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Invited review

The role of pituitary adenylyl cyclase-activating polypeptide in the motivational effects of addictive drugs

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HIGHLIGHTS

- PACAP and its receptors (PAC1, VPAc1 and VPAC2) are expressed in the CNS.
- PACAP is implicated in physiological responses, such as the stress response.
- PACAP is also involved in the motivational effects of addictive drugs.
- We reviewed the role of PACAP in the actions of morphine, nicotine, ethanol, etc.

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ABSTRACT

Pituitary adenylyl cyclase activating polypeptide (PACAP) was originally isolated from the hypothalamus and found to stimulate adenylyl cyclase in the pituitary. Later studies showed that this peptide and its receptors (PAC1, VPAC1, and VPAC2) are widely expressed in the central nervous system (CNS). Consistent with its distribution in the CNS, the PACAP/PAC1 receptor system is involved in several physiological responses, such as mediation of the stress response, modulation of nociception, regulation of prolactin release, food intake, etc. This system is also implicated in different pathological states, e.g., affective component of nociceptive processing, anxiety, depression, schizophrenia, and post-traumatic stress disorders. A review of the literature on PubMed revealed that PACAP and its receptors also play a significant role in the actions of addictive drugs. The goal of this review is to discuss the literature regarding the involvements of PACAP and its receptors in the motivational effects of addictive drugs. We particularly focus on the role of this peptide in the motivational effects of morphine, alcohol, nicotine, amphetamine, methamphetamine, and cocaine.

1. Introduction

Pituitary adenylyl cyclase-activating polypeptide (PACAP) was originally isolated from the ovine hypothalamus (Miyata et al., 1989) and showed to activate the enzyme adenylyl cyclase and stimulate production of 5′-cyclic adenosine monophosphate (cAMP) in anterior pituitary cells. This polypeptide belongs to the vasoactive intestinal polypeptide (VIP)/secretin/growth hormone-releasing hormone/glucagon superfamily (Sherwood et al., 2000), and is shown to act as a neurotransmitter, neuromodulator and neurotrophic factor in the central and peripheral nervous systems (Hashimoto et al., 2006; Miyata et al., 1989). PACAP is encoded by the *Adcyap1* gene, and this peptide occurs in two active forms, namely PACAP-38 and PACAP-27 (Lauff et al., 1999).

PACAP exerts its effects via three guanine regulatory protein-coupled receptors (PAC1, VPAC1, and VPAC2). VPAC1 and VPAC2 receptors recognize both VIP and PACAP. On the other hand, PAC1 receptor is known to be a PACAP-preferring receptor (Harmar et al., 1998). PACAP is predominately expressed in the hypothalamus, but also found in septum, cingulate and entorhinal cortex, nucleus accumbens (NAc), globus pallidus, hippocampus, amygdala, in particular in the bed nucleus of stria terminalis (BNST) and central nucleus of amygdala (CeA), central thalamic nuclei, habenula, ventral tegmental area (VTA), substantia nigra, cerebellum, and sacral region of the spinal cord (Arimura, 1992; Arimura et al., 1994; Hannibal, 2002). Consistent with its distribution in the CNS, the PACAP/PAC1 receptor system is

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involved in several physiological responses, such as the stress response, nociceptive processing, and food intake. This system is also implicated in pathological states, such as affective component of pain (Missig et al., 2017), anxiety, schizophrenia, depression, and post-traumatic stress disorders [reviewed in (Lutfy and Shankar, 2019),].

Mice lacking PACAP or PAC1 receptors have been generated and used to assess the role of the endogenous PACAP/PAC1 receptor system in different physiological responses and pathological states. Adult mice lacking PACAP have been shown to exhibit hyperactivity and increased exploratory behavior (Hashimoto et al., 2001; Marquez et al., 2009), reduced anxiety (Hashimoto et al., 2001; Hattori et al., 2012; Otto et al., 2001b), impaired memory performance (Matsuyama et al., 2003; Otto et al., 1999, 2001a) and decreased depression-like behaviors (Hattori et al., 2012). However, there are some inconsistencies in the literature regarding these phenotypes [(Ago et al., 2013; Gaszner et al., 2012; Hashimoto et al., 2001, 2009, 2010; Matsuyama et al., 2003; Tanaka et al., 2010) also reviewed in (Lutfy and Shankar, 2019)]. Nevertheless, the increased exploratory behaviors have consistently been reported in PACAP (PACAP−/−) or PAC1 receptors (PAC1R−/−) knockout mice (Martin et al., 2003), suggesting that PACAP acts via the PAC1 receptors to regulate locomotor activity. Consistent with increased basal locomotor activity in the absence of PACAP or PAC1 receptors, we have reported that intracerebroventricular administration of high doses of PACAP (1.0 μg, i.c.v.) caused motor suppression in male and female C57BL/6 mice (Marquez et al., 2009). The PACAP/PAC1 receptor system has also been implicated in the actions of addictive drugs. The goal of this article is to review the literature regarding the role of this polypeptide in the motivational effects of addictive drugs, such as morphine, nicotine, alcohol, amphetamine, methamphetamine, and cocaine.

