Physiology & Behavior 161 (2016) 140–144

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Central & peripheral glucagon-like peptide-1 receptor signaling differentially regulate addictive behaviors

Sunil Sirohi [b,*], Jennifer D. Schurdak [a], Randy J. Seeley [c], Stephen C. Benoit [a], Jon F. Davis [a,b]

[a] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, USA
[b] Department of Integrative Physiology and Neuroscience, Washington State University, Pullman, WA, USA
[c] Department of Surgery, University of Michigan, Ann Arbor, MI, USA

HIGHLIGHTS

- Mice received (Ex-4, a GLP-1 analog) following disruption of CNS GLP-1R signaling.
- Amphetamine reward, alcohol intake and hedonic feeding were examined thereafter.
- Ex-4 failed to reduce amphetamine reinforcement behavior and alcohol consumption.
- Hedonic feeding behavior was partially attenuated following Ex-4 pretreatment.
- Data elucidate mechanisms whereby GLP-1 signaling regulates reinforced behaviors.

ARTICLE INFO

Article history:
Received 15 December 2015
Received in revised form 21 March 2016
Accepted 8 April 2016
Available online 9 April 2016

Keywords:
GLP-1
GLP-1R
Amphetamine reinforcement
Alcohol intake
Hedonic feeding

ABSTRACT

Recent data implicate glucagon-like peptide-1 (GLP-1), a potent anorexigenic peptide released in response to nutrient intake, as a regulator for the reinforcing properties of food, alcohol and psychostimulants. While, both central and peripheral mechanisms mediate effects of GLP-1R signaling on food intake, the extent to which central or peripheral GLP-1R signaling regulates reinforcing properties of drugs of abuse is unknown. Here, we examined amphetamine reinforcement, alcohol intake and hedonic feeding following peripheral administration of EX-4 (a GLP-1 analog) in FLOX and GLP-1R KD^{Nestin} (GLP-1R selectively ablated from the central nervous system) mice (n = 13/group). First, the effect of EX-4 pretreatment on the expression of amphetamine-induced conditioned place preference (Amp-CPP) was examined in the FLOX and GLP-1R KD^{Nestin} mice. Next, alcohol intake (10% v/v) was evaluated in FLOX and GLP-1R KD^{Nestin} mice following saline or EX-4 injections. Finally, we assessed the effects of EX-4 pretreatment on hedonic feeding behavior. Results indicate that Amp-CPP was completely blocked in the FLOX mice, but not in the GLP-1R KD^{Nestin} mice following EX-4 pretreatment. Ex-4 pretreatment selectively blocked alcohol consumption in the FLOX mice, but was ineffective in altering alcohol intake in the GLP-1R KD^{Nestin} mice. Notably, hedonic feeding was partially blocked in the GLP-1R KD^{Nestin} mice, whereas it was abolished in the FLOX mice. The present study provides critical insights regarding the nature by which GLP-1 signaling controls reinforced behaviors and underscores the importance of both peripheral and central GLP-1R signaling for the regulation of addictive disorders.

1. Introduction

Glucagon-like peptide-1 (GLP-1), a feeding peptide with anorectic properties, is secreted by the gastrointestinal tract [1,2] and released from neurons in the nucleus of the solitary tract (NTS) [3,4,5]. Both GLP-1 and Exendin-4 (EX-4, a synthetic GLP-1 analog) administration attenuate the reinforcing properties of food, alcohol and psychostimulants [6–8], suggesting a role for GLP-1 that extends beyond regulation of energy homeostasis. The appetite suppressive effects of GLP-1 require both vagal afferent and central nervous system (CNS) signaling mechanisms [7]. Recent studies indicate that peripheral administration of GLP-1 attenuates psychostimulant-reinforced behaviors [9] and that GLP-1R stimulation within brain reward circuitry reduces alcohol consumption and food reinforcement [3,8,10]. However, it is unknown if activation of peripheral or CNS GLP-1R signaling regulates the reinforcing properties of psychostimulant drugs. It is also unclear what role peripheral GLP-1R signaling plays in the regulation of alcohol and palatable food intake. We hypothesized that peripheral GLP-1R signaling (i.e. vagal afferent signaling) regulates alcohol consumption and hedonic feeding behavior whereas central GLP-1R

* Corresponding author at: Washington State University, Pullman, WA 99164, Office: Room 253, Veterinary Biomedical Research Building, USA.
E-mail addresses: sunil.sirohi@wsu.edu, sunilsirohi@outlook.com (S. Sirohi).

http://dx.doi.org/10.1016/j.physbeh.2016.04.013
0031-9384/

signaling controls psychostimulant reinforcement. To test this hypothesis, we evaluated amphetamine reward, alcohol consumption and hedonic food intake following peripheral administration of EX-4 in GLP-1R KD^{Nestin} mice in which GLP-1R was selectively ablated from the CNS.

