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GLP-1 analog attenuates cocaine reward

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Letter to the Editor

Glucagon-like peptide-1 (GLP-1) is released in response to food intake and acts through both peripheral and central mechanisms to regulate energy homeostasis and feeding behavior. Exendin-4 (Ex-4) is an analog of GLP-1 with a significantly longer half-life and greater potency (1) and is marketed synthetically as exenatide (Byetta™ and Bydureon™) as a treatment for type 2 diabetes mellitus. We show that administration of exendin-4 attenuates the rewarding effects of cocaine in mice, thus highlighting the therapeutic potential of GLP-1 receptor (GLP-1R) agonists for the treatment of psychostimulant addiction.

Emerging data suggest that hormones and peptides that play a role in feeding behavior, such as insulin, GLP-1, leptin, orexin, and ghrelin, may also be involved in drug reward (2, 3) and could thereby be targeted as therapies for the treatment of addiction. GLP1-Rs are expressed within the brain, including in the ventral tegmental area (VTA) and the nucleus accumbens (NAc) (4, 5). These brain regions are part of the mesolimbic reward circuit considered to play a major role in the rewarding properties of drugs, including the cocaine (6). Activation of mesolimbic GLP-1Rs decreases the intake of highly palatable foods, suggesting that GLP-1R activation contributes to the hedonic components of food intake (4). Drug reward and feeding behavior utilize overlapping brain circuitry and mechanisms, thus we hypothesized that the GLP-1R agonist Ex-4 would reduce the rewarding effects of cocaine.

In a test of conditioned place preference (CPP), a significant cocaine-induced CPP was achieved (SAL/Cocaine group, Fig. 1). However, the rewarding effects of cocaine were attenuated in mice pretreated with Ex-4 (Ex-4/Cocaine group, regardless of pretreatment dose), suggesting that Ex-4 reduces the hedonic effects of cocaine. This response was not influenced by Ex-4-induced hypoactivity, as Ex-4 pretreatment did not significantly lessen cocaine's locomotor-stimulating properties (Supplementary Fig. 1C). As hypothesized, Ex-4-pretreated mice spent more time in the treatment chamber during the test phase following cocaine treatment but not to the same extent as cocaine-treated mice without the Ex-4 pretreatment, and this finding was not contingent upon the Ex-4 dose used. Notably,

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Conflict of Interest
The authors declare no conflict of interest.

Ex-4 treatment alone at any of the doses investigated did not condition an aversion (or a preference) to the treatment-associated chamber as there was no significant change in the amount or percentage of time spent in the treatment chamber (Fig. 1, all Ex-4/SAL groups).

How Ex-4 exerts this decrease in cocaine reward is unknown. Ex-4 readily crosses the blood brain barrier (7), GLP-1Rs are present in brain reward circuitry (4, 5), and local administration of Ex-4 into the mesolimbic dopamine system alters hedonic responses to food (4). It is thus likely that Ex-4 blunts cocaine CPP by targeting GLP-1Rs within the NAc or ventral midbrain. A previous study has shown that GLP-1Rs can specifically interact with the G-protein coupled receptor sorting protein (GASP-1) (8), and genetic knockout loss of GASP-1, in turn, alters cocaine-induced behavioral responses (9). Therefore, GLP-1Rs in the hypothalamus may mediate homeostatic regulation of food intake (10), whereas GLP-1Rs in the VTA and NAc might instead represent hedonic value, perhaps through alterations in dopamine transporter and/or receptor function (9, 11). However, other mechanisms, including a role of peripheral GLP-1Rs, cannot be ruled out at this time.