2. The role of the PACAP/PAC1 receptor system in the motivational effects of morphine

Earlier studies have examined the role of the PACAP/PAC1 receptor system in morphine tolerance and dependence. However, conflicting results have been reported. Macsai et al. (2002) have shown that PACAP administration facilitated the development of antinociceptive tolerance induced by morphine pellet implantation in male inbred CFLP mice (LATI, Gödölló, Hungary). These authors also showed a shorter latency of naloxone-precipitated withdrawal jumping in morphine dependent mice treated with PACAP (500 ng, i.c.v.) (Macsai et al., 2002), suggesting that PACAP may function to facilitate tolerance and dependence at low doses. On the other hand, Martin and colleagues demonstrated that exogenous PACAP-38 (16 μg/kg, i.c.v.) reduced global signs of naloxone-precipitated withdrawal and that mice lacking PAC1 receptors exhibited greater global signs of withdrawal compared to their wild-type controls (Martin et al., 2003). In another study in morphine dependent male outbred CFLP mice (Domaszék, Hungary), naloxone induced anxiolysis and hypothermia (0.1 mg/kg or 0.2 mg/kg, s.c.) but greater signs of withdrawal (1 mg/kg, s.c.). These responses were blocked by PACAP administration (500 ng, i.c.v.), suggesting that PACAP may differentially regulate the somatic and affective signs of withdrawal (Liptak et al., 2012). However, unlike the results of the above studies, Szabo and colleagues showed no effect of PACAP (2 pg - 2 μg, s.c. or 200 pg-200ng, i.c.v.) on signs of morphine withdrawal in male inbred CFLP mice (SZOTE, Animal Husbandry, Szeged, Hungary) (Szabo et al., 1998). The difference in the direction of the regulatory actions of PACAP on morphine dependence may be due to the use of different mouse strains and different concentrations of PACAP in these studies (Table 1).

Martin et al. (2003) studied the role of PAC1 receptor in the antinociception and rewarding actions of morphine as well as in somatic signs of morphine withdrawal. These authors also examined changes in LC neuronal activity following withdrawal in mice lacking PAC1 and their wild-type controls. There was an increase in basal motor activity but no change in motor stimulation induced by morphine (15 mg/kg, s.c.). Locomotor sensitization induced by morphine (15 mg/kg, s.c., twice daily for a period of 15 days) was also not different between mice of the two genotypes. Likewise, morphine-induced conditioned place preference (CPP), a measure of rewarding actions of morphine, was comparable between mice lacking PAC1 receptor and their wild-type controls after repeated conditioning with morphine (5 mg/kg, s.c.; 3 saline and 3 morphine conditioning on alternate days). On the other hand, as stated above, mice lacking PAC1 receptor exhibited greater somatic signs of withdrawal. Corresponding to this, LC activity was also reduced in mice lacking PAC1 receptor, showing that PAC1 receptor may be involved in opioid dependence (Martin et al., 2003). These results suggest that endogenous PACAP acting on PAC1 receptor in the LC may facilitate signs of withdrawal (Fig. 1). However, further studies are needed to fully characterize the role of PACAP and its receptors in somatic and affective signs of opiate withdrawal given that discrepant results have been reported in the literature (Table 1).

