphin
μ-,δ-opioid receptors
Enkephalin
Inhibitory GABA (-)
A10 DA
VTA
Arcuate N. of Hypothalamus
β-Endorphin Neurons

Microinjections of opioid antagonists into specific areas of the brain (VTA) attenuate, or abolish alcohol induced increase of Dopamine release in the NAcb.
(Spanagel et al., 1990, Spanagel et al.,1992).
However, it is not known which opioid peptides are involved

PROPOSED HYPOTHESIS

If we accept that endogenous opioids mediate, at least in part, some of the reinforcing effects of ethanol

THEN

Acute ethanol exposure should alter the activity of distinct components of the endogenous opioid system.

THUS

↑ expression of opioid peptides and/or receptors

↑ binding of opioid ligands to receptors

↑ activity of opioid receptors

↑ release of opioid peptides from synapse

In brain regions associated with the processes of Reward and reinforcement.

OBJECTIVE OF THE PRESENTATION

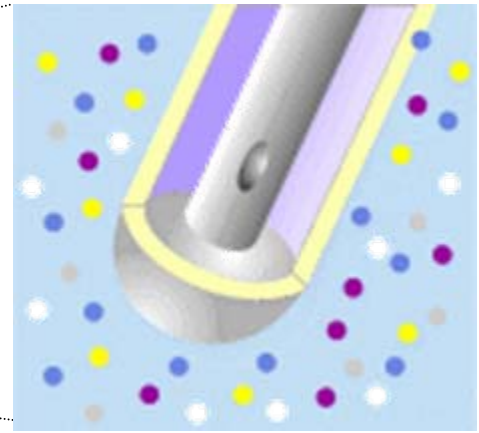
Is to demonstrate that acute alcohol administration stimulates the release of opioid peptides

Endorphins,
Enkephalins and
Dynorphins

In brain regions associated with the processes of reward and reinforcement such as:

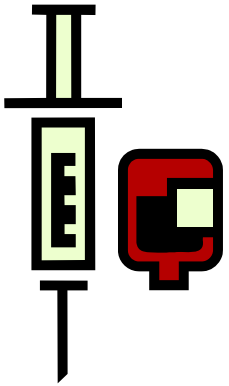
Ventral tegmental area (VTA)
Nucleus accumbens (NAcb)
Central amygdala (CeA)

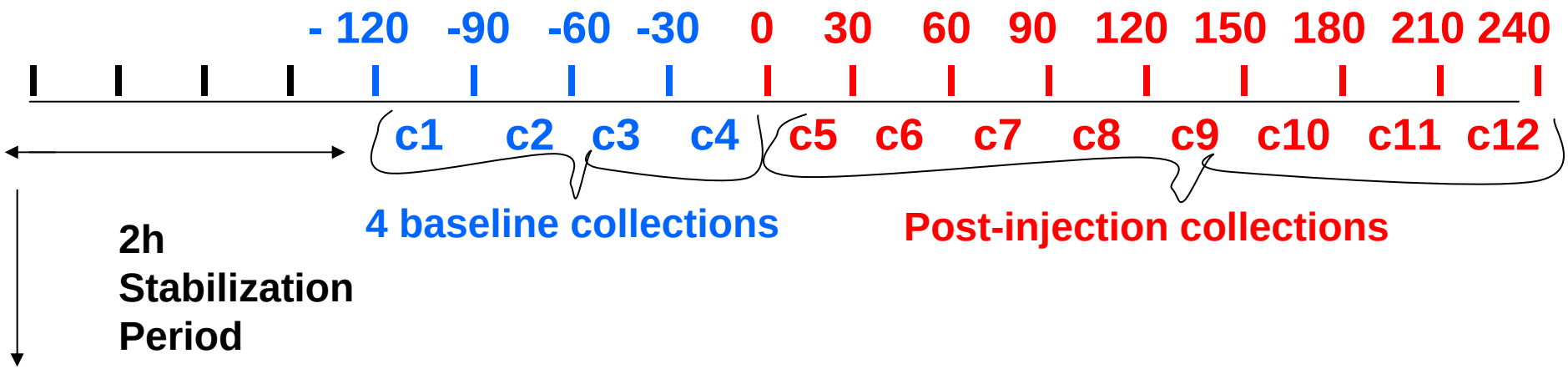
In vivo Microdialysis



Experimental Design: *In vivo* Microdialysis

i.p. injection of saline or various doses of alcohol





Flow rate Turned to 2.0 μl/min

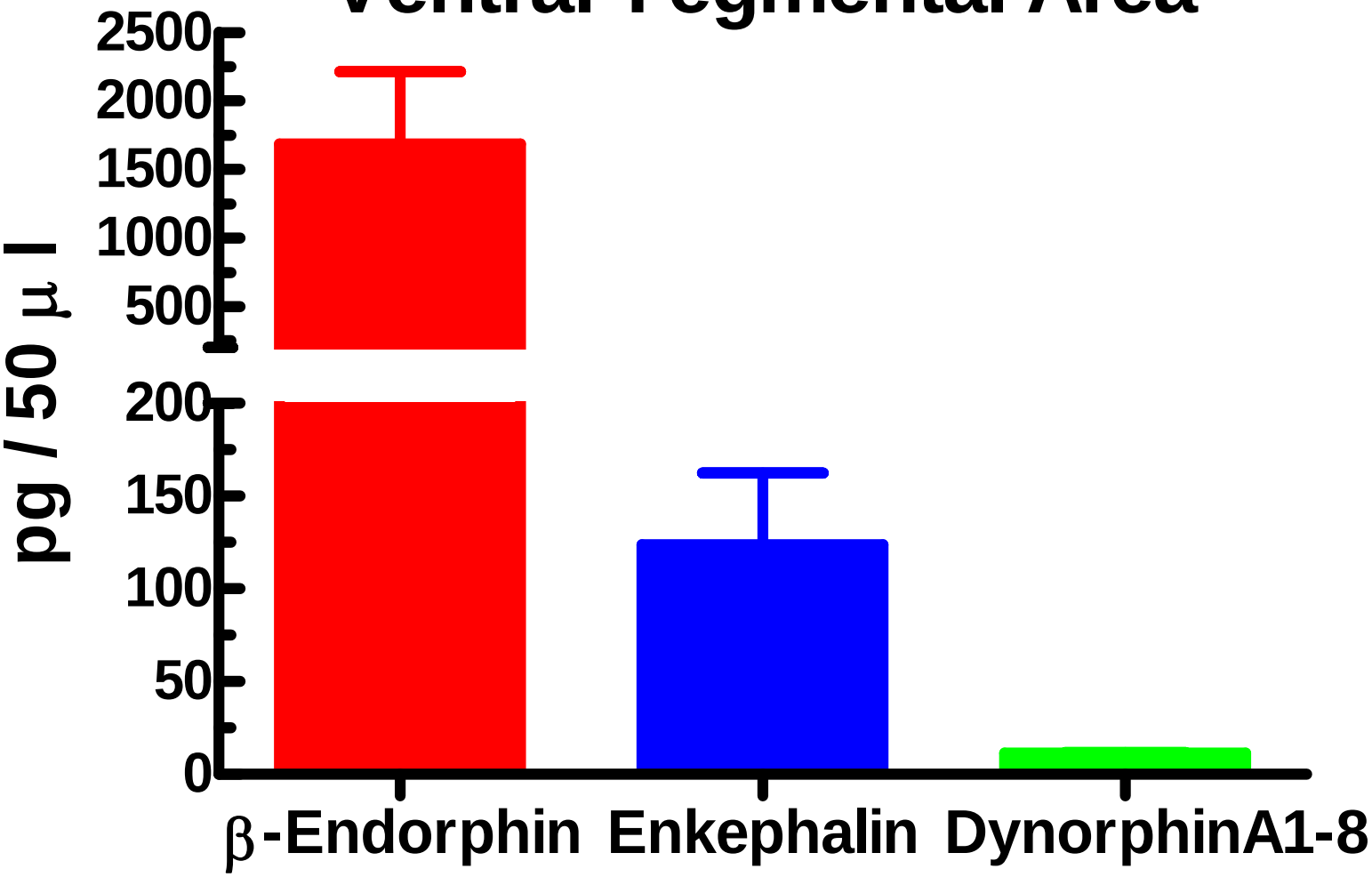
Basal Release = Mean of the 4 baseline collections