2. Methods and materials

2.1. Animals

GLP-1R KD^{Nestin} mice, where GLP-1R was selectively ablated from the CNS, along with their respective wild-type littermates were generated as reported previously [11]. Genetic ablation involved inserting *loxP* sites surrounding *glp1r* gene (FLOX) and crossbreeding with nestin-*Cre* mice, generating GLP-1R KD^{Nestin} mice. Study animals were derived from crosses between heterozygous animals back-crossed >10 generations onto a C57BL6/J genetic background. Current studies were performed with male mice, which were housed in a 12-h light/dark cycle with regular chow and water available ad lib, except when indicated. All animal procedures were carried out in accordance with NIH guidelines and were in accordance with the guidelines set forth by the Institutional Animal Care and Use Committee at the University of Cincinnati.

2.2. Diets

All mice were maintained on ad libidum chow (Teklad, 3.41 kcal/g, 0.51 kcal/g from fat) and water unless noted. The hedonic feeding experiments utilized high-fat diet (HFD) (Research Diets, New Brunswick, NJ, 4.41 kcal/g, 1.71 kcal/g from fat). Dietary composition of standard rodent chow and HFD used in the present study has been described previously [12].

2.3. Drugs

The effects of GLP-1 manipulation were measured using the synthetic GLP-1 agonist exendin-4 (30 μg/kg) (Bachem, Torrance, CA), a dose selected based on its ability to reduce cocaine reward in mice [9].

2.4. Amphetamine-induced conditioned place preference

We utilized conditioned place preference (CPP) to examine effects of EX-4 on amphetamine reward in FLOX and GLP-1R KD^{Nestin} mice. The CPP studies were conducted as described previously [13,14]. All mice (n = 13/group) were habituated to the CPP apparatus for 15 min. On the next day (CPP-Day 1), mice (n = 6–7/group) received either saline or D-amphetamine (1.0 mg/kg, i.p.), were placed into one side of the chamber and were detained in the chamber for 30 min. On the following day (CPP-Day2), the treatment (saline or D-amphetamine) was reversed and mice were detained into the opposite side of the chamber. The treatment (amphetamine or saline) and side of chamber (black or white) were counterbalanced across 12 consecutive days of testing. On the test day (CPP-Day 13), mice were placed in the center chamber following saline or EX-4 (30 μg/kg; i.p.) injections and allowed free access to all chambers for 15 min. Time spent in each chamber and locomotor activity was determined using a computerized tracking system (TopScan, Clever Sys, Inc., Reston, VA). Data are presented as percent of total time spent in saline- or amphetamine-paired side following saline or EX-4 pretreatment for both FLOX and GLP-1R KD^{Nestin} mice.

2.5. Alcohol intake

FLOX and GLP-1R KD^{Nestin} mice (n = 13/group) were allowed to consume 10% alcohol solution or water in their home cage in a two-bottle choice paradigm and 24 h alcohol intake was recorded. Next, mice were divided in groups (n = 6–7/group), matched based on the baseline alcohol consumption, and alcohol (10%) intake was recorded for 90 min following saline or EX-4 (30 μg/kg; i.p.) injections. Alcohol intake is expressed as intake per kilogram of body weight (g/kg).