We studied the effect of low doses of PACAP on morphine-induced hyperlocomotion and discovered that low doses of PACAP (0.03 and 0.3 μg, i.c.v.) that had no effect on basal locomotor activity, increased morphine-induced locomotor stimulation in mice (Marquez et al., 2009). Consistent with this result, mice lacking PACAP displayed reduced hyperlocomotion following morphine administration (5 or 10 mg/kg, s.c.) as well as a blunted CPP response following single (1 saline and 1 morphine on alternate days) but not repeated (4 saline and 4 morphine on alternate days) morphine (10 mg/kg, s.c.) conditioning (Marquez et al., 2009). The lack of a difference in the rewarding action of morphine between mice lacking PACAP and their wild-type controls following repeated conditioning with morphine is consistent with an earlier study (Martin et al., 2003), where no difference in morphine-induced CPP was observed in mice lacking PAC1 receptors compared to their wild-type controls (Table 1). However, Martin et al. (2003) did not utilize the single conditioning paradigm to determine the role of the endogenous PACAP/PAC1 receptor system in the rewarding action of acute morphine. Considering that there was no change in the magnitude of the CPP response following repeated as compared to single conditioning in wild-type mice (Marquez et al., 2009), it is possible that tolerance may have developed to the rewarding action of morphine in wild-type mice and endogenous PACAP may have been involved in this phenomenon, as shown to be the case for morphine antinociceptive tolerance (Macsai et al., 2002). Alternatively, given that PACAP has been implicated in learning and memory (Matsuyama et al., 2003; Otto et al., 2001a), it is possible that PACAP-deficient mice may have deficiency in learning and memory to express the conditioned response in the short-term. Therefore, further studies are needed to test this possibility. Additionally, further studies are needed to determine if tolerance develops to the rewarding action of morphine and PACAP is involved in this phenomenon.

3. The role of the PACAP/PAC1 receptor system in the motivational effects of alcohol

The role of endogenous PACAP in the actions of alcohol has been studied using mice lacking PACAP and their wild-type controls (Table 1). Male PACAP−/− mice on an ICR genetic background exhibit comparable latency for the loss of righting reflex compared to their wild-type controls following a high dose of ethanol (4 g/kg, i.p.), suggesting no alterations in the initiation of sedative effects of ethanol (Tanaka et al., 2004). However, these mice exhibit reduced duration of righting reflex loss as well as hypothermia compared to their wild-type controls (Tanaka et al., 2004). These changes are not due to differences in blood alcohol concentrations between mice of the two genotypes (Tanaka et al., 2004), suggesting that PACAP may be involved in the duration but not initiation of sedative and hypothermic effects of alcohol.

Regarding the role of PACAP receptors, PAC1 receptors are

Table 1
Summary of the studies showing the goal of each study, the subject used, the drug, its dosage and route of administration as well as the outcome of each study.