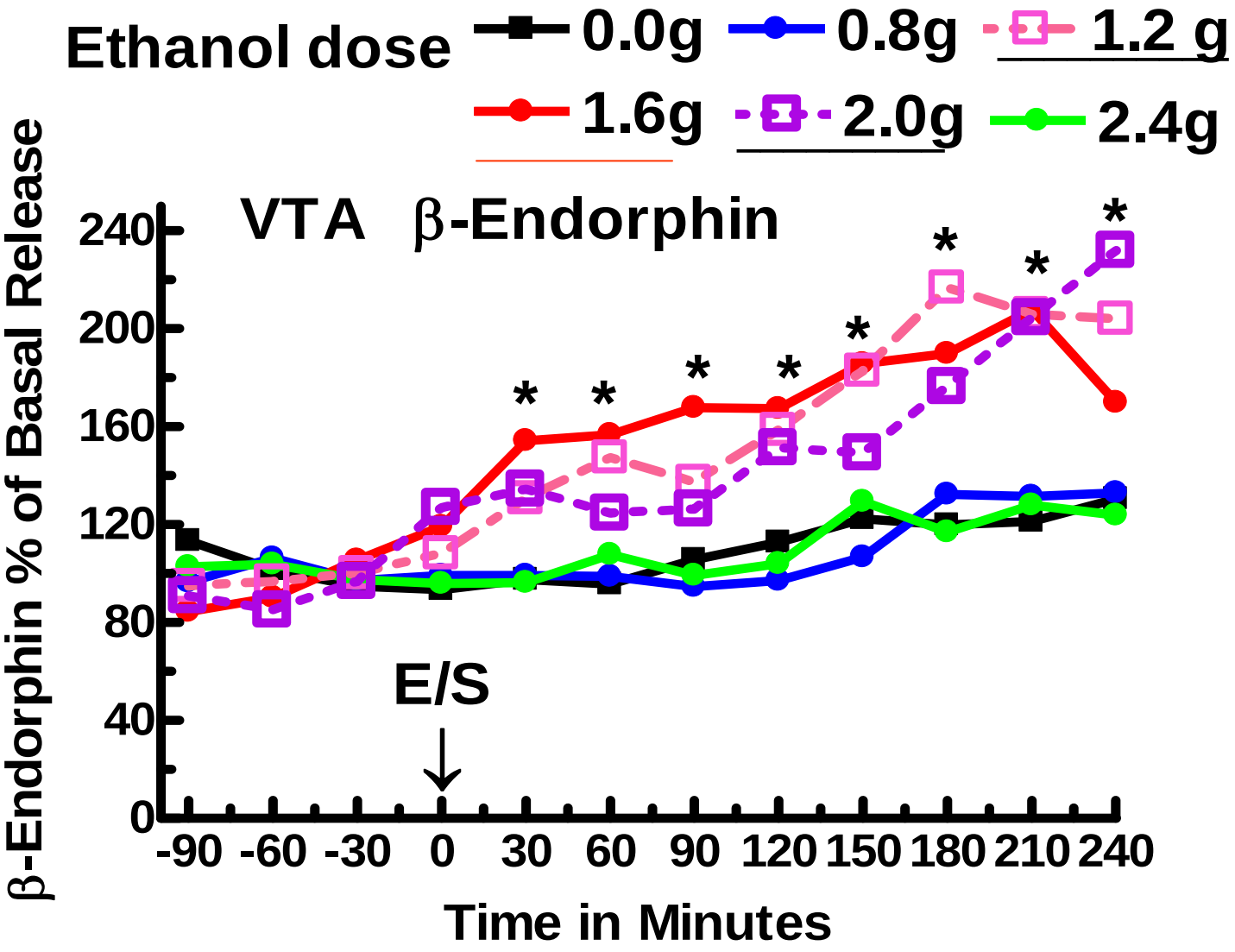
Response = % change from basal release

Data is analyzed with a 2-way Mixed ANOVA + Tukey HSD

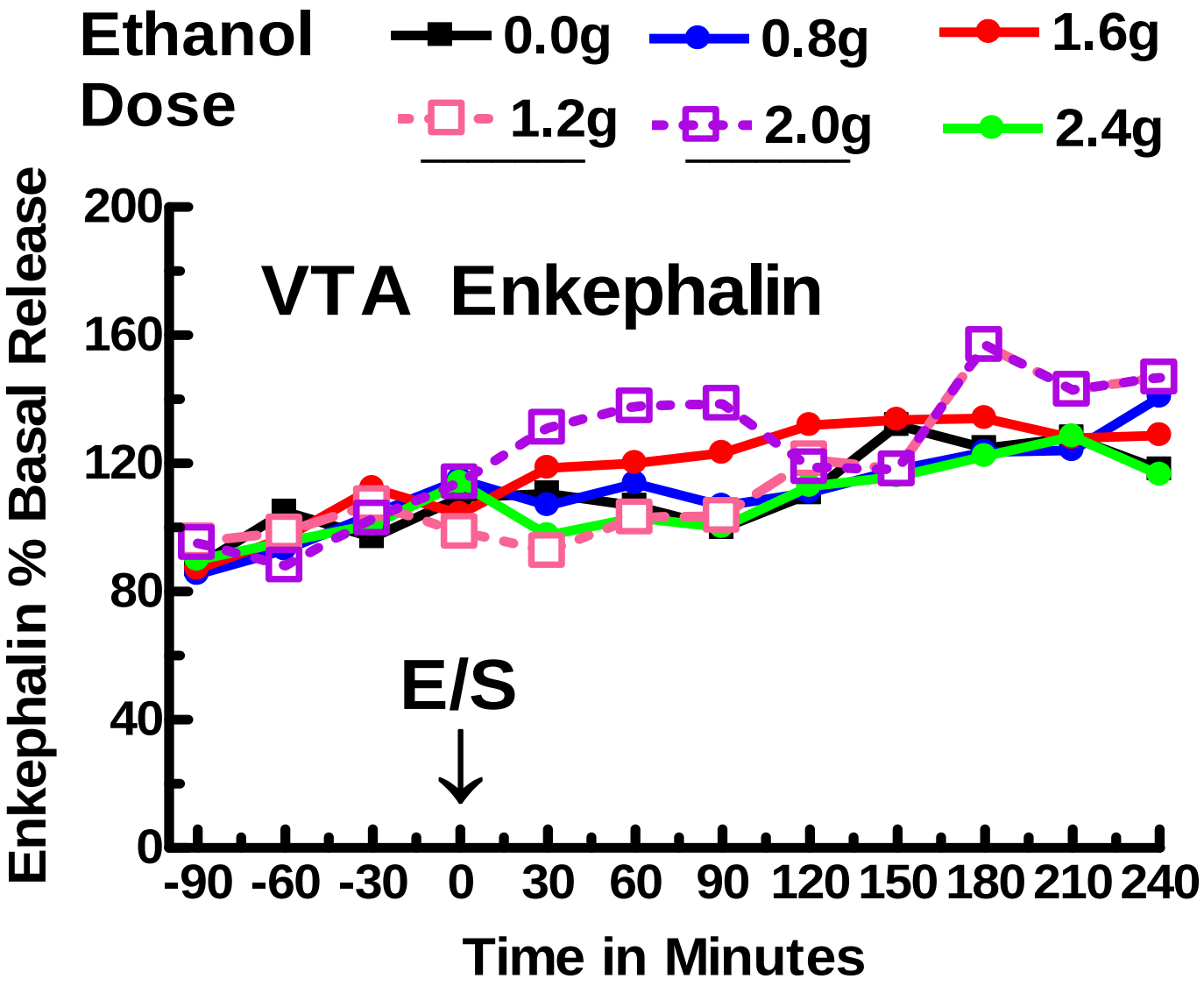
EFFECT OF ALCOHOL ON THE RELEASE OF OPIOID PEPTIDES AT THE LEVEL OF VTA

Basal Peptide Levels in Ventral Tegmental Area





Jarjour et al Alc Clin Exp Res (under revision)



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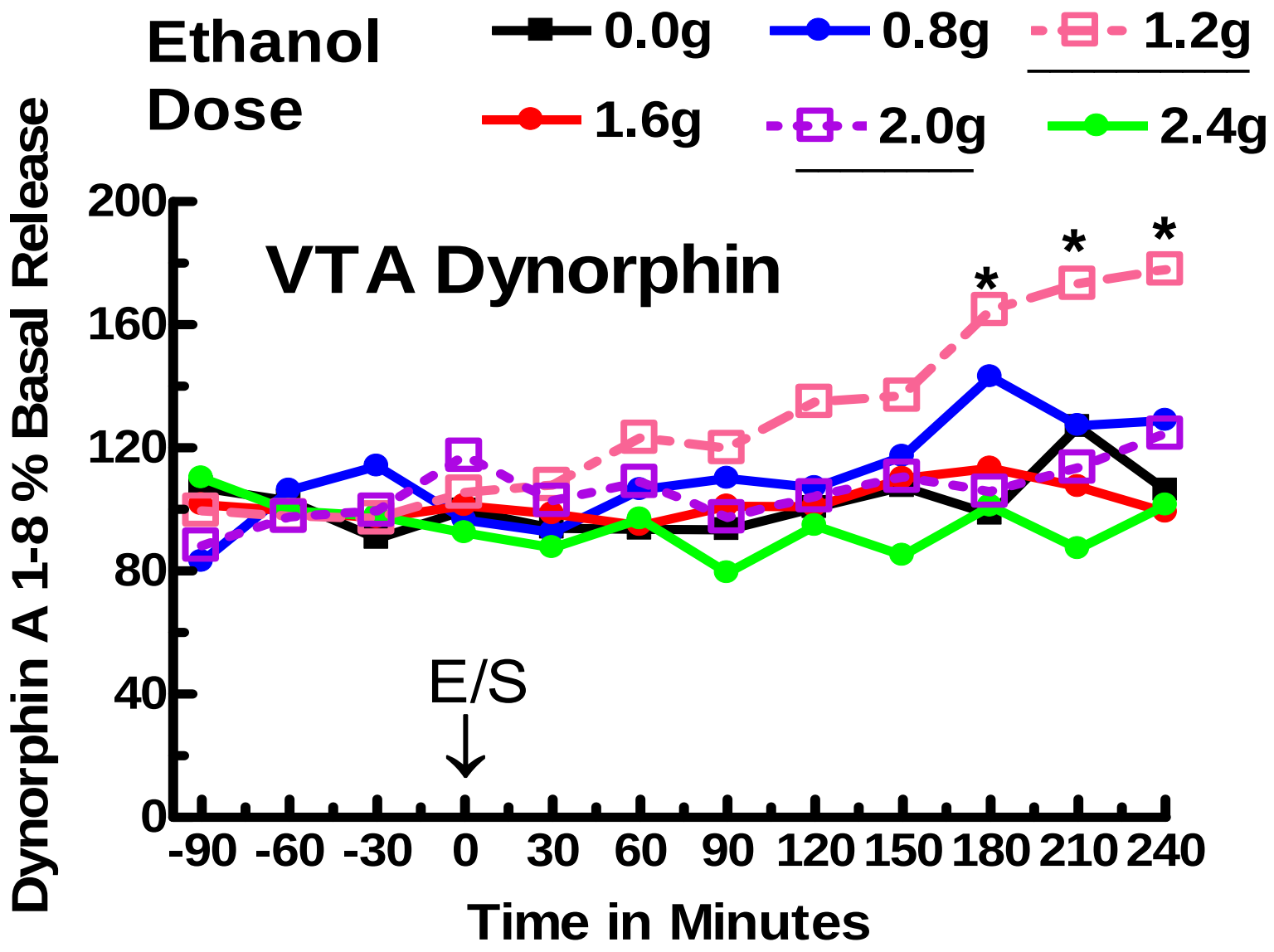