2.6. Hedonic feeding

We utilized a feeding paradigm in which rodents voluntarily consume a palatable test diet following a non-palatable preload to determine the effects of central or peripheral GLP-1R signaling on hedonic feeding behavior [15,16]. GLP-1R KD^{Nestin} mice along with their wild type littermates (n = 6–7/group) were pre-exposed to HFD to prevent neophobia. Subsequently, all mice were food deprived for twenty-one hours. The next day, chow food hoppers were weighed, placed in each cage and subsequently reweighed each hour for 2 h. To investigate the effects of GLP-1R signaling on hedonic feeding, mice received a single peripheral EX-4 injection after the first hour of chow exposure only. The nature of this manipulation allowed us to examine the effect GLP-1R activation on re-feeding that occurred during the second hour of chow exposure. Following the second hour of chow access, a separate set of food hoppers containing HFD was weighed and placed in each cage beside the previously placed chow hoppers. The opportunity to consume HFD after re-feeding on chow constitutes the hedonic portion of this test. At the conclusion of the test (4 h after food was returned), both sets of food hoppers (chow and HFD) were re-weighed to determine effects of EX-4 on HFD intake after re-feeding.

2.7. Statistical analysis

CPP data were analyzed by mixed-model two-way ANOVA to compare percent of total time spent in saline or amphetamine-paired side following saline or EX-4 treatment, with post-hoc paired-sample *t*-tests to compare within group effects. Alcohol intake data were analyzed using a univariate analysis of variance to compare the effect of saline or EX-4 on alcohol drinking. A mixed-model two-way ANOVA compared the effect of saline or EX-4 pretreatment on chow intake, with post-hoc paired sample t-tests to compare within group effects. A univariate analysis of variance was used to compare HFD intake in the FLOX and GLP-1R KD^{Nestin} mice following saline or EX-4 pretreatment. To determine the extent to which EX-4 pretreatment affected HFD intake in FLOX and GLP-1R KD^{Nestin} mice, we compared 3rd hour HFD intakes to zero (indicating no food intake) using one-sample t-test. All statistical comparisons were conducted at 0.05α level.

3. Results

3.1. GLP-1R regulation of amphetamine CPP

A mixed model ANOVA revealed a main effect of exposure during conditioning suggesting that amphetamine induced a strong CPP in both FLOX and GLP-1R KD^{Nestin} ($F_{1,11} = 7.493$, $p = 0.019$) mice. Following training, EX-4 pretreatment completely blocked the expression of Amp-CPP in the FLOX mice without affecting locomotion in either group. However, this treatment was ineffective at reducing Amp-CPP in the GLP-1R KD^{Nestin} mice (Fig. 1).

3.2. GLP-1R regulation of alcohol consumption

Baseline alcohol consumption did not differ among any of the groups (data not shown). Alcohol intake on the test day was not significantly different compared to baseline intake in saline injected FLOX ($t(5) = 2.041$, $p > 0.05$) or GLP-1R KD^{Nestin} ($t(5) = 0.4341$, $p > 0.05$) mice. However, Ex-4 pretreatment selectively blocked ($F_{1,11} = 8.7$, $p = 0.013$) alcohol consumption in the FLOX mice, but was ineffective in the GLP-1R KD^{Nestin} mice (Fig. 2). Furthermore, there was no difference in body weight 24 h following EX-4 injections in either group (Table 1).

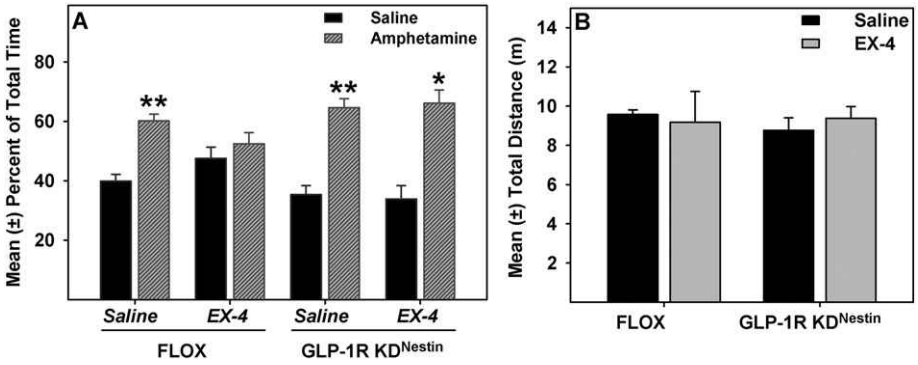

Fig. 1. Effect of EX-4 pretreatment on amphetamine-induced conditioned place preference and locomotor activity in the floxed and GLP-1R KD^{Nestin} mice. A) Data represent mean (±) percent of total time spent on saline and amphetamine paired sides for the floxed and GLP-1R KD^{Nestin} mice (n = 6–7/group) on the test day. A significant ($p < 0.05$) amphetamine induced CPP was achieved in control groups (saline treated Floxed/GLP-1R KD^{Nestin} mice). EX-4 pretreatment selectively extinguished amphetamine induced CPP in the floxed mice, an effect not observed in the GLP-1R KD^{Nestin} mice. $^{**}p < 0.01$, $^{*}p < 0.05$ compared to the saline. B) Ex-4 pretreatment did not impact locomotor activity in either group compared to saline.

