# Systemic Administration of a Glucagon-like Peptide-1 Receptor Agonist Attenuates Cocaine Seeking in Rats

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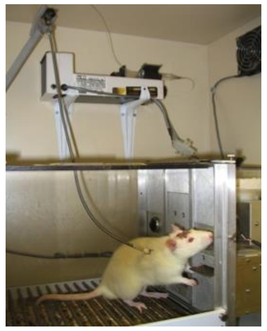
## INTRODUCTION

Cocaine addiction is a global public health issue with more than 1.5 million users in the United States[1]. Cocaine has a high rate of relapse and there are no FDA-approved pharmacotherapies to treat cocaine addiction[6]. Thus, it is vital to discover and develop innovative pharmacological treatments for this brain disorder.

Glucagon-like Peptide-1 (GLP-1) is an incretin hormone produced both peripherally and centrally[5,6]. Endogenous GLP-1 stimulates insulin secretion, reduces blood glucose levels and controls normal food intake[2]. GLP-1 receptors are expressed widely throughout the brain including the VTA and nucleus accumbens, two brain regions known to mediate the reinforcing effects of both drugs of abuse and natural rewards[5]. Importantly, GLP-1 receptor agonists are FDA-approved for treating type II diabetes and obesity[3]. Recent studies suggest that peripheral administration of a GLP-1 receptor agonist reduces cocaine self-administration and cocaine-induced conditioned place preference (CPP)[2,3,6]. However, the role of these receptors in the reinstatement of cocaine-seeking behavior, an animal model of relapse, remains unclear.

Since GLP-1 regulates addiction-like behaviors[6], we hypothesized that peripheral administration of a GLP-1 receptor agonist would attenuate reinstatement of cocaine seeking in rats.

## METHODS

**Pre-treatment:**

Fluoro-Exendin-4 (0.0, 0.01, 0.1, 0.2, 1.0, 3.0 µg/kg, i.p.)

1 hr

**Cocaine Priming Injection (10 mg/kg, i.p.)**

## RESULTS

### Systemic administration of Exendin-4 attenuates cocaine-seeking behavior

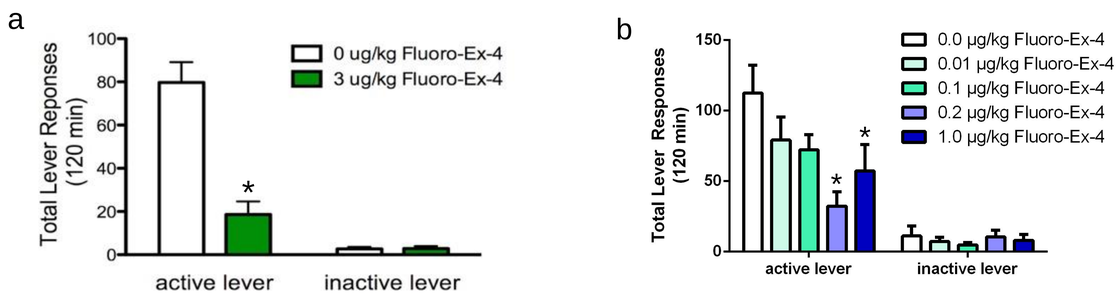



**Figure 1: Systemic administration of a GLP-1 receptor agonist reduces cocaine seeking during reinstatement test sessions. (a)** Peripheral administration of Fluoro-Exendin-4 (3.0 µg/kg, i.p.) prior a cocaine priming injection reduces active lever responses during reinstatement test sessions (n=10). **(b)** Peripheral administration of Fluoro-Exendin-4 reduces active lever responses dose-dependently (n=9). There was no effect on inactive lever presses. Statistical analysis was performed using a Two-way ANOVA test. * $p < 0.05$ compared to vehicle (Tukey's HSD)