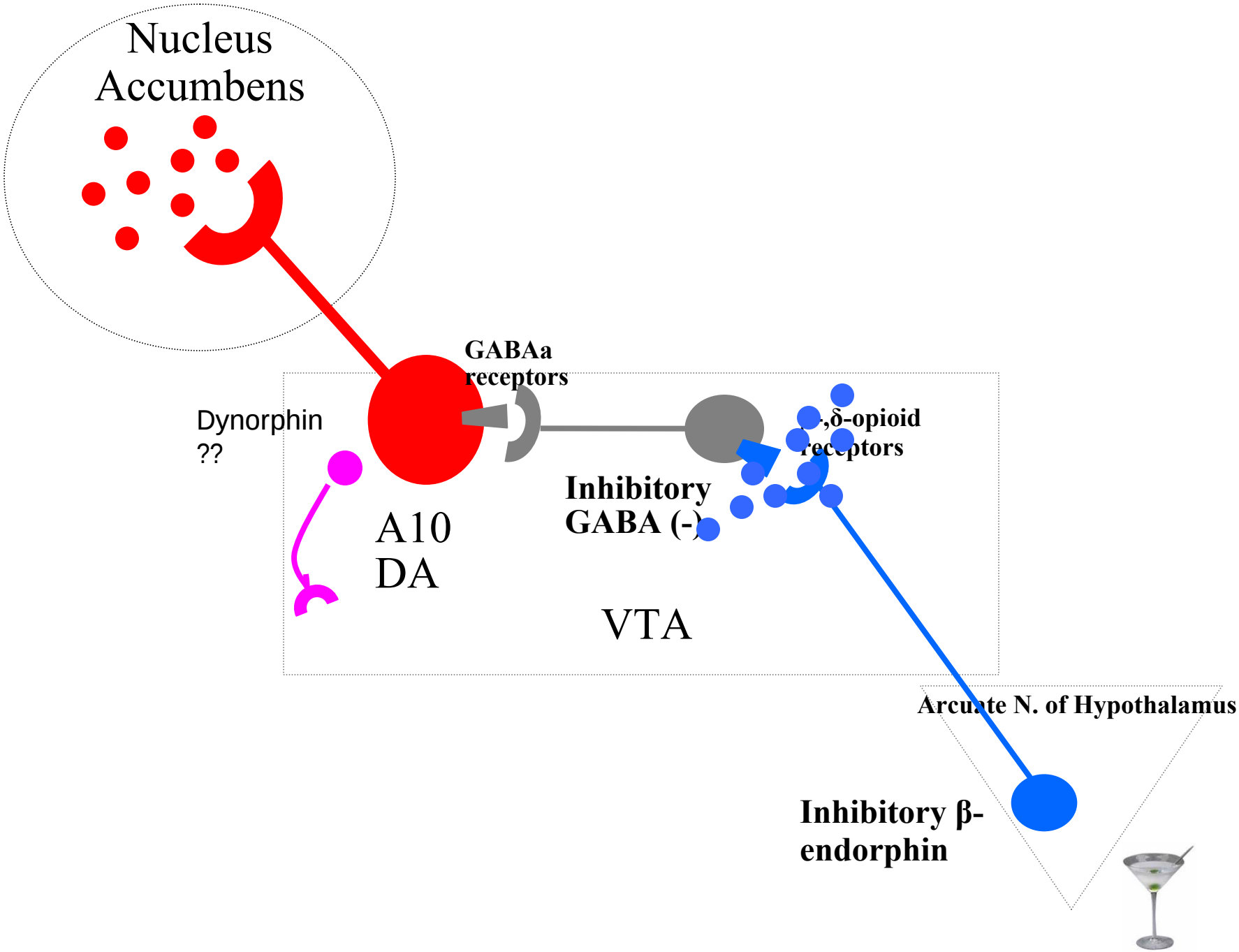
Jarjour et al Alc Clin Exp Res (under revision)

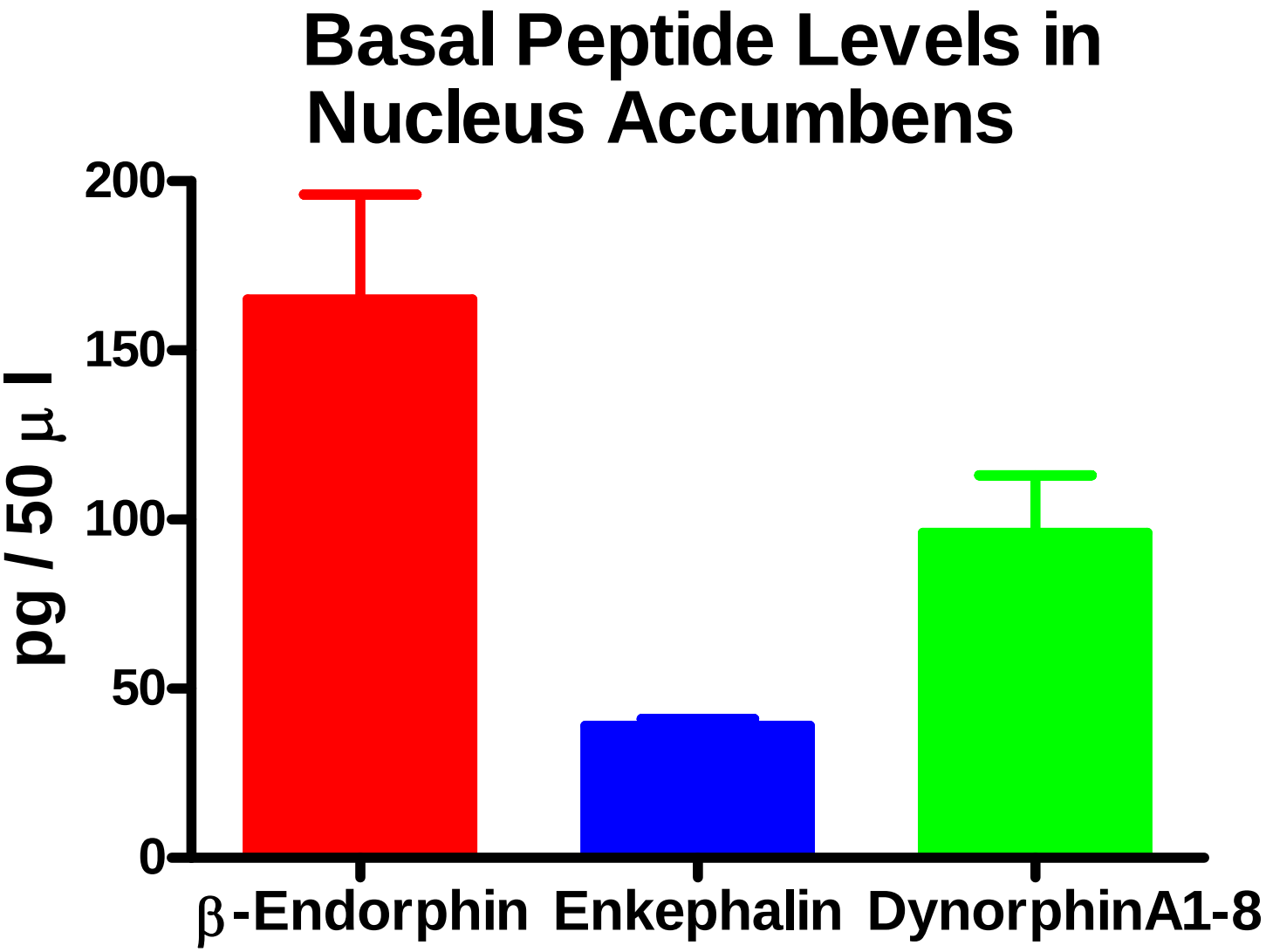
VTA: Dose Dependent effect

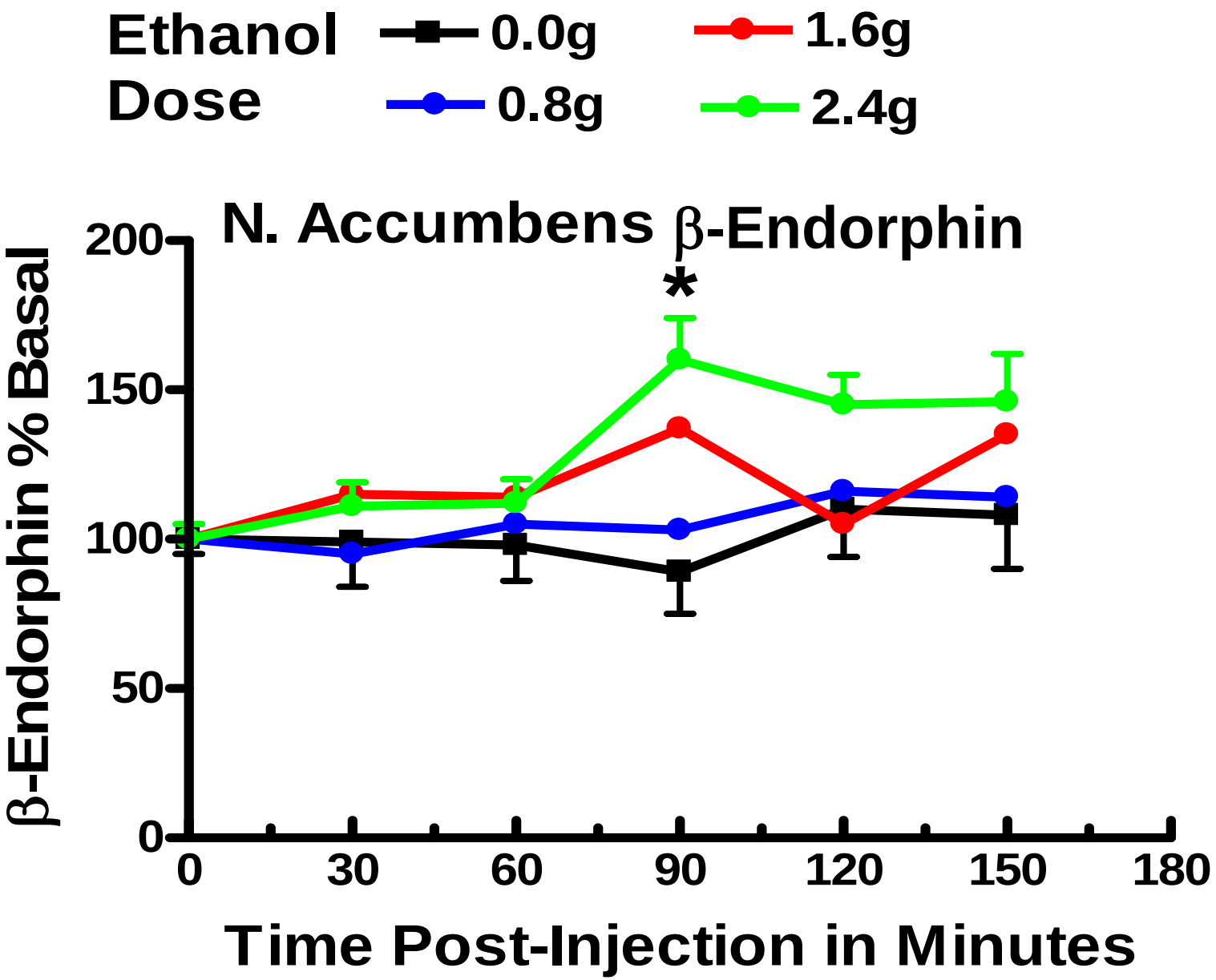
. **Early long lasting increase of β-endorphin release (1.2; 1.6 and 2.0 g dose) supports its role in the inhibition of GABAergic neurons leading to the disinhibition of DAminergic neurons and increased DA release at the level of nucleus accumbens.**

