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The glucagon-like peptide 1 (GLP-1) receptor agonist exendin-4 reduces cocaine self-administration in mice

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HIGHLIGHTS

- GLP-1 receptor stimulation reduces acute and chronic cocaine self-administration.
- Exendin-4 reduces cocaine-induced elevation of striatal DA and c-fos expression.
- GLP-1 receptor stimulation decreases DA D1 receptor agonist induced hyperactivity.

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ABSTRACT

Glucagon-like peptide 1 (GLP-1) analogues are used for the treatment of type 2 diabetes. The ability of the GLP-1 system to decrease food intake in rodents has been well described and parallels results from clinical trials. GLP-1 receptors are expressed in the brain, including within the ventral tegmental area (VTA) and the nucleus accumbens (NAc). Dopaminergic neurons in the VTA project to the NAc, and these neurons play a pivotal role in the rewarding effects of drugs of abuse.

Based on the anatomical distribution of GLP-1 receptors in the brain and the well-established effects of GLP-1 on food reward, we decided to investigate the effect of the GLP-1 analogue exendin-4 on cocaine- and dopamine D1-receptor agonist-induced hyperlocomotion, on acute and chronic cocaine self-administration, on cocaine-induced striatal dopamine release in mice and on cocaine-induced c-fos activation. Here, we report that GLP-1 receptor stimulation reduces acute and chronic cocaine self-administration and attenuates cocaine-induced hyperlocomotion. In addition, we show that peripheral administration of exendin-4 reduces cocaine-induced elevation of striatal dopamine levels and striatal c-fos expression implicating central GLP-1 receptors in these responses. The present results demonstrate that the GLP-1 system modulates cocaine's effects on behavior and dopamine homeostasis, indicating that the GLP-1 receptor may be a novel target for the pharmacological treatment of drug addiction.

1. Introduction

Drug abuse and drug dependence are major health problems, and effective pharmacological interventions to treat them are lacking. To develop novel treatment strategies, a better understanding of the complex neurobiology involved in drug abuse and drug dependence is needed. Midbrain dopaminergic neurons projecting to the nucleus accumbens (NAc) are believed to mediate the reinforcing effects of drugs of abuse [1,2], which play a pivotal role in the development of drug abuse and drug dependence. Therefore, research efforts have focused on the development of candidates that interact with the dopamine reward system.

Glucagon-like peptide 1 (GLP-1) is a peptide produced in enteroendocrine L-cells of the intestinal mucosa [3] and secreted from

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the intestinal tract in response to food intake [4]. However, GLP-1 is also localized in the neurons of the brainstem nucleus of the solitary tract (NTS), which has widespread projections within the central nervous system (CNS) [5]. GLP-1 receptors are expressed in the ventral tegmental area (VTA) and NAc [6] and it has recently been shown that GLP-1-producing NTS neurons project directly to the VTA and the shell and core regions of the NAc [7].

Selective GLP-1 receptor agonists, e.g., liraglutide (Victoza©) and exenatide (Byetta©), increase insulin secretion, decrease glucagon secretion and gastric emptying and are used in the clinic to treat type 2 diabetes [8]. GLP-1 is also known to reduce food intake and body weight in rodents, most likely mediated via a central effect [9,10], and similar effects have also been reported in humans [11].

Exendin-4 (Ex-4) is a selective GLP-1 agonist. The native hormone is produced in the gut of the Gila monster *Heloderma suspectum*, a desert reptile, and found at a high concentration in its saliva. Ex-4 is able to cross the blood–brain barrier [12,13] and has been shown to regulate food reward in rats by a central mode of action [14]. Emerging data suggest that GLP-1 receptor signaling may modulate hedonic behaviors [15]. For instance, Ex-4 attenuates D-amphetamine-induced hyperactivity [16] as well as cocaine-induced place preference [17] and self-administration of alcohol in mice [18].

Considering the anatomical and functional relationship between GLP-1 receptors and the brain reward system, we decided to further investigate whether GLP-1 receptor stimulation modulates the addictive properties of the indirect dopamine receptor agonist cocaine. To this end, we studied the effects of Ex-4 on acute and chronic cocaine self-administration and show for the first time, that Ex-4 attenuates these effects. In addition we show that Ex-4 can inhibit dopamine D1 receptor- and cocaine-induced hyperlocomotion as well as cocaine-induced striatal dopamine release and striatal c-fos expression in mice.

2. Methods

2.1. Animals

Male NMRI mice (Taconic, Denmark) that weighed 28–35 g were used for microdialysis and locomotor activity experiments, male NMRI mice that weighed 20–22 g were used for the acute self-administration experiment and male C57Bl/6 mice weighing 20–24 g were used for chronic self-administration experiments. All mice were housed in Makrolon cages (20 × 35 × 15 cm) enriched with cardboard housing and nesting material. The animals were kept at room temperature (22°C ± 2) in a 12-hour light/dark cycle (lights on at 6:00 A.M.) with free access to food and water. All experiments were performed during the light cycle between 9:00 A.M. and 4:00 P.M. The mice were allowed to acclimatize to the animal facility for 6–9 days prior to initiation of the experiments. All experiments were approved by the Danish Experimental Animal Inspectorate and were in accordance with the directives of the "Principles of Laboratory Animal Care" (NIH publication No. 85-23, revised 1985) and the council of the European Communities (86/809/EEC).