### Colocalization of Fluoro-Exendin-4 with neurons and astrocytes in the VTA and nucleus accumbens

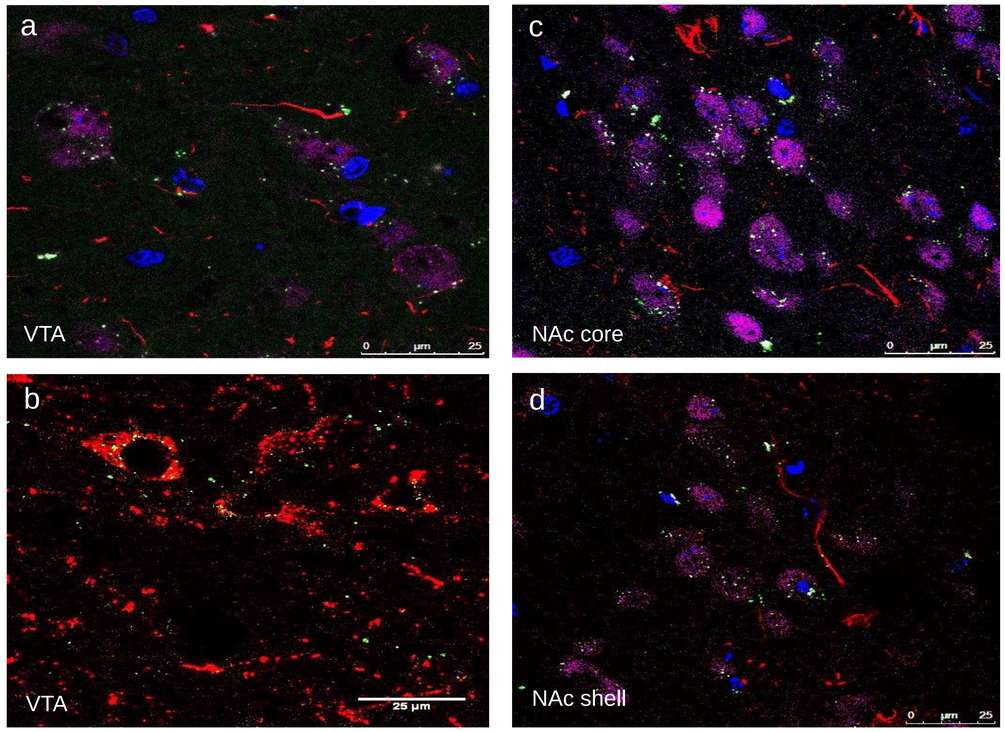



**Figure 2: Systemic administered Fluro-Exendin-4 penetrates the brain and colocalized with neurons and astrocytes in the VTA and nucleus accumbens. (a, c, d)** Fluoro-Exendin-4 stained in green, GFAP stained in red, NeuN stained in magenta and DAPI stained in blue. **(b)** Fluoro-Exendin-4 stained in green, TH stained in red.

## SUMMARY & CONCLUSIONS

- Systemic administration of Exendin-4, a GLP-1 receptor agonist, is sufficient to reduce cocaine-seeking behavior in rats.
- Peripherally administered Fluoro-Exendin-4 penetrated the brain and colocalized with neurons and astrocytes in the VTA and nucleus accumbens.
- Behavioral effects of Exendin-4 may be mediated by activation of GLP-1 receptors in the brain.
- FDA-approved GLP-1 receptor agonists could be re-purposed for treating cocaine addiction.

## FUTURE DIRECTIONS

- Using quantitative PCR analyses, measure changes in GLP-1 receptor levels in the VTA and accumbens during extinction after cocaine self-administration compared to saline-yoked controls.
- Specifically activate GLP-1 efferents to the VTA and accumbens using Designer Receptors Exclusively Activated by Designer Drugs (DREADDS) to determine the role of central GLP-1 signaling in cocaine seeking.
- Measure extracellular dopamine levels in the accumbens using microdialysis after an intra-VTA Exendin-4 injection to determine if activating VTA GLP-1 receptor results in an attenuation of cocaine-induced dopamine release in the accumbens.

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