Study By	Assessment	Subject	Drug (Dose, Route)	Findings
Szabo et al. (1998)	To evaluate the effects of PACAP on morphine analgesia	Male inbred CFLP mice	• Morphine Pellets (35 mg) • PACAP (2 pg–2 μg, s.c., 200 pg–200 ng, i.c.v.) • Morphine (2 mg/kg, s.c.)	No change in morphine analgesia
	To examine the effects of PACAP on morphine tolerance		• Morphine Pellets (35 mg) • PACAP (2 pg–2 μg, s.c., 200 pg–200 ng, i.c.v.) • Morphine (2 mg/kg, s.c.)	No effect of PACAP on morphine tolerance
	To assess the effects of PACAP on EtOH-induced sedation		• PACAP (2 pg–2 μg, s.c., 200 pg–200 ng, i.c.v.) • EtOH (4 g/kg, i.p.)	PACAP did not alter the duration of loss of righting reflex
	To assess the effects of PACAP on EtOH-induced hypothermia		• PACAP (2 pg–2 μg, s.c., 200 pg–200 ng, i.c.v.) • EtOH (2 g/kg, i.p.)	PACAP enhanced hypothermic effect of EtOH but no change in tolerance to this effect of EtOH by PACAP
Macsai et al. (2002)	To examine effects of PACAP on morphine tolerance	Male inbred CFLP mice	• Morphine (35 mg s.c. pellet) • Morphine (5 mg/kg, s.c.) in the presence or absence of PACAP (500 ng, i.c.v.)	PACAP facilitated the development of morphine antinociceptive tolerance
	To examine effects of PACAP on naloxone-precipitated withdrawal jumping		• Morphine (35 mg s.c. pellet) • Naloxone (1 mg/kg, i.p.) in the presence or absence of PACAP (500 ng, i.c.v.)	PACAP shortened the latency of withdrawal jumping
Martin et al. (2003)	To determine the role of PAC1R in morphine-induced antinociception	Male & female PAC1R−/− and PAC1 ^{CamKCre2} mice	Morphine hydrochloride (5 mg/kg, s.c.)	No significant change in somatic pain and morphine analgesia
	To examine the role of PAC1R in morphine-induced locomotor sensitization		Morphine hydrochloride (15 mg/kg, s.c.) twice daily for 15 days	No change in sensitization between wild-type and PAC1R−/− mice
	To assess the role of PAC1R in morphine rewards		Morphine hydrochloride (5 mg/kg, s.c.) or saline every other day for 6 consecutive days in place conditioning paradigm	No change in morphine CPP in PAC1R−/− mice
	To determine the effect of PACAP-38 on morphine withdrawal		• Morphine hydrochloride (20–100 mg/kg, s.c.) twice daily for 5 days • PACAP-38 (16 μg/kg, i.c.v.) • Naloxone hydrochloride (1 mg/kg, i.p.)	Somatic signs of morphine withdrawal were significantly reduced by PACAP-38
	To determine the role of PAC1R in morphine withdrawal and firing rates in the LC		• Morphine hydrochloride (20–100 mg/kg, s.c.) twice daily for 5 days • Naloxone hydrochloride (1mg/kg, i.p.)	Naloxone precipitated withdrawal increased in PAC1R−/− mice and firing rates in LC was reduced in PAC1R−/− mice
Marquez et al. (2009)	To examine the effect of PACAP on basal motor activity and morphine-induced motor stimulation	Male & female C57BL/6J PACAP+/+ and PACAP−/− mice	• Morphine sulphate (5 mg/kg, s.c.) PACAP (0, 0.03, 1.0, and 3.0 μg/3.0 μL of aCSF, i.c.v.)	Motor suppression at higher doses of PACAP and higher basal motor activity in PACAP deficient mice Low doses of PACAP did not alter basal motor activity but enhanced the action of morphine
	To determine the role of PACAP in morphine-induced hyperlocomotion and CPP		Morphine sulphate (5 or 10 mg/kg, s.c.)	Displayed reduced hyperlocomotion following morphine administration Blunted CPP response following single but not repeated morphine conditioning
Liptak et al., 2012	To assess the influence of PACAP on naloxone-precipitated morphine withdrawal symptoms	Male outbred CFLP mice	• Morphine (20–80 mg/kg, s.c.) twice daily for 4 days • PACAP-38 (500 ng, i.c.v.) • Naloxone (1 mg/kg, s.c.) 2 h after the last morphine dose	PACAP shortened jumping latency
	To examine the effects of PACAP on withdrawal-induced hypothermia		• Morphine (20–80 mg/kg, s.c.) twice daily for 4 days • PACAP-38 (500 ng, i.c.v.) • Naloxone (1 mg/kg, s.c.) 2 h after the last morphine dose	PACAP showed no effect on hypothermia induced by naloxone in morphine dependent mice
	To determine the effect of PACAP on withdrawal-induced anxiety		• Morphine (20–40 mg/kg, s.c.) twice daily for 3 days & 20 mg/kg on day 4 • PACAP-38 (500 ng, i.c.v.) • Naloxone (0.1–0.2 mg/kg, s.c.)	Both doses of PACAP increased the open arm time/total time rate but had no effect on total activity
Ericson et al. (1998)	To assess effects of MLA injected locally in the VTA on voluntary EtOH intake and the associated accumbal DA overflow in rats	Male Wistar rats	• EtOH (6%) • MLA (100 μM, intra VTA)	MLA antagonized the accumbal DA-elevating effect of EtOH

(*continued on next page*)

Table 1 (*continued*)