. **Small delayed increase in the release of dynorphin peptides in response to 1.2 g ethanol dose Significance??**

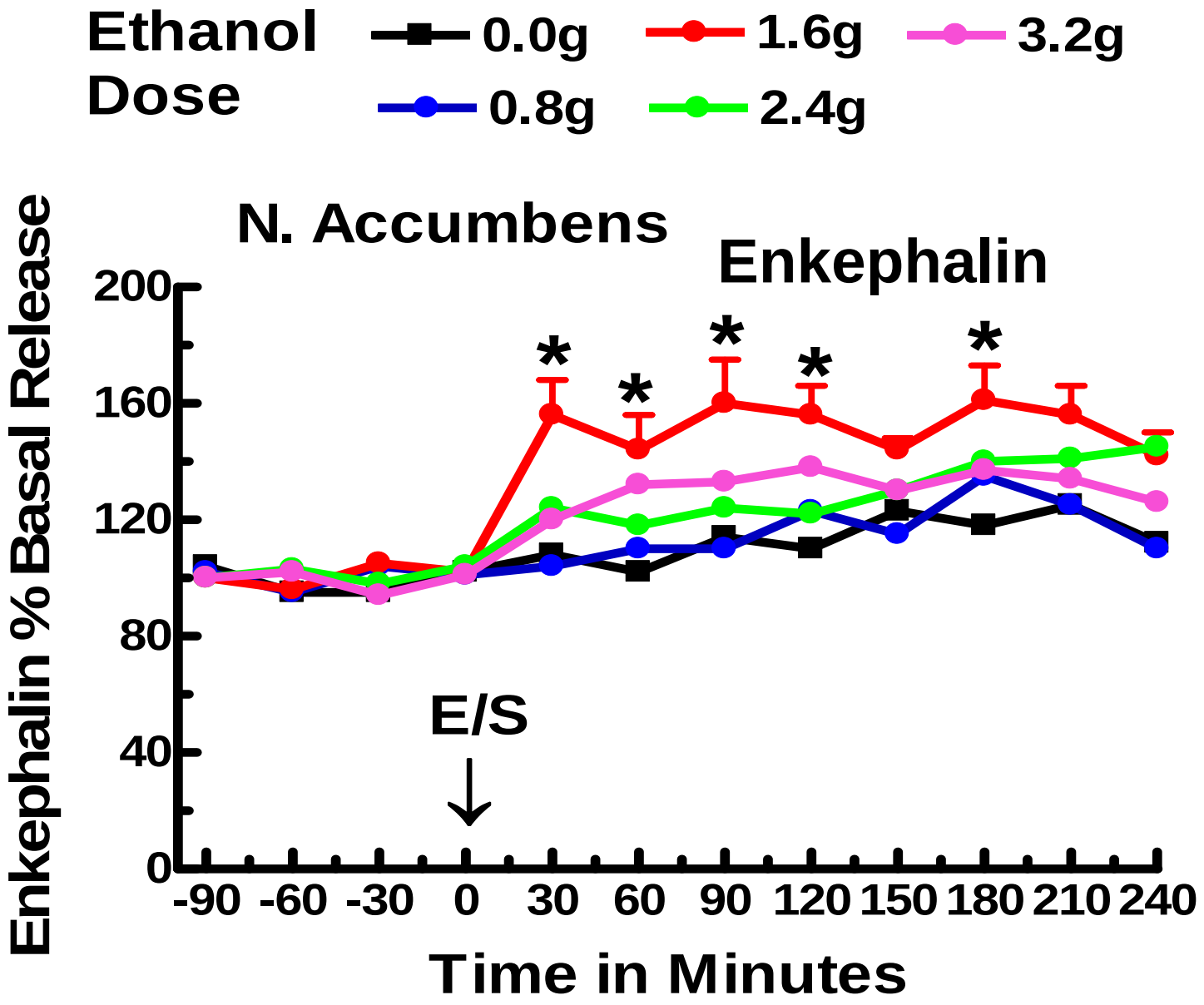
. **No significant responses of enkephalin in the ethanol doses used .**


Nucleus
Accumbens
GABAa
receptors
Dynorphin
??
A10
DA
Inhibitory
GABA (-)
VTA
Arcuate N. of Hypothalamus
Inhibitory β-
endorphin

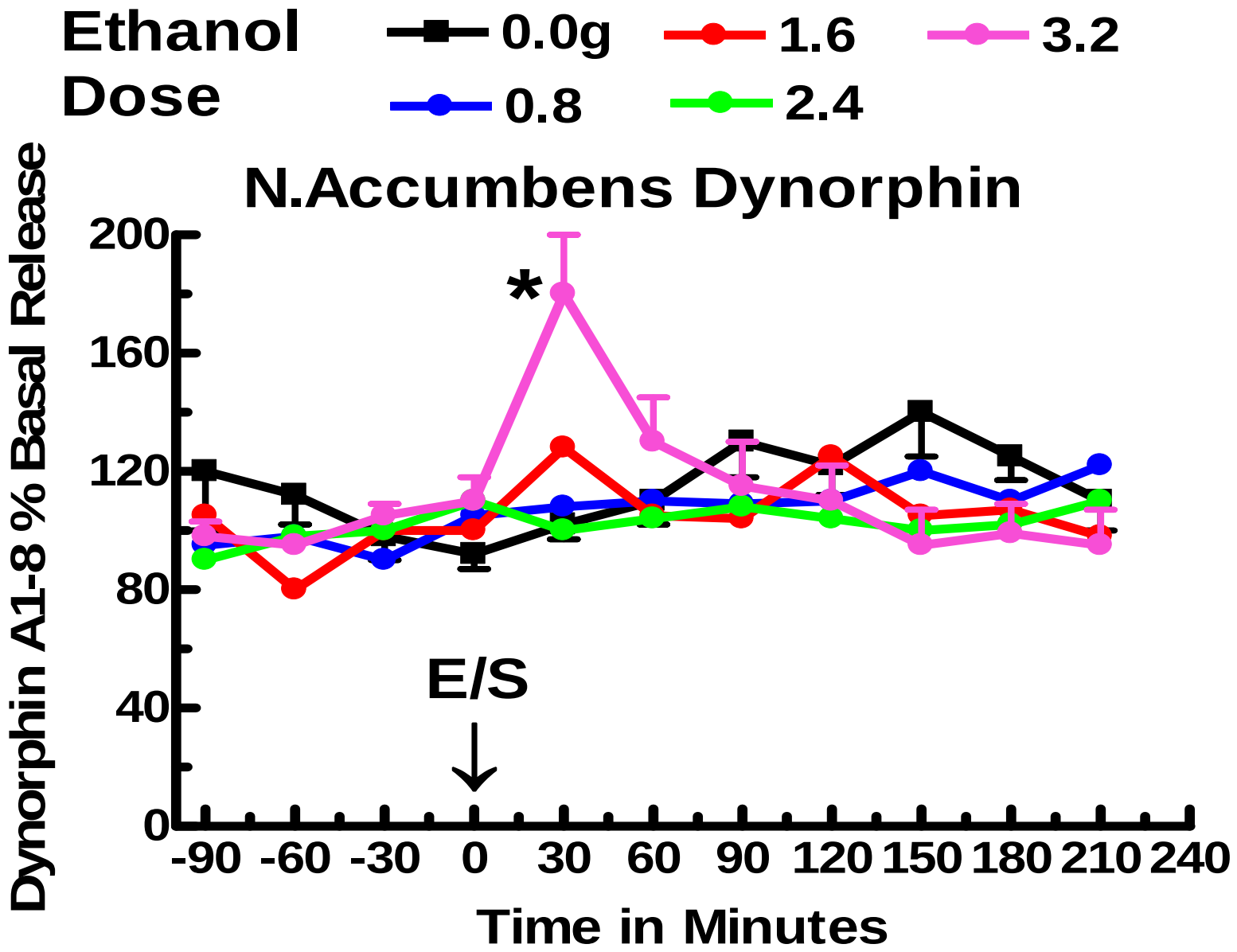

Basal Peptide Levels in
Nucleus Accumbens
200
150
100
50
0
pg / 50 µ l
β-Endorphin
Enkephalin
DynorphinA1-8