3.3. GLP-1R regulation of hedonic feeding behavior

A mixed-model two-way ANOVA revealed a significant main effect of time (hourly chow intake; $F_{1, 11} = 24.428$, $p = 0.000$) and a significant time × treatment (saline or EX-4) interaction ($F_{1, 11} = 4.890$, $p = 0.049$) for chow intake in FLOX mice (Fig. 3A). Post-hoc analysis revealed that Ex-4 completely ($p < 0.01$) abolished the second hour chow intake in the FLOX mice. In GLP-1R KD^{Nestin} mice, a significant main effect of time (hourly chow intake; $F_{1, 11} = 9.462$, $p = 0.011$) was also reported by mixed-model two-way ANOVA. Post-hoc analysis indicated that EX-4 pretreatment completely ($p < 0.05$) blocked chow intake in the GLP-1R KD^{Nestin} mice (Fig. 3A). Notably, after re-feeding, both FLOX ($t(5) = -3.254$, $p < 0.05$) and GLP-1R KD^{Nestin} ($t(5) = -6.655$, $p < 0.01$) mice consumed significantly more HFD compared to the chow intake in hour 1 or 2 of re-feeding. EX-4 pretreatment significantly blocked intake of HFD in both FLOX ($F_{1, 11} = 13.77$, $p = 0.003$) and GLP-1R KD^{Nestin} relative to saline controls ($F_{1, 11} = 11.264$, $p = 0.006$) (Fig. 3B). We next determined the extent EX-4 pretreatment affected HFD intake in FLOX and GLP-1R KD^{Nestin} mice and discovered that EX-4 pretreatment only partially blocked ($p < 0.0104$) the HFD intake in GLP-1R KD^{Nestin} mice, whereas it was completely abolished ($p > 0.3559$) in the FLOX mice (Fig. 3 B).

4. Discussion

The goal of the present study was to assess the necessity of central vs. peripheral GLP-1R signaling for the control of amphetamine reward, alcohol consumption and hedonic feeding behavior. Our results indicate that disruption of central GLP-1R signaling completely abolished the ability of EX-4 to reduce amphetamine-induced CPP and alcohol consumption. These effects were not due to non-specific motoric effects as EX-4 pretreatment was ineffective in altering locomotion in either group. In contrast, hedonic feeding behavior was only partially blocked following EX-4 treatment in mice with disrupted central GLP-1R signaling. Collectively, these results describe specific roles for central GLP-1R signaling in the control of psychostimulant reinforcement and alcohol consumption and highlight the importance of both peripheral and central GLP-1R signaling for the regulation of hedonic feeding behavior.

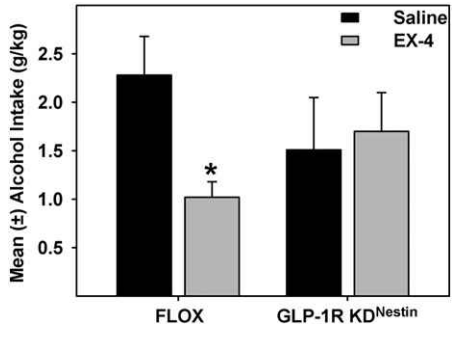

Fig. 2. Effect of EX-4 Pretreatment on Alcohol Intake in the Floxed and GLP-1R KD^{Nestin} mice. Data represent mean (±) alcohol intake for the floxed and GLP-1R KD^{Nestin} mice (n = 6–7/group). Ex-4 pretreatment selectively decreased ($p < 0.05$) alcohol consumption in the floxed (control) mice, whereas alcohol consumption in the GLP-1R KD^{Nestin} mice was not affected. $^{*}p < 0.05$ compared to saline.