Study By	Assessment	Subject	Drug (Dose, Route)	Findings
Thiele et al. (2000)	To determine the role of PKA in EtOH sensitivity	Male & female RIIβ$^{-/-}$ and RIIβ$^{+/+}$ mice	EtOH 4.0 g/kg, i.p.	low sensitivity to intoxicating level of EtOH in mice lacking the RIIβ subunit of PKA
Otto et al. (2001b)	To examine the role of PAC1R in sensitivity to EtOH	Male PAC1R−/− & PAC1R^{CaMKCre2} mice	3.5 g/kg EtOH, i.p.	PAC1R−/− mice do not display enhanced sensitivity towards EtOH
Ericson et al. (2003)	To examine if accumbal DA levels are increased via indirect activation of VTA nAChR by EtOH	Male Wistar rats	• EtOH (10, 100, and 300 mM or 1 M, intra-VTA OR intra-accumbal) • MLA (100 μM, intra-VTA OR intra-accumbal)	Intra-VTA MLA antagonized the accumbal DA-elevating effect of intra-accumbal EtOH
Tanaka et al. (2004)	To assess the role of PACAP in EtOH-induced sedation	Male PACAP−/− and wild-type mice	• EtOH 2.5 g/kg, i.p. • EtOH 4.0 g/kg, i.p.	Latency to loss of righting reflex was not different between PACAP+/+ and PACAP−/− mice Sleep time (duration of the loss of righting reflex) was significantly shortened in PACAP−/− mice
	To examine the role of PACAP in EtOH-induced hypothermia		EtOH 2.5 g/kg, i.p.	Reduced sensitivity to EtOH-induced hypothermia in PACAP−/− compared to PACAP+/+ mice No change in EtOH blood concentration
Ericson et al. (2008)	To assess the role of nAChRs in anterior vs. posterior VTA on EtOH-induced elevation of accumbal DA levels	Male Wistar rats	• EtOH (300 mM, intra-VTA OR intra-accumbal) • MLA (100 μM, intra-VTA)	Local injection of MLA in anterior, but not posterior part of the VTA reduced the effect of EtOH on accumbal DA
Tanaka et al. (2010)	To assess the role of PACAP in EtOH preference in TBC and CPP	Male PACAP$^{-/-}$ mice	EtOH 0%–10% [conc. increases every 3 days]	PACAP−/− mice displayed increased preference to EtOH
	To assess the role of PACAP in sucrose preference		Sucrose (1.7%)	Sucrose preference was not changed
	To assess the role of PACAP in quinine preference		Quinine (0.1 mM)	Quinine preference was not altered
	To assess the role of PACAP in EtOH CPP		EtOH 1 g/kg, i.p.	No change in CPP between PACAP−/− and PACAP+/+ mice
Gupta et al. (2018)	To assess changes in PACAP-27 and PACAP-38 Gene Expression in the PVT in response to EtOH Drinking	Male Long-Evans rats	20% EtOH	EtOH consumption increased levels of PACAP-27 in the PVT
Tseng et al. (2019)	Role of PACAP in Nicotine self-administration	Female PACAP-deficient mice	Nicotine bitartrate (20–80 μg/mL), TBC paradigm	Increased nicotine preference in PACAP−/− mice
	To determine the role of PACAP in CPP induced by nicotine		• Nicotine bitartrate (0.25 mg/kg, s.c.)	No change in CPP between PACAP−/− & wild-type mice
	To assess the role of PACAP in CPA induced by nicotine		• Nicotine bitartrate (1 mg/kg, s.c.) for CPA	Nicotine-induced CPA was blunted in PACAP−/− mice
Tizabi et al. (2007)	To determine the effects of systemic EtOH and nicotine on accumbal DA	Male Wistar rats	• EtOH (0.5–2.0 g/kg, i.p.) • Nicotine (0.25–1.0 mg/kg, i.p.)	The combination increased accumbal DA to a significantly greater level compared to nicotine or EtOH alone
Leao et al. (2015)	To determine effects of nicotine on EtOH SA	Male Wistar rats	• EtOH (10% w/v) OR Water • Nicotine (0.8 mg/kg, s.c. on daily basis)	Early escalation of 10% w/v EtOH drinking in the operant conditioning paradigm
	To examine the effects of MLA on EtOH drinking in nicotine pre-exposed rats		• EtOH (10%) OR Water • Nicotine (0.8 mg/kg, s.c. on daily basis) • MLA (1 mg/kg, s.c.)	MLA reduced EtOH intake in nicotine pre-exposed rats
Tanaka et al. (2006)	To determine the role of PACAP in basal motor activity and amphetamine-induced hyperlocomotion	Male & female PACAP$^{-/-}$ mice	Amphetamine (2 or 10 mg/kg, i.p.)	PACAP−/− mice showed increased motor activity and this hyperlocomotion was reduced by amphetamine
Fujii et al. (2007)	To determine the role of PACAP in methamphetamine-induced hyperactivity	Male & female PACAP$^{-/-}$ mice	Methamphetamine (1 and 2 mg/kg, i.p.)	No change in locomotor stimulatory action of methamphetamine in PACAP−/− mice
	To examine the role of PACAP in methamphetamine-induced locomotor sensitization		Methamphetamine (1 mg/kg, i.p.) once daily for seven consecutive days and challenged on day 15	No change in locomotor sensitization in PACAP−/− vs. PACAP+/+ was observed
Miles et al. (2018)	To assess the changes in PACAP gene expression following cocaine SA	Male Sprague Dawley rats	SA of Cocaine hydrochloride (3.0 mg/ml, FR1 for 1 h) for 10 days	10 days of cocaine SA increased PACAP mRNA transcript levels in the BNST Acute cocaine exposure (1d) did not alter PACAP expression compared with control) No change in CRH or VIP
	To determine effects of PACAP-38 in reinstatement of cocaine SA		PACAP-38 (1.0 μg, intra-BNST infusion) immediately before the test session	PACAP mimicked the action of stress
	To examine effects of PACAP6-38 in reinstatement of extinguished cocaine		PACAP6-38 (1.0 μg, intra-BNST infusion) immediately before the test session	PACAP6-38 blocked reinstatement of stress-induced cocaine SA