Peter Marinelli et al Psychopharmacology 169:60-67, 2003



Peter Marinelli et al. Alc. Clin. Exp. Res. 29:1821-1825, 2005



Peter Marinelli et al. Alc. Clin Exp. Res. 30:982-990, 2006

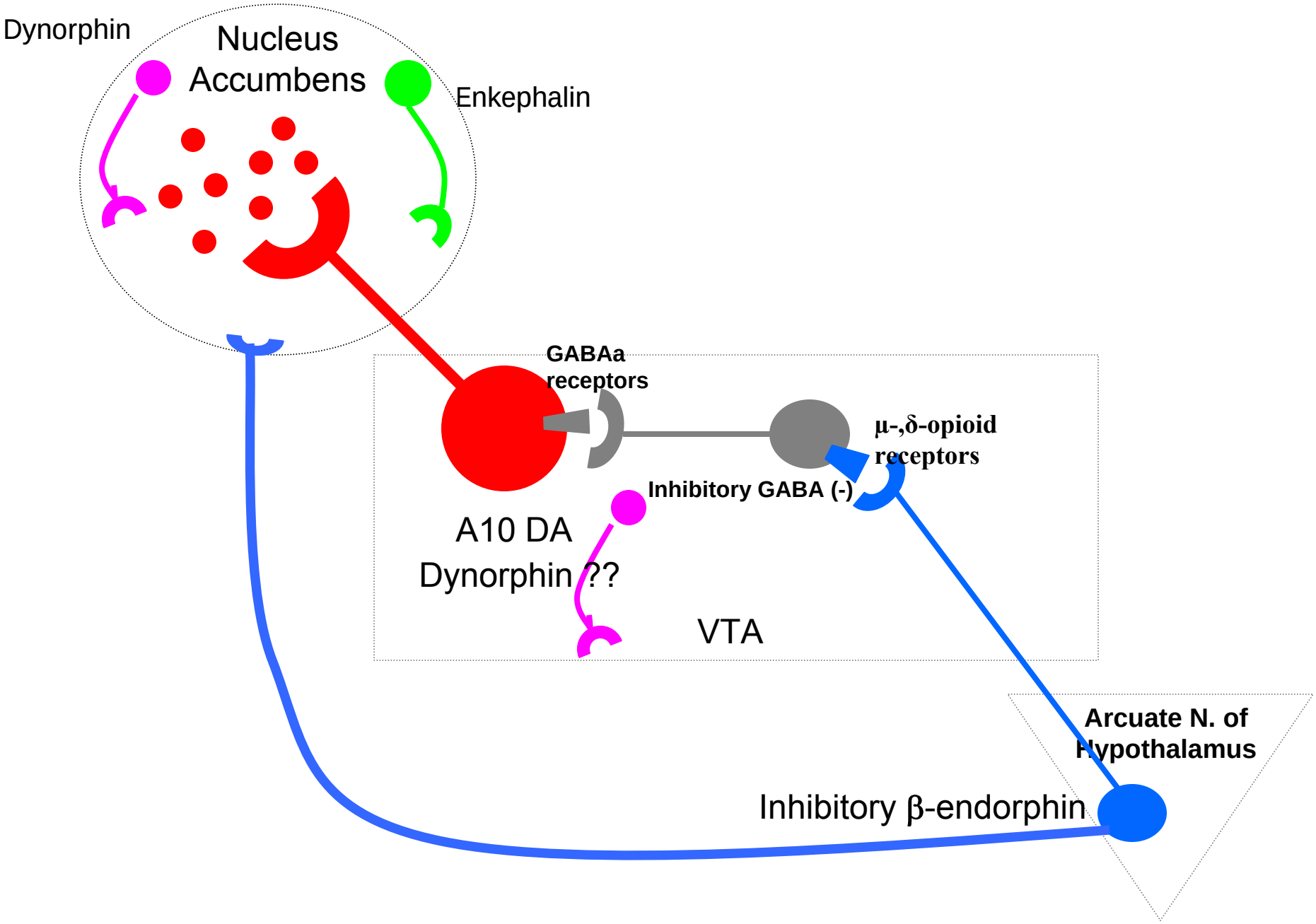
CONCLUSIONS

Nucleus Accumbens: Dose Dependent effect

. Delayed increase of β-endorphin release (2.4 g ETOH dose at 90 minutes) in agreement with previous findings by Olive et al. (2001)

. Early and long lasting increase of Enkephalin release (1.6g/kg dose)

. Early short lasting increase of Dynorphin release (3.2g/kg dose)


Dynorphin
Nucleus Accumbens
Enkephalin
GABAa receptors
μ-,δ-opioid receptors
Inhibitory GABA (-)
A10 DA
Dynorphin ??
VTA
Arcuate N. of Hypothalamus
Inhibitory β-endorphin

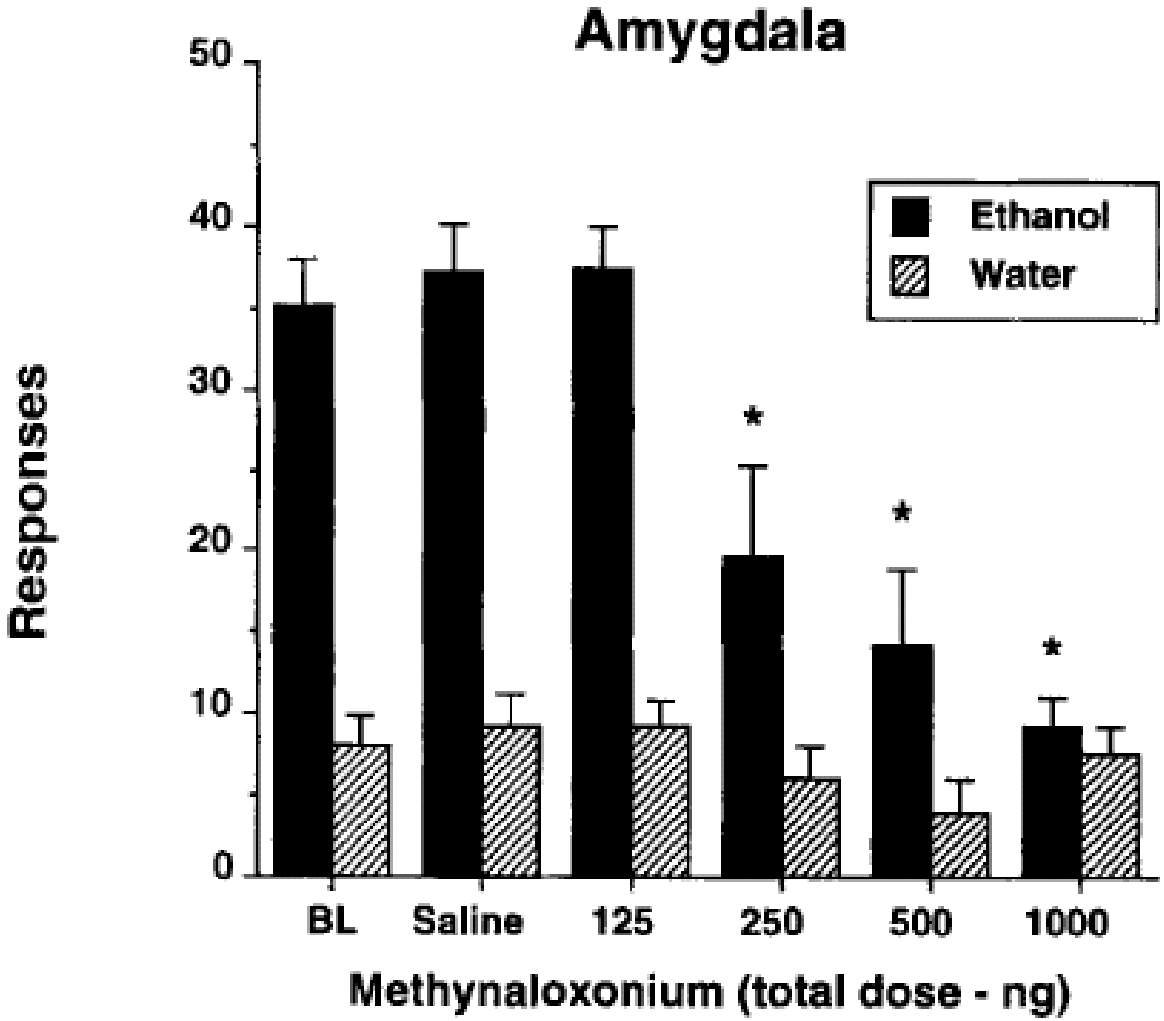
Central Amygdala
Opioids and Alcohol Consumption

The central division of the amygdala is part of a larger neural complex called the Extended Amygdala Complex consisting of:

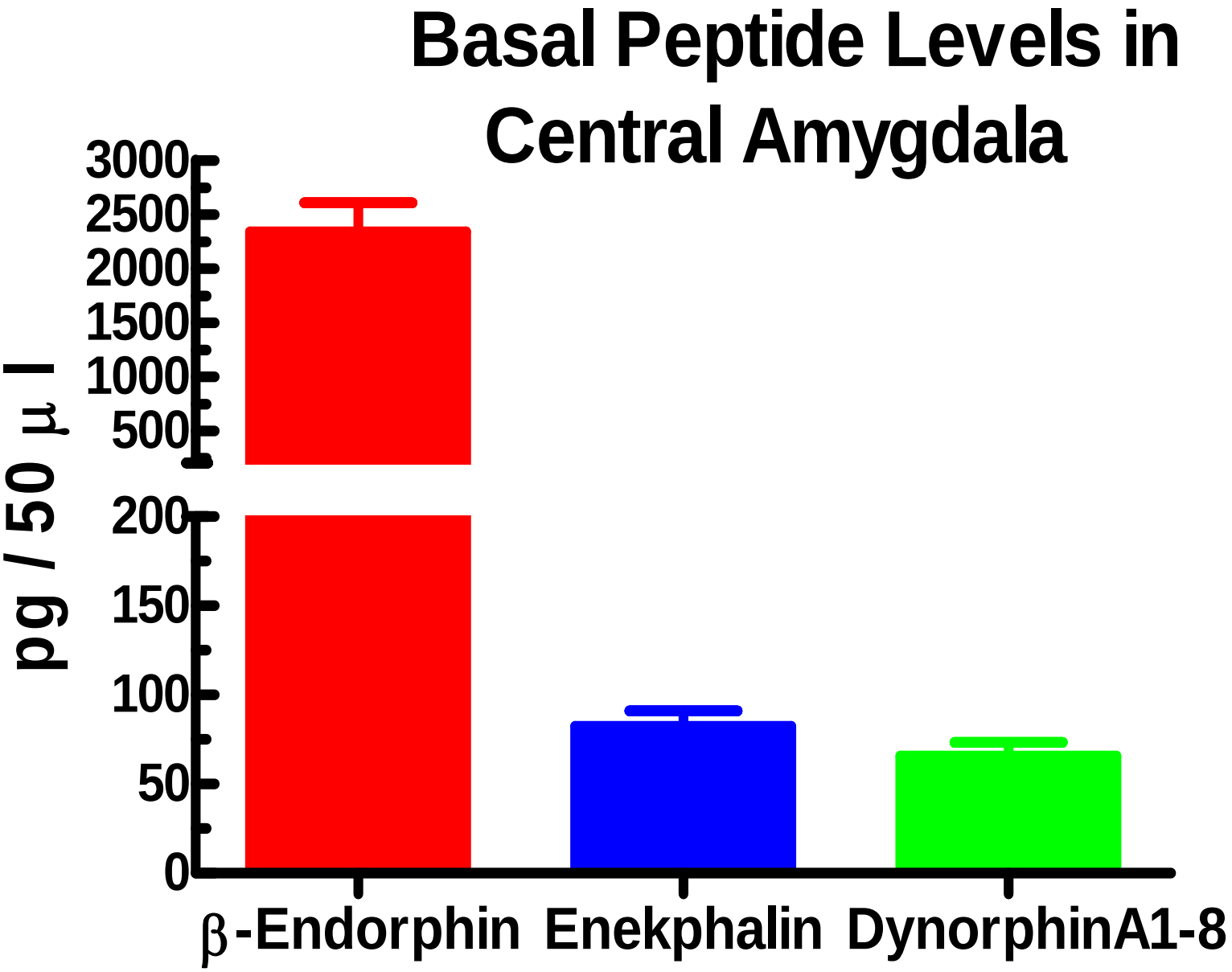
- **Central Amygdala**
- **Shell Region of the Nucleus Accumbens**
- **Sublenticular Substantia Inominata and**
- **Bed Nucleus of the Stria Terminalis**

A role of the endogenous opioid system in central amygdala on alcohol consumption has been suggested by the observation that blocking the activity of the endogenous opioid system in central amygdala attenuates alcohol consumption (Heyser et al 1999; McBride 2002).