Peripheral EX-4 pretreatment has been shown to reduce amphetamine and cocaine-CPP, as well as cocaine-induced accumbal dopamine release [6,9] suggesting that GLP-1 signaling could be capable of impacting psychostimulant reinforcement. However, in those studies peripheral dosing regimens precluded the possibility to determine if central or peripheral activation of GLP-1R receptors regulated the observed decreases in expression of psychostimulant-induced CPP and dopamine release. In the present study, Ex-4 pretreatment blocked the expression of Amp-CPP in the FLOX mice without impacting locomotor activity (Fig. 1). However, EX-4 treatment had no effect on the expression of Amp-induced CPP in GLP-1R KD^{Nestin} mice. These data are first to demonstrate that the ability of EX-4 to reduce amphetamine is exclusively controlled by central GLP-1R signaling.

In terms of alcohol intake, our prior work indicated that Ex-4 treatment was sufficient to reduce alcohol intake in alcohol-preferring rats, P-rats [13], a finding which has been independently replicated in other rodent models [8,17]. Moreover, peripheral administration of EX-4 also negates alcohol-induced CPP [8,17]. Our observation that Ex-4 pretreatment selectively attenuated alcohol consumption in the FLOX but not in the GLP-1R KD^{Nestin} mice (Fig. 2) indicates that similar to amphetamine CPP, preferential GLP-1 action at central GLP-1R's is required to attenuate alcohol intake.

Involvement of GLP-1 signaling in regulation of homeostatic food intake is well documented and is based on the interaction of GLP-1 within key CNS regions (e.g., hypothalamus, nucleus tractus solitarius) involved in the homeostatic regulation of feeding [2,4,18]. Recent data indicate that direct activation of GLP-1Rs in mesolimbic regions decreases palatable food intake and operant responding for palatable foods [3,10,

Table 1
Mean (±SEM) body weight (gm) before and following saline or EX-4 injections.

Body weight (gm)	Before	After
FLOX		
Saline	39.86 (2.1)	39.84 (2.0)
EX-4	33.70 (2.3)	33.67 (2.3)
GLP-1R KD^{Nestin}		
Saline	36.91 (1.1)	37.00 (1.3)
EX-4	36.82 (1.5)	37.17 (1.7)