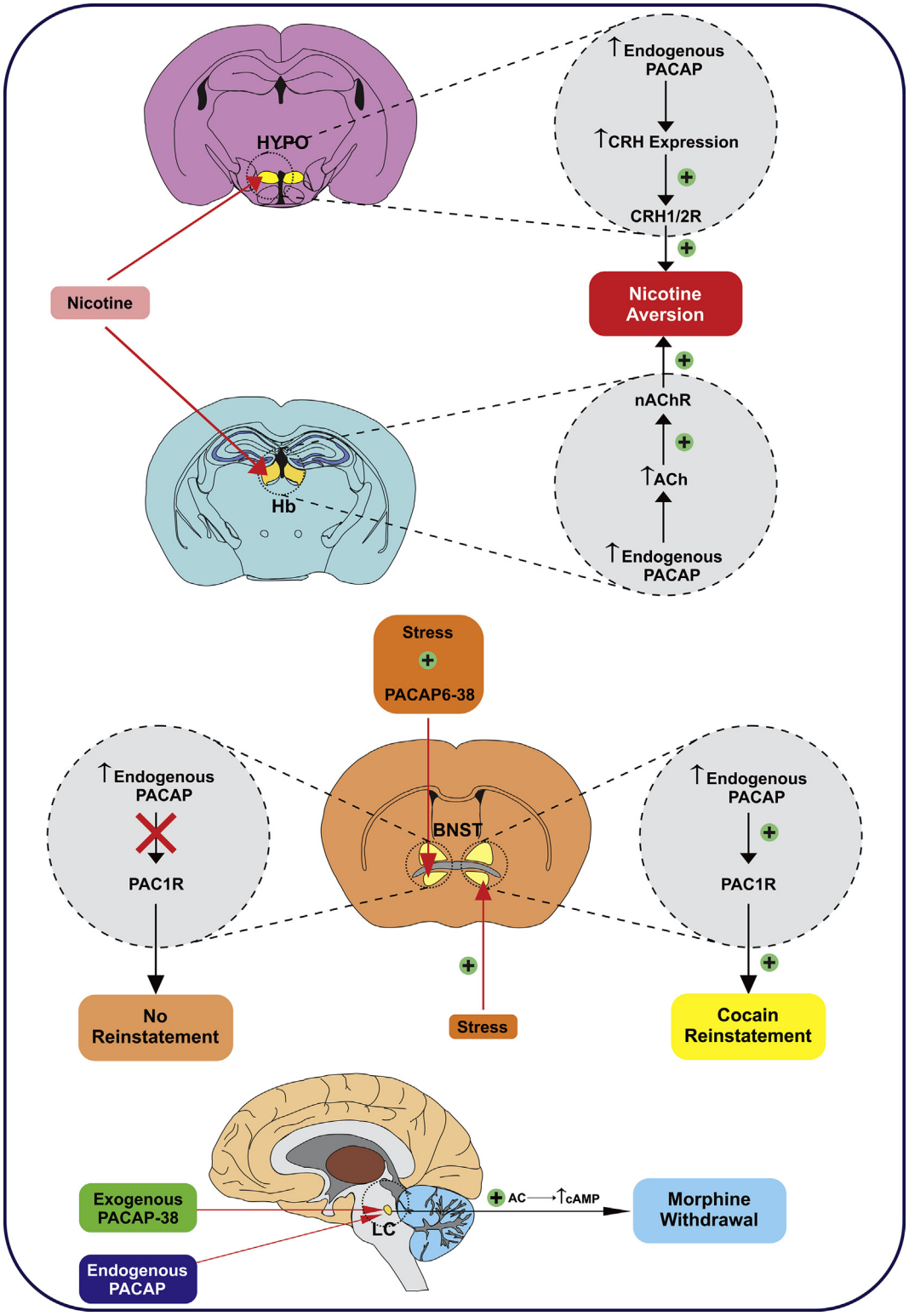

Fig. 1. The purported mechanism of regulatory action of PACAP on the motivational effects of addictive drugs. Nicotine may cause the release of PACAP in the hypothalamus (HYPO), where PACAP binds to and activates PAC1 receptor (PAC1R) and can increase the expression of CRH which in turn by binding to it receptors (CRH R1/2) can exert aversion. Alternatively, nicotine may cause the release of PACAP in the habenula (Hb), where it could regulate the release of acetylcholine (ACh). The latter neurotransmitter by acting on nicotinic acetylcholine receptors (nAChRs) can cause aversion. As shown by Miles et al. (2018), changes in the level of PACAP in the bed nucleus of stria terminalis (BNST) can alter stress-induced reinstatement. For example, stress may cause the release of PACAP in the BNST. PACAP by binding to PAC1 receptor mediates reinstatement because when stress was applied in the presence of PACAP6-38, a PACAP receptor antagonist, stress failed to induce reinstatement. Martin et al. (2003) demonstrated that PACAP may be acting in the locus coeruleus (LC) to increase the activity of adenylyl cyclase (AC) and increase cAMP levels, leading to alterations in morphine withdrawal although this may be in contrary to the cAMP overshoot theory.

probably not involved in the sedative effect of PACAP, as no alteration in the sedative effect of ethanol was found in PAC1 receptor knockout mice compared to their wild-type controls. This suggests that receptors other than PAC1 may be involved in the modulatory role of endogenous PACAP in the sedative and hypothermic effects of ethanol (Tanaka et al., 2004). Reduced sensitivity of PACAP-deficient mice to intoxicating blood level of ethanol (Tanaka et al., 2004) might be explained through PACAP's actions on VPAC receptors, because mice lacking PAC1 receptors have been shown to display normal sensitivity to ethanol (3.5 g/kg, i.p.) (Otto