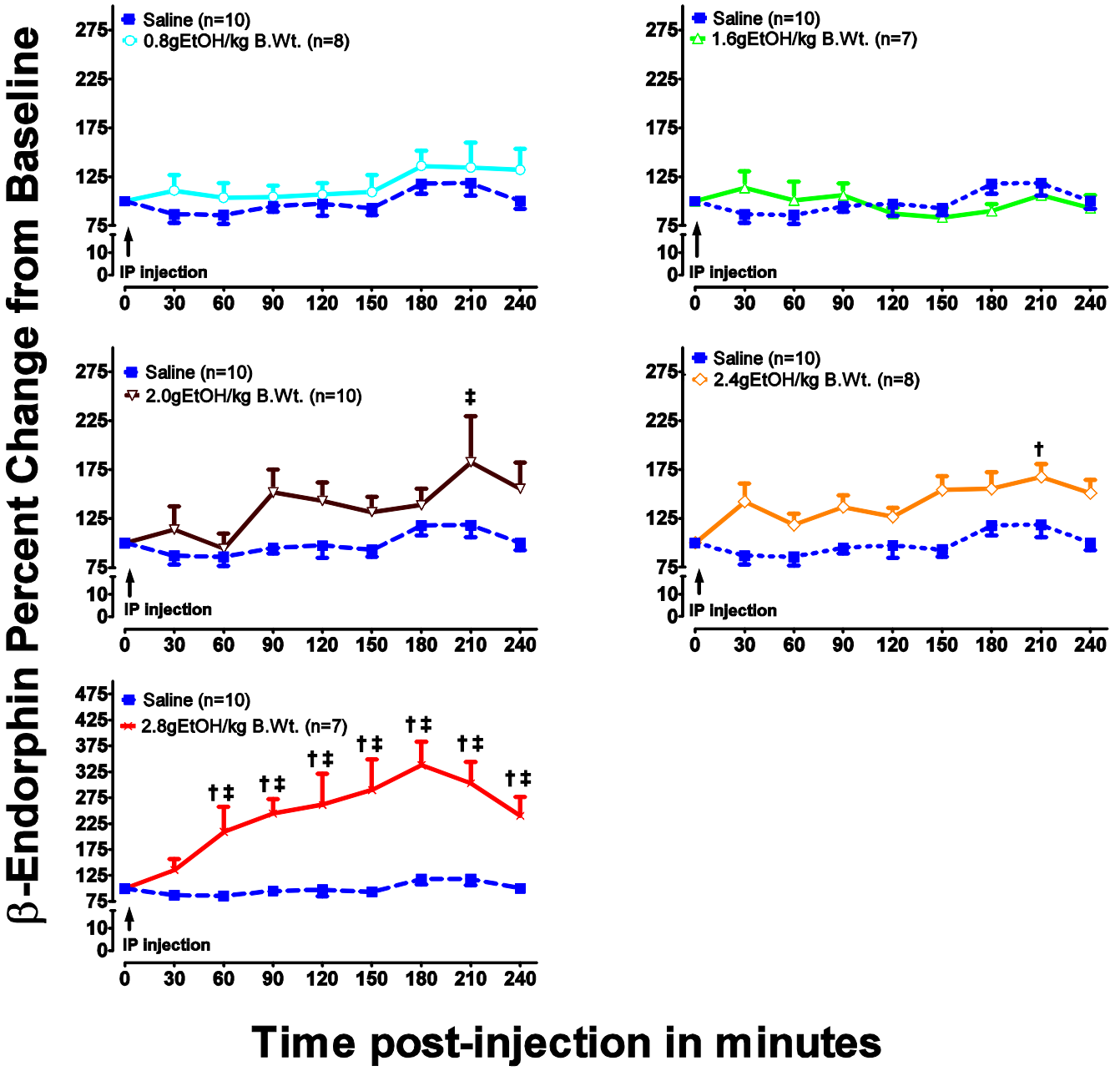
Opioid antagonist in central amygdala attenuates EtOH consumption



Heyser et al.1999.Alcohol Clin Exp Res.23(9).1468-1476.


Basal Peptide Levels in Central Amygdala
pg / 50 µ l
3000
2500
2000
1500
1000
500
200
150
100
50
0
β-Endorphin
Enekphalin
DynorphinA1-8

Lam et al. (2008). Psychopharmacology. Epub ahead of print.



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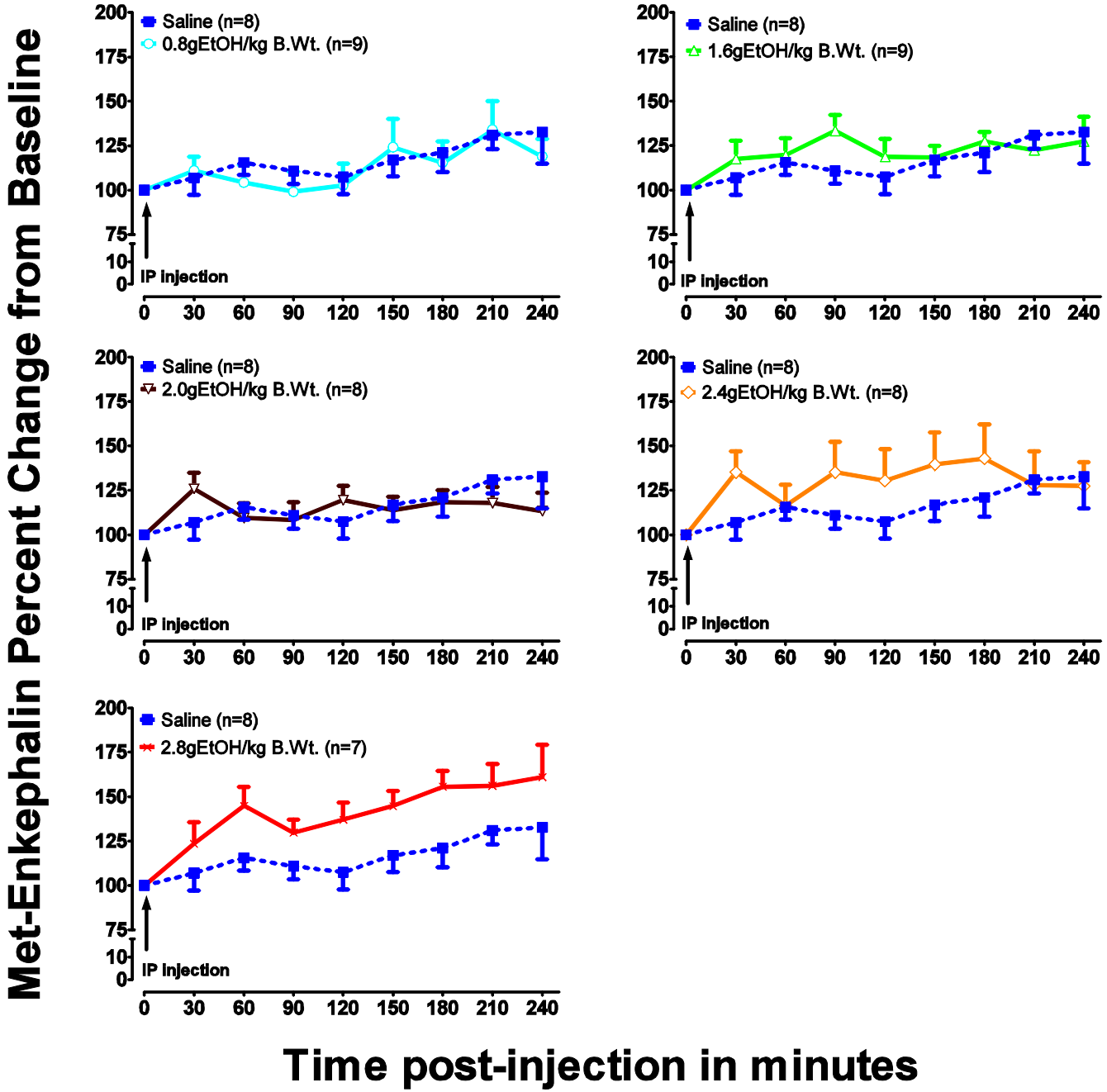