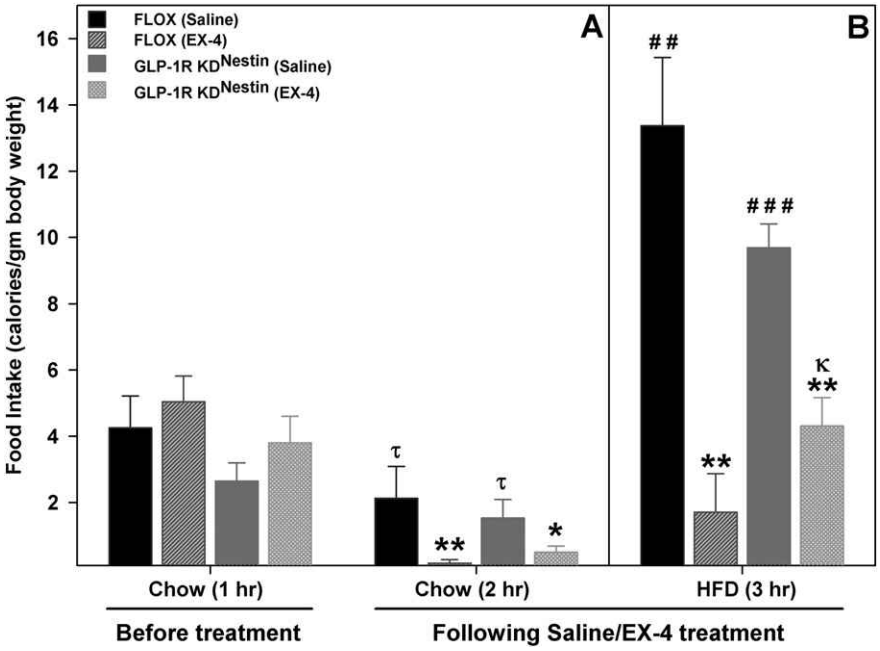

Fig. 3. Effect of EX-4 pretreatment on chow and high fat diet intake in floxed and GLP-1R KD^{Nestin} mice. Data represent mean (±) chow/high fat diet (HFD) intake for the floxed and GLP-1R KD^{Nestin} mice (n = 6–7/group). Chow was presented following 21 h of deprivation. Chow was weighed each hour for the first two hours then HFD was presented and weighed during third testing hour. Mice received a single peripheral saline or EX-4 injection after the first hour of chow exposure only. A) Ex-4 pretreatment significantly attenuated ($p < 0.05$) 2nd hour chow intake in both floxed and GLP-1R KD^{Nestin} mice. B) HFD intake was significantly increased in both floxed and GLP-1R KD^{Nestin} mice following re-feeding on chow. EX-4 pretreatment significantly attenuated this effect in both floxed and GLP-1R KD^{Nestin} mice. Importantly, when compared to zero, EX-4 pretreatment completely abolished the HFD intake in the floxed mice whereas HFD intake in the GLP-1R KD^{Nestin} mice was only partially reduced. $^{\#\#}p < 0.01$, $^{\#}p < 0.05$ compared to 2nd hour chow intake. $^{**}p < 0.01$, $^{*}p < 0.05$ compared to saline treatment. κ $p < 0.05$ compared to zero. τ = anon-significant trend.

19,20]. Moreover, increases in plasma GLP-1 are observed prior to meal initiation [21]; raising the possibility that anticipatory increases in plasma GLP-1 may be capable of influencing palatable food intake. While, both central and peripheral mechanisms are involved in mediating effects of GLP-1R signaling on food intake per se [7], the extent to which these separate mechanisms regulate hedonic feeding behavior is unknown. The model we used here measured deprivation-induced feeding (homeostatic) and selective consumption of a palatable HFD following the re-feeding period (hedonic). Using this model, mice consumed roughly 3× as much HFD in the third hour compared to the first hour of re-feeding after deprivation (Fig. 3B). We operationally define this selective feeding from HFD, when chow intake has been virtually reduced to zero, as a hedonic feeding response. In terms of homeostatic control of feeding, Ex-4 pretreatment significantly blocked chow intake in both FLOX and GLP-1R KD^{Nestin} mice (Fig. 3A). These data support previous findings that GLP-1-induced decreases in homeostatic feeding are controlled by peripheral GLP-1Rs [7]. Interestingly, EX-4 treatment in FLOX mice decreased HFD to a greater degree than that observed in the GLP-1R KD^{Nestin} mice (Fig. 3B). We interpret this finding to indicate that both peripheral and central GLP-1R signaling participate in the regulation of hedonic feeding behavior. Overall, the present findings extend previous studies and suggest that peripheral and central GLP-1 signaling mechanisms are potent regulators of deprivation-induced feeding and selective intake of palatable food after re-feeding has been initiated.

Importantly, GLP-1 receptor activation is linked with aversive side effects and it is argued that both satiating and aversive responses to GLP-1R activation mediate the anorectic effects of GLP-1 on feeding behavior [22–24]. In the present study, we did not detect changes in locomotor activity or body weight following EX-4 treatment, surrogate measures of aversion in rodents (Fig. 1B and Table 1). However, it is important to note that the peripheral dose of EX-4 we used is far higher than those reported to induce nausea in rats [25]. Therefore, acute aversive properties of EX-4 likely regulate the GLP-1R-induced decreases in amphetamine CPP, alcohol intake, and hedonic feeding we observed. We choose this dose of EX-4 (30 μg/kg) based on previous work using this compound to evaluate cocaine CPP [9]. When selecting this dose, we wanted to ensure that this treatment would reduce each of our endpoint variables, a condition that would allow us to evaluate contributions of peripheral and/or central GLP-1R activation for the control of multiple forms of addictive behavior. Nevertheless, irrespective of the underlying physiological or psychological mechanisms following this dose of EX-4, the data we present here delineate critical roles of peripheral and central GLP-1 signaling for the control of psychostimulant reward, alcohol intake and hedonic feeding behavior.

5. Conclusion

Collectively, these data extend the current framework of understanding regarding how analogs of GLP-1 target peripheral and/or central signaling mechanisms to impact addictive behavior. A limitation in this area is the lack of studies that determine how and when the GLP-1 system becomes engaged in the context of addictive behavior. Therefore, future studies that evaluate activation of peripheral and/or central GLP-1 signaling mechanisms across the cycle of addiction (initiation, maintenance, and dependence) are critical next steps for the development of GLP-1 analogs to combat addictive behaviors.