Our study extends the potential therapeutic value of GLP-1R stimulation beyond metabolic disorders and identifies a new molecular target for the treatment of psychostimulant abuse. Moreover, even the lowest dose of Ex-4 used (10 μg/kg) produced a blunted cocaine CPP response, suggesting a GLP-1R-dependent mechanism involved in drug reward in addition to those already known involving neurotransmitters (e.g., dopamine, serotonin, norepinephrine, glutamate, and the opioids). Importantly, these data and that of others (5) indicate that Ex-4 treatment alone appears to be neither aversive nor pleasurable, suggesting that patient compliance due to negative side-effects or the potential for addiction to Ex-4, respectively, is of little concern. Ex-4, marketed in its synthetic form as exenatide, is already approved for human use as a treatment for type 2 diabetes. Whether these findings extend to other psychostimulants (e.g. amphetamines) and other drug classes has yet to be determined. Additional studies will also be required to examine full doseresponse functions, as it appears that even the 10 μg/kg dose was sufficient to attenuate cocaine-induced CPP; the duration of effectiveness; and the blockade or reversal of the cellular and molecular neuroadaptations that accompany chronic drug use and addiction. Self-administration studies will also be needed to fully explore the ability of GLP-1 signaling to regulate addictive processes. Finally, it is also worth noting that, although effective, even the highest dose of Ex-4 (100 μg/kg) did not completely eliminate cocaine-induced CPP. Thus our data also demonstrate the presence of a GLP-1 receptor-independent component to cocaine reward, suggesting exenatide treatment as a possible complementary therapy of drug abuse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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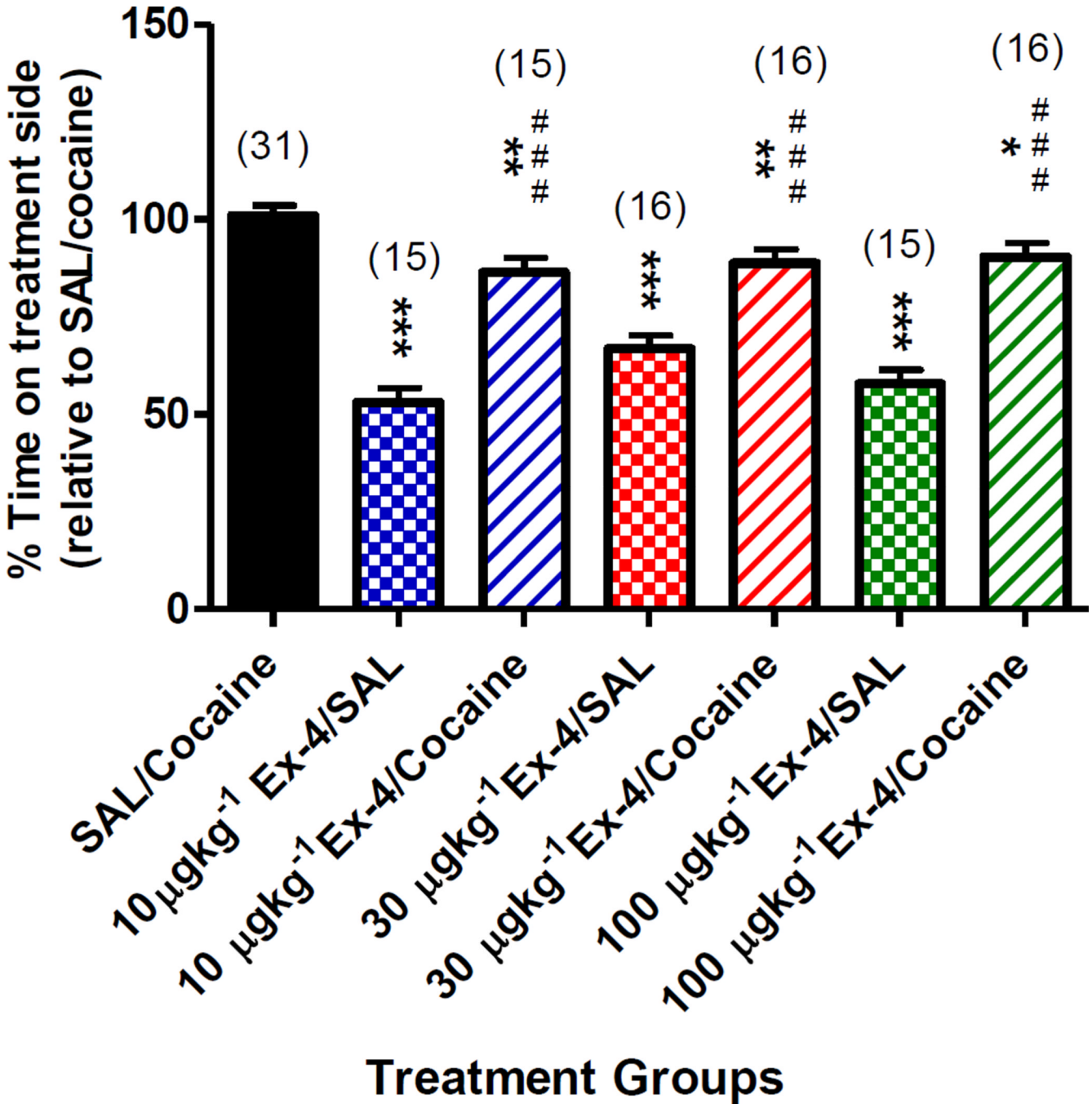

Figure 1.

Percent time spent on the treatment-affiliated compartment during the CPP test phase. A main effect of Treatment was found ($F(6,117)=31.66$, $p<0.0001$). Data are normalized against the SAL/cocaine group. Sample size for each group is indicated in parentheses above each bar. $^{**}p < 0.01$, $^{***}p < 0.001$ vs. SAL/cocaine group; $^{\#\#\#}p < 0.001$ vs. respective Ex-4/cocaine-treated group.