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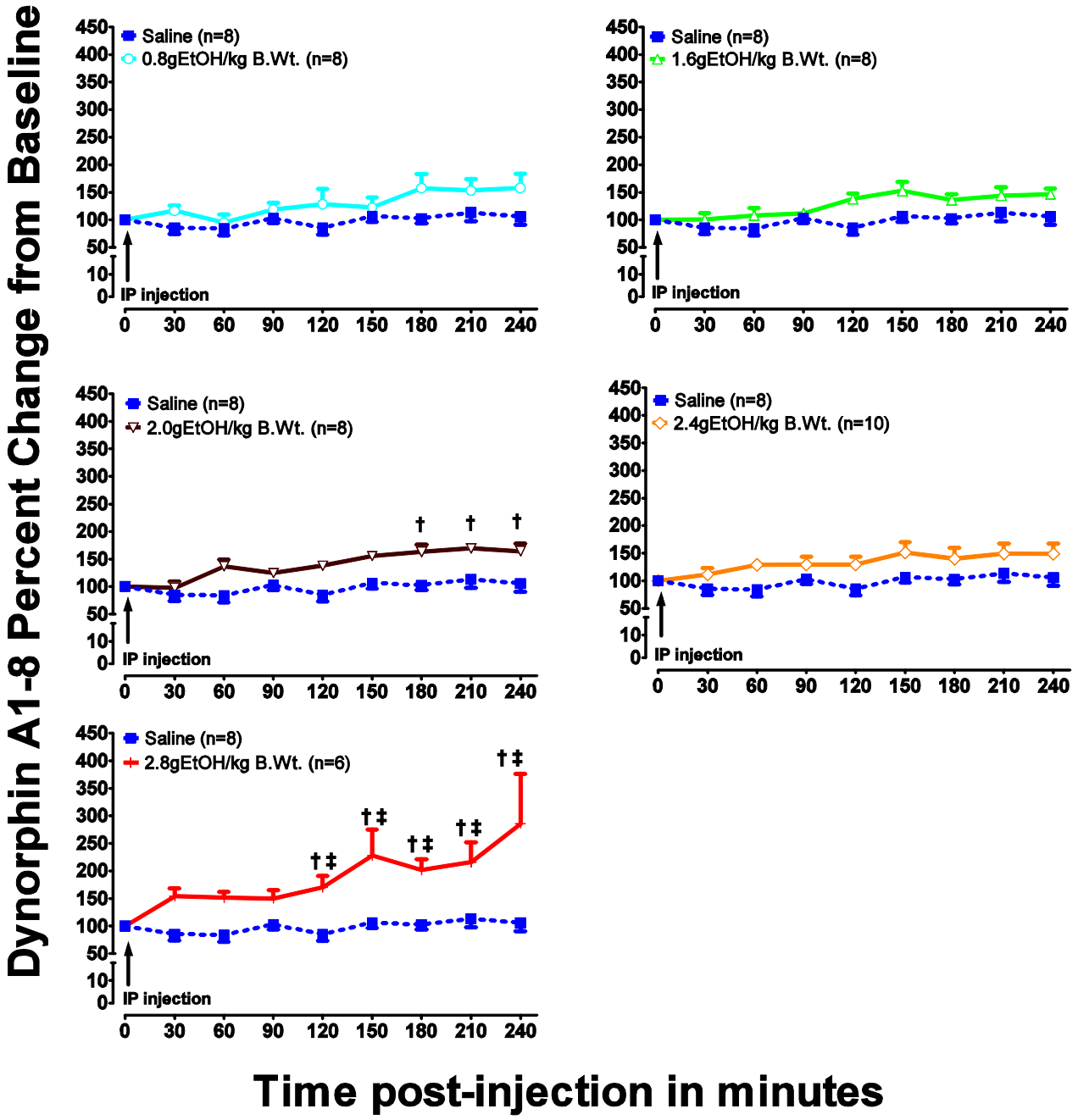


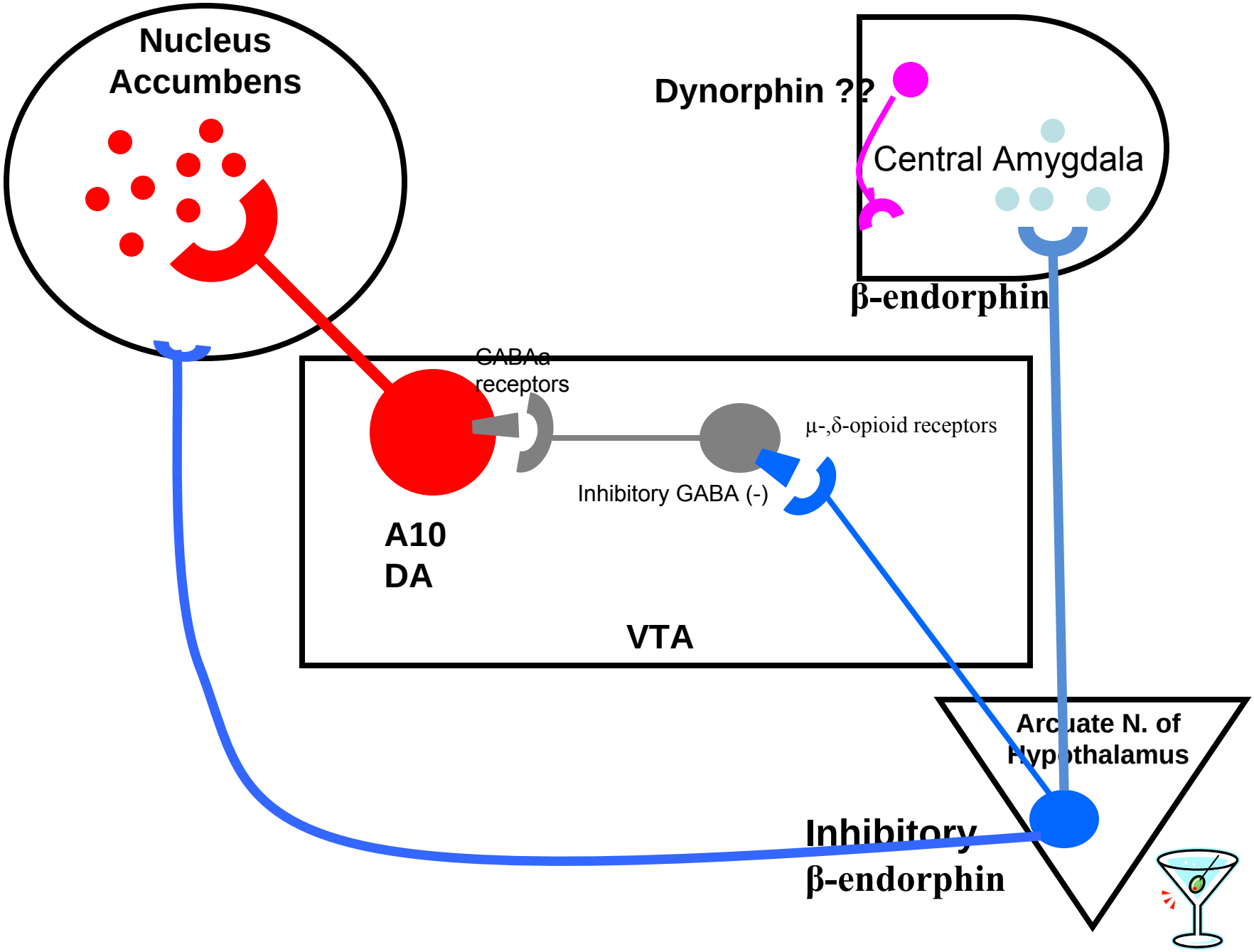
CONCLUSIONS

Central Amygdala: Dose Dependent effect.

. **Early long lasting increase of β-endorphin release (2.0; 2.4 and 2.8 g doses) supports the observation by Heyser et al. (1999) that a lower dose of opioid antagonist is required in the Central Amygdala than in the N. Accumbens to decrease alcohol consumption**

. **No significant responses of Enkephalin**

. **Delayed increase in the release of Dynorphin peptides in response to 2.8 g ethanol dose.**


Nucleus Accumbens
Dynorphin ??
Central Amygdala
β-endorphin
GABAa receptors
μ-,δ-opioid receptors
Inhibitory GABA (-)
A10 DA
VTA
Arcuate N. of Hypothalamus
Inhibitory β-endorphin

GENERALCONCLUSIONS (1)

Alcohol INCREASES the release of opioid peptides BY DINSTINCT BRAIN REGIONS.

General Conclusions(2)

The dose inducing a response or maximum response seems to be different for the different opioid peptide systems and specific brain region.

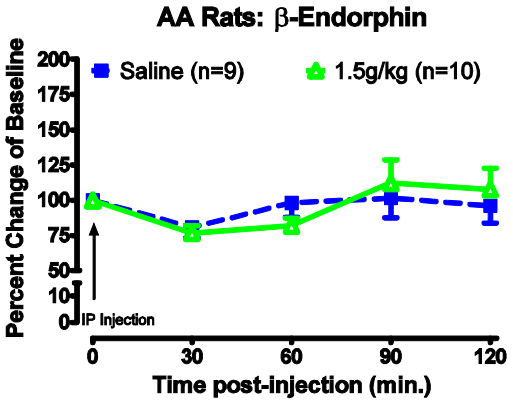
Brain Region	Maximum Response
VTA Endorphin	1.6 g Ethanol / Kg B.Wt.
VTA Enkephalin	No significant response
VTA Dynorphin	1.2 g Ethanol / Kg B.Wt.
NAC Endorphin	2.4 g Ethanol / Kg B.Wt.
NAC Enkephalin	1.6 g Ethanol / Kg B.Wt.
NAC Dynorphin	3.2 g Ethanol / Kg B.Wt.
C.Amy Endorphin	2.8 g Ethanol / Kg B.Wt.
C.Amy Enkephalin	No significant response
C.Amy Dynorphin	2.8 g Ethanol / Kg B.Wt.

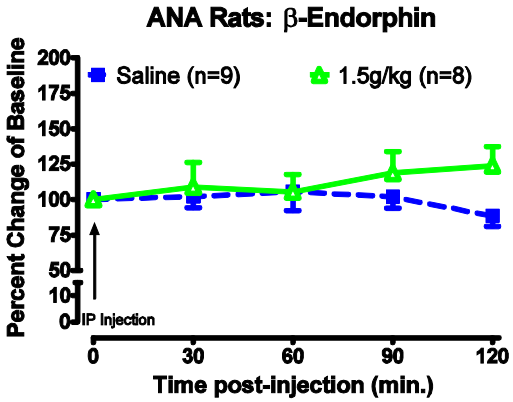
CONCLUSIONS (3)

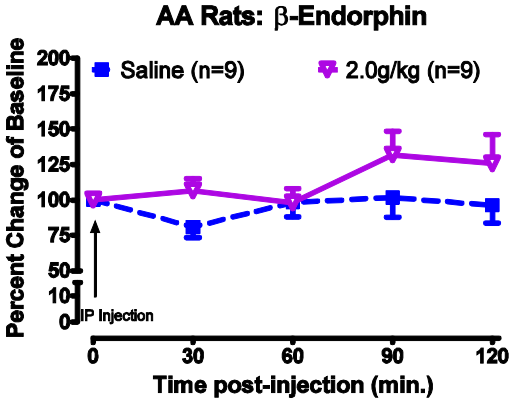
We must always keep in mind that,

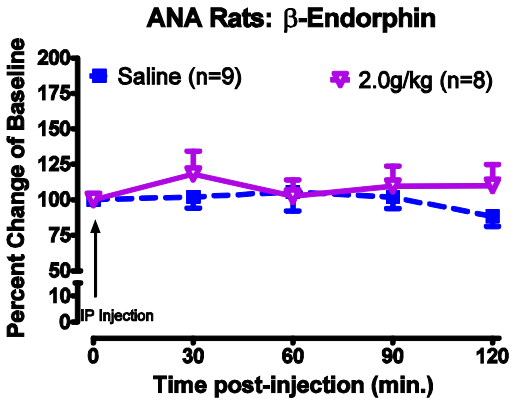
The low sensitivity of the method in detecting low levels of release of the opioid peptides could lead to the false conclusion that a specific dose of ethanol has no effect on the release of specific opioid peptides by specific brain regions.