Acknowledgements

This project was supported, in part, by NIH grant DK093848 from National Institute of Diabetes and Digestive and Kidney Diseases awarded to RJS. SCB and RJS received research support from Ethicon Endo Surgery. RJS is a consultant and have received research support from Novo Nordisk, Endobetix, Novartis, Nestle, Takeda, Eisai, Boehringer-Ingelheim, Sanofi, Circuit Therapeutics and Givaudan.

Authors declare no conflict of interest.

References

[1] R. Perfetti, P. Merkel, Glucagon-like peptide-1: a major regulator of pancreatic beta-cell function, Eur. J. Endocrinol. 143 (2000) 717–725.

[2] M.D. Turton, D. O'Shea, I. Gunn, S.A. Beak, C.M. Edwards, K. Meeran, S.J. Choi, G.M. Taylor, M.M. Heath, P.D. Lambert, J.P. Wilding, D.M. Smith, M.A. Ghatei, J. Herbert, S.R. Bloom, A role for glucagon-like peptide-1 in the central regulation of feeding, Nature 379 (1996) 69–72, http://dx.doi.org/10.1038/379069a0.

[3] A.L. Alhadeff, L.E. Rupprecht, M.R. Hayes, GLP-1 neurons in the nucleus of the solitary tract project directly to the ventral tegmental area and nucleus accumbens to control for food intake, Endocrinology 153 (2012) 647–658, http://dx.doi.org/10.1210/en.2011-1443.

[4] P.J. Larsen, M. Tang-Christensen, J.J. Holst, C. Orskov, Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem, Neuroscience 77 (1997) 257–270.

[5] I. Merchenthaler, M. Lane, P. Shughrue, Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system, J. Comp. Neurol. 403 (1999) 261–280.

[6] E. Egecioglu, J.A. Engel, E. Jerlhag, The glucagon-like peptide 1 analogue, exendin-4, attenuates the rewarding properties of psychostimulant drugs in mice, PLoS One 8 (2013), e69010, http://dx.doi.org/10.1371/journal.pone.0069010.

[7] S.E. Kanoski, S.M. Fortin, M. Arnold, H.J. Grill, M.R. Hayes, Peripheral and central GLP-1 receptor populations mediate the anorectic effects of peripherally administered GLP-1 receptor agonists, liraglutide and exendin-4, Endocrinology 152 (2011) 3103–3112, http://dx.doi.org/10.1210/en.2011-0174.

[8] R.H. Shirazi, S.L. Dickson, K.P. Skibicka, Gut peptide GLP-1 and its analogue, exendin-4, decrease alcohol intake and reward, PLoS One 8 (2013), e61965, http://dx.doi.org/10.1371/journal.pone.0061965.

[9] D.L. Graham, K. Erreger, A. Galli, G.D. Stanwood, GLP-1 analog attenuates cocaine reward, Mol. Psychiatry 18 (2013) 961–962, http://dx.doi.org/10.1038/mp. 2012.141.

[10] S.L. Dickson, R.H. Shirazi, C. Hansson, F. Bergquist, H. Nissbrandt, K.P. Skibicka, The glucagon-like peptide 1 (GLP-1) analogue, exendin-4, decreases the rewarding value of food: a new role for mesolimbic GLP-1 receptors, J. Neurosci. 32 (2012) 4812–4820, http://dx.doi.org/10.1523/JNEUROSCI.6326-11.2012.

[11] S. Sisley, R. Gutierrez-Aguilar, M. Scott, D.A. D'Alessio, D.A. Sandoval, R.J. Seeley, Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect, J. Clin. Invest. 124 (2014) 2456–2463, http://dx.doi.org/10.1172/JCI72434.

[12] J.F. Davis, S.J. Melhorn, J.D. Shurdak, J.U. Heiman, M.H. Tschöp, D.J. Clegg, S.C. Benoit, Comparison of hydrogenated vegetable shortening and nutritionally complete high-fat diet on limited access-binge behavior in rats, Physiol. Behav. 92 (2007) 924–930, http://dx.doi.org/10.1016/j.physbeh. 2007.06.024.

[13] J.F. Davis, J.D. Schurdak, I.J. Magrisso, J.D. Mul, B.E. Grayson, P.T. Pfluger, M.H. Tschöp, R.J. Seeley, S.C. Benoit, Gastric bypass surgery attenuates ethanol consumption in ethanol-preferring rats, Biol. Psychiatry 72 (2012) 354–360.