2.2. Drugs

Cocaine hydrochloride was obtained from the Copenhagen University Hospital Pharmacy, Denmark. Ex-4 was purchased from Tocris Bioscience, UK, and SKF-82,958 hydrobromide was purchased from Sigma-Aldrich. Ex-4 (0.3–100 μg/kg), cocaine and SKF-82,958 were dissolved in 0.9% saline solution (10 ml/kg). In all experiments, Ex-4 was administered intraperitoneally (i.p.) 90–100 min prior to cocaine, which was administered subcutaneously (s.c.) or intravenously (i.v.).

2.3. Locomotor activity measurements

The locomotor activity cages were equipped with 5 × 8 infrared light sources plus photocells [19]. The light beams crossed the cage 1.8 cm above the bottom of the cage. During the test session, locomotor activity was recorded as crossings of infrared light beams. All experiments were conducted in a clean cage with a scant lining of bedding material. In the first experiment, NMRI mice were injected i.p. with Ex-4 (0.3–30 μg/kg) or saline, placed into the activity cages, injected s.c. with cocaine (30 mg/kg) or saline 90 min later and replaced into the activity cages for an additional 60 min. In the second experiment, NMRI mice were injected i.p. with Ex-4 (30 μg/kg) or saline, placed into the activity cages, injected s.c. with SKF-82,958 (0.01, 0.1, and 1 mg/kg) or saline 90 min later and replaced into the activity cages for an additional 60 min.

2.4. Acute cocaine self-administration

The self-administration procedure and apparatus were described previously [19]. The self-administration apparatus consisted of transparent plastic boxes (8 × 8 × 8 cm) with a centered frontal nose-poke hole (12 mm diameter) 1 cm above the floor and a centered posterior vertical opening (width: 5 mm) through which the tail extended. Dual photocells projected an infrared beam 1 mm in front of the nose-poke hole. Immediately before being placed in the test boxes, the mice were left for approximately 3 min 30–35 cm below a 150 W infrared light bulb to induce vasodilatation, thus facilitating the insertion of the infusion needle (27 G, 0.4 × 40 mm, Sterican®, B. Braun) into their tail veins. A fixed ratio 1 (FR-1) schedule was used, with no delay between nose-poke and infusion, so that each nose-poke induced the i.v. infusion of 1.4 μl cocaine or vehicle. After placing the mouse in the self-administration box for a 10-min habituation period during which nose-poking did not induce infusions, one priming infusion was given by the experimenter immediately before starting a 30-min session. Immediately after the session, the correct placement of the infusion needle was verified by manual infusion of the tested drug by an experimenter blind to the number of nose-pokes produced, and the animals were quickly sacrificed. Mice were excluded from further analysis if they had not produced at least five nose-pokes during the self-administration session or correct placement of the infusion needle could not be verified.

Two acute cocaine self-administration experiments were performed. In the first experiment, NMRI mice received i.p. administration of the GLP-1 agonist Ex-4 at doses of 10 (n = 12), 30 (n = 14), or 100 (n = 12) μg/kg or the corresponding vehicle (n_{saline} = 11, $n_{cocaine}$ = 13). Ninety minutes later, the animals were subjected to the self-administration procedure described above with access to i.v. administration of saline or cocaine at 0.03 mg/kg/infusion, previously shown to be the optimal dose for self-administration [19]. In the second experiment, NMRI mice received i.p. administration of 30 μg/kg Ex-4 or saline. 90 min later, the animals were subjected to the self-administration procedure described above with access to i.v. administration of cocaine doses of 0.01 ($n_{vehicle}$ = 11, $n_{Ex\text{-}4}$ = 12), 0.03 ($n_{vehicle}$ = 14, $n_{Ex\text{-}4}$ = 12), 0.1 ($n_{vehicle}$ = 12, $n_{Ex\text{-}4}$ = 14), or 0.3 ($n_{vehicle}$ = 11, $n_{Ex\text{-}4}$ = 11) mg/kg/infusion or saline ($n_{vehicle}$ = 15, $n_{Ex\text{-}4}$ = 12).

2.5. Chronic cocaine self-administration

Equipment and training procedures were previously described [20]. Operant chambers (Med Associates, USA) contained two nose-poke holes 10 mm above the grid floor, both equipped with photocells and a discriminative cue light, positioned on either side of a small dish-shaped plate into which liquid food could be delivered. Responding in the right hole resulted in delivery of a reinforcer and illumination of the cue light for 20 s, during which additional responses were counted but had no scheduled consequences (i.e., post-reinforcer timeout).