Large number of doses should be tested.


AA Rats: β-Endorphin
Saline (n=9)
1.5g/kg (n=10)
Percent Change of Baseline
200
175
150
125
100
75
50
10
0
IP Injection
0
30
60
90
120
Time post-injection (min.)


ANA Rats: β-Endorphin
Saline (n=9)
1.5g/kg (n=8)
Percent Change of Baseline
200
175
150
125
100
75
50
10
0
IP Injection
0
30
60
90
120
Time post-injection (min.)


AA Rats: β-Endorphin
Saline (n=9)
2.0g/kg (n=9)
Percent Change of Baseline
200
175
150
125
100
75
50
10
0
IP Injection
0
30
60
90
120
Time post-injection (min.)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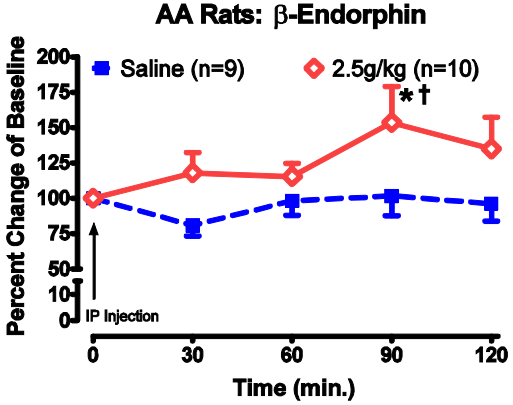
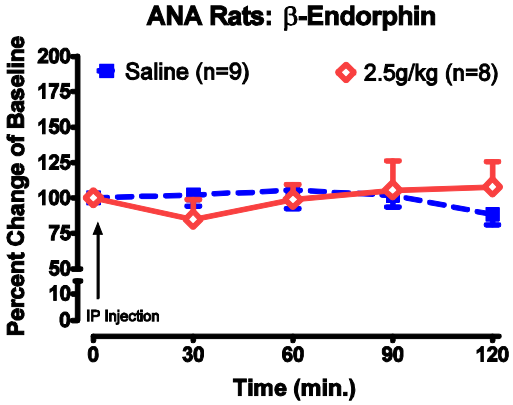

AA Rats: β-Endorphin
Saline (n=9)
2.5g/kg (n=10)
*†
Percent Change of Baseline
200
175
150
125
100
75
50
10
0
IP Injection
0
30
60
90
120
Time (min.)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Percent Change of Baseline
200
175
150
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50
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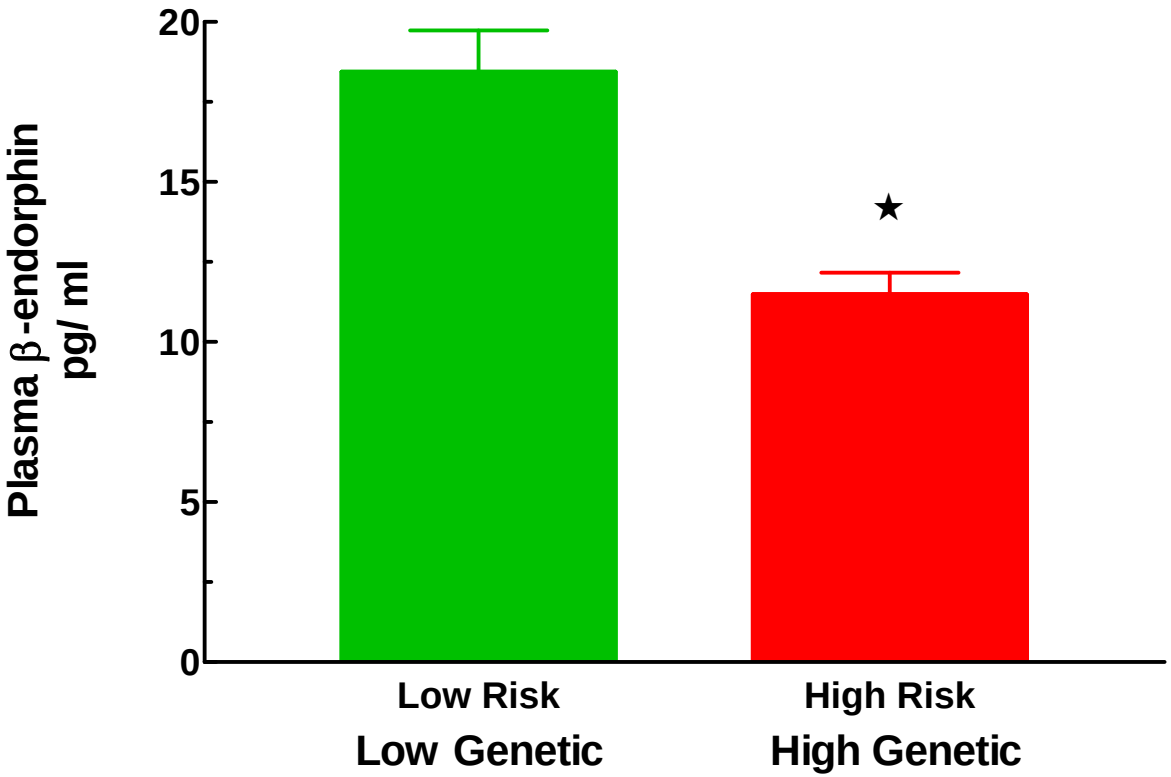
0
30
60
90
120
Time (min.)

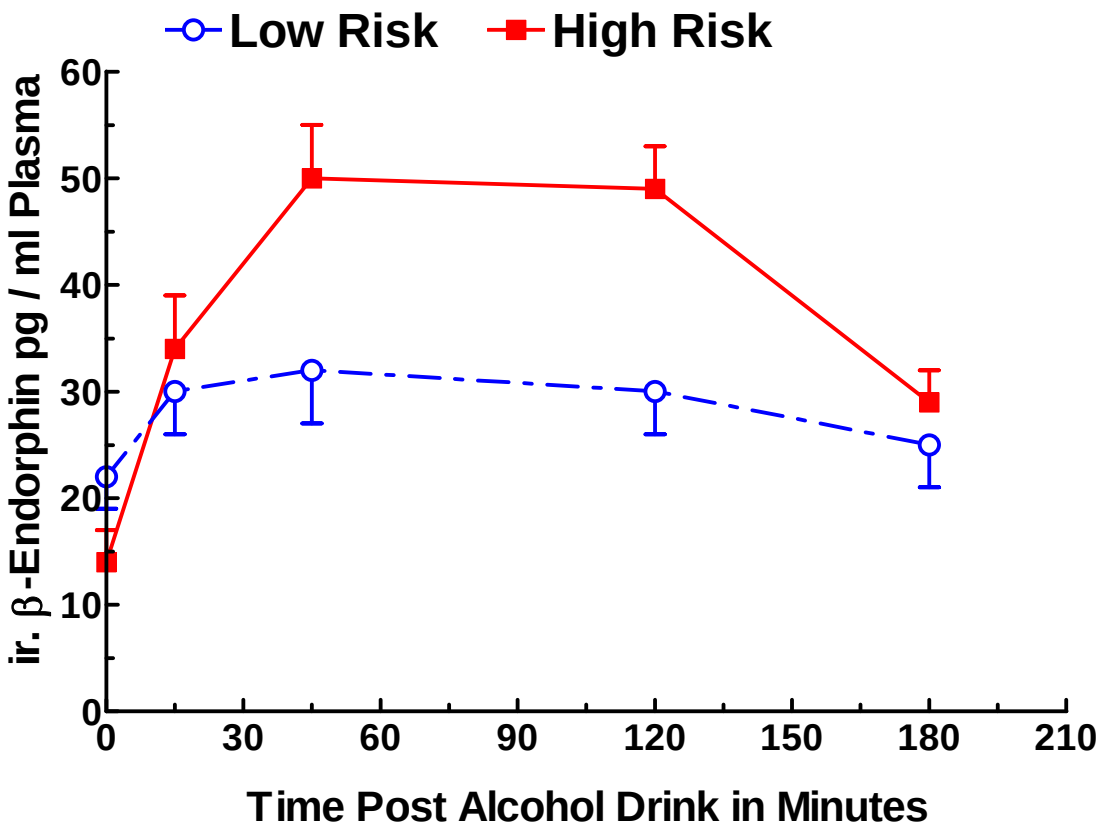
Impact of Genetic Factors on the Plasma β-Endorphin level under basal conditions in human



Low Risk = No Alcoholics in their Family

High Risk = Alcoholics (Father, Grandfather +++)

Effect of 0.75 g ethanol /Kg B.Wt. on the release of Pituitary β-Endorphin in Low Risk and High Risk Subjects



IMPORTANT COMMENTS

Genetically determined differences in ENDORPHINS may Play a role in the increased predisposition to develop Alcoholism by some individuals.

Differences in endorphins are not the only component of the endogenous opioid system associated with high alcohol consumption. SNP OF μ OPIOID RECEPTOR have been found to be associated with alcohol consumption.

Genetically determined differences associated with alcoholism have been found in OTHER NEUROTRANSMITTER SYSTEMS

Differences in components of either the opioid or other neurotransmitter system may not be inherited by all individuals genetically predisposed to develop alcoholism.

Most Important Contributors

Peter Marinelli
Minh Lam
Sam Jarjour
Li Bai

Natural Sciences and Engineering Research Council of Canada and Canadian Institutes on Health Research

NSERC
CRSNG

CIHR IRSC

Thank you