et al., 2001b). Moreover, male and female RIIb−/− and RIIb+/+ mice with protein kinase A (PKA) subunit deletion show low sensitivity to intoxicating level of ethanol (4.0 g/kg, i.p.), suggesting that PACAP may be acting via VPAC receptors and cAMP/PKA (PKA) signaling to mediate the sedative effect of ethanol (Thiele et al., 2000).

The endogenous PACAP has also been implicated in alcohol self-administration. PACAP-deficient mice display increased alcohol preference in the two-bottle choice paradigm, with no preference towards the ethanol-paired compartment in the place conditioning paradigm compared to their wild-type controls (Tanaka et al., 2010). On the other hand, preference for sucrose (1.7%) and quinine (0.1 mM) was not altered in PACAP knockout mice compared to their wild-type controls (Tanaka et al., 2010), suggesting that PACAP is selectively involved in alcohol preference in the two-bottle choice paradigm. However, further studies are needed to delineate the role of PACAP and its receptors in the reinforcing actions of alcohol.

PACAP not only regulates the action of alcohol but alcohol also alters the level of endogenous PACAP (Table 1). Recently, intermittent alcohol self-administration has been shown to regulate the level of PACAP-27 in the paraventricular nucleus of thalamus (PVT), a brain region implicated in alcohol consumption (Gupta et al., 2018). In this study, adult male Long Evans rats were trained to consume a 20% ethanol solution under an intermittent alcohol consumption paradigm. The results showed that rats engaged in alcohol self-administration had a significantly greater level of PACAP mRNA in the PVT. However, further studies are needed to assess if alcohol self-administration would change the release of PACAP. Additional research is also needed to establish a functional role for the changes in PVT PACAP mRNA in alcohol consumption versus other behavioral effects of alcohol.