[14] J.F. Davis, A.L. Tracy, J.D. Schurdak, M.H. Tschöp, J.W. Lipton, D.J. Clegg, S.C. Benoit, Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic dopamine turnover in the rat, Behav. Neurosci. 122 (2008) 1257–1263.

[15] D.L. Choi, J.F. Davis, M.E. Fitzgerald, S.C. Benoit, The role of orexin-A in food motivation, reward-based feeding behavior and food-induced neuronal activation in rats, Neuroscience 167 (2010) 11–20, http://dx.doi.org/10.1016/j.neuroscience. 2010.02.002.

[16] D.L. Choi, J.F. Davis, I.J. Magrisso, M.E. Fitzgerald, J.W. Lipton, S.C. Benoit, Orexin signaling in the paraventricular thalamic nucleus modulates mesolimbic dopamine and hedonic feeding in the rat, Neuroscience 210 (2012) 243–248, http://dx.doi.org/10.1016/j.neuroscience. 2012.02.036.

[17] E. Egecioglu, P. Steensland, I. Fredriksson, K. Feltmann, J.A. Engel, E. Jerlhag, The glucagon-like peptide 1 analogue exendin-4 attenuates alcohol mediated behaviors in rodents, Psychoneuroendocrinology 38 (2013) 1259–1270, http://dx.doi.org/10.1016/j.psyneuen. 2012.11.009.

[18] L.L. Baggio, D.J. Drucker, Biology of incretins: GLP-1 and GIP, Gastroenterology 132 (2007) 2131–2157, http://dx.doi.org/10.1053/j.gastro. 2007.03.054.

[19] E.G. Mietlicki-Baase, P.I. Ortinski, D.J. Reiner, C.G. Sinon, J.E. McCutcheon, R.C. Pierce, M.F. Roitman, M.R. Hayes, Glucagon-like peptide-1 receptor activation in the nucleus accumbens core suppresses feeding by increasing glutamatergic AMPA/kainate signaling, J. Neurosci. 34 (2014) 6985–6992, http://dx.doi.org/10.1523/JNEUROSCI.0115-14.2014.

[20] E.G. Mietlicki-Baase, P.I. Ortinski, L.E. Rupprecht, D.R. Olivos, A.L. Alhadeff, R.C. Pierce, M.R. Hayes, The food intake-suppressive effects of glucagon-like peptide-1 receptor signaling in the ventral tegmental area are mediated by AMPA/kainate receptors, Am. J. Physiol. Endocrinol. Metab. 305 (2013) E1367–E1374, http://dx.doi.org/10.1152/ajpendo.00413.2013.

[21] T.P. Vahl, D.L. Drazen, R.J. Seeley, D.A. D'Alessio, S.C. Woods, Meal-anticipatory glucagon-like peptide-1 secretion in rats, Endocrinology 151 (2010) 569–575, http://dx.doi.org/10.1210/en.2009-1002.

[22] T.E. Thiele, R.J. Seeley, D. D'Alessio, J. Eng, I.L. Bernstein, S.C. Woods, G. van Dijk, Central infusion of glucagon-like peptide-1-(7-36) amide (GLP-1) receptor antagonist attenuates lithium chloride-induced c-fos induction in rat brainstem, Brain Res. 801 (1998) 164–170.

[23] T.E. Thiele, G. Van Dijk, L.A. Campfield, F.J. Smith, P. Burn, S.C. Woods, I.L. Bernstein, R.J. Seeley, Central infusion of GLP-1, but not leptin, produces conditioned taste aversions in rats, Am. J. Phys. 272 (1997) R726–R730.

[24] G. van Dijk, T.E. Thiele, Glucagon-like peptide-1 (7-36) amide: a central regulator of satiety and interoceptive stress, Neuropeptides 33 (1999) 406–414, http://dx.doi.org/10.1054/npep.1999.0053.

[25] S.E. Kanoski, L.E. Rupprecht, S.M. Fortin, B.C. De Jonghe, M.R. Hayes, The role of nausea in food intake and body weight suppression by peripheral GLP-1 receptor agonists, exendin-4 and liraglutide, Neuropharmacology 62 (5–6) (2012) 1916–1927, http://dx.doi.org/10.1016/j.neuropharm. 2011.12.022.