4. The role of the PACAP/PAC1 receptor system in the motivational effects of nicotine

The role of PACAP in the actions of nicotine has not been fully characterized. In a recent study, we found that female mice lacking PACAP fully backcrossed on a C57BL/6 mouse strain exhibited increased nicotine (20–80 μg/mL) self-administration in the two-bottle choice paradigm. However, these mice showed a comparable CPP following a low dose of nicotine (0.25 mg/kg, i.p.) compared to their wild-type controls (Tseng et al., 2019). These changes are reminiscent of the differences observed in alcohol preference and ethanol-induced CPP between PACAP-deficient and their wild-type controls (Tanaka et al., 2010). We also discovered that nicotine (1 mg/kg, s.c.) induced conditioned place aversion (CPA) in wild-type mice and this response was blunted in PACAP-deficient mice compared to their wild-type controls (Tseng et al., 2019). Together, these results suggest that while the rewarding effect of nicotine was not altered in the absence of PACAP, the increased nicotine self-administration in the absence of PACAP may be due to a decrease in the aversive effect of nicotine (Tseng et al., 2019). However, further studies are needed to identify the site of regulatory action of PACAP. Given that PACAP increases the expression of corticotropin releasing hormone (CRH, also known as CRF) in the paraventricular nucleus (PVN) of the hypothalamus (Agarwal et al., 2005; Grinevich et al., 1997; Stroth et al., 2011) and CRH elicits aversion (Cador et al., 1992) as well as taste aversion (Benoit et al., 2000) in rodents, we hypothesize that PACAP may be acting at the level of PVN to mediate the aversive effects of nicotine. Alternatively, PACAP may be acting in the habenula to alter the aversive effect of nicotine (Fig. 1). Indeed, PACAP and its receptors are found in the habenula [for a review, see (Vaudry et al., 2000)], a brain region implicated in nicotine-induced aversion [reviewed in (Fowler and Kenny, 2014)]. However, further studies are needed to identify the neuroanatomical site of action of PACAP as well as the network-level action of PACAP. Likewise, further studies are needed to determine the role of PACAP in other actions of nicotine. Studies are in progress in our laboratory to determine the role of PACAP in nicotine dependence. Our preliminary data show that male and female mice lacking PACAP and their wild-type littermates/age- and sex-matched controls, fully backcrossed on a C57BL/6 mouse background strain, show reduced anxiety-like behaviors in the elevated plus maze paradigm following mecamylamine-precipitated withdrawal and there may be some sex-related differences in this response.

5. The role of the PACAP/PAC1 receptors in the crosstalk between nicotine and alcohol

Alcohol is mostly co-abused with nicotine and based on epidemiological studies, alcohol drinking is more prevalent in smokers in comparison to nonsmokers (Britt and Bonci, 2013; DiFranza and Guerrera, 1990; Harrison et al., 2008; Harrison and McKee, 2008). An earlier study in adult male Wistar rats has shown that nicotine (0.8 mg/kg, s.c., on daily basis) produces early escalation of 10% alcohol drinking in the operant conditioning paradigm (Leao et al., 2015). In particular, the facilitating effect of nicotine on escalation of alcohol drinking was associated with recruitment of discrete neuronal population in the NAc core, dorsomedial prefrontal cortex, CeA, BNST, and VTA (Leao et al., 2015). In the very same study, administration of mecamylamine (1 mg/kg, s.c.), the nicotinic receptor (nAChRs) antagonist, reduced alcohol intake in nicotine pre-exposed rats (Leao et al., 2015). Interestingly, local administration of mecamylamine (100 μM) in the VTA of male Wistar rats has been shown to completely antagonize the accumbal dopamine-elevating effect of ethanol (300 μM) administered into the NAc (Ericson et al., 1998).

The reinforcing effect of nicotine (as nicotine bitartrate 0.03 mg/kg/infusion) on mesolimbic dopaminergic system has been demonstrated in previous studies in male Long-Evans rats (Corrigall et al., 1992), as well as the role of VTA nicotinic receptors on increased dopamine release by ethanol (2–6%) in male Wistar rats where ethanol-stimulated dopamine release was blocked by intra-VTA administration of 100 μM mecamylamine (Ericson et al., 1998, 2003). Local intra-VTA application of 100 μM mecamylamine in anterior, but not posterior part of the VTA reduced the increase in accumbal dopamine release induced by application of ethanol (300 μM) in the NAc (Ericson et al., 2008). Similarly, administration of nicotine enhanced dopamine release in the NAc (Di Chiara, 2000), while blockade of nAChRs in the NAc reduced alcohol intake and the ensuing dopamine release in rats (Di Chiara, 2000; Ericson et al., 1998). The above findings suggest that there is a crosstalk between nicotine and alcohol in altering the activity of the mesolimbic dopaminergic neurons. Interestingly, co-administration of nicotine (0.25–1.0 mg/kg, i.p.) and ethanol (0.5–2.0 g/kg, i.p.) increases the level of extracellular dopamine in the NAc to a significantly greater level compared to nicotine alone or alcohol alone in adult male Wistar rats (Tizabi et al., 2007).

Considering that PACAP has been implicated in the action of alcohol and nicotine (Tanaka et al., 2010; Tseng et al., 2019), the PACAP/PAC1 receptor system may also be involved in the crosstalk between alcohol and nicotine. However, there is scarcity of literature to show the involvement of PACAP in the crosstalk between nicotine and alcohol except a single study which shows that PACAP is found to block toxicity induced by high alcohol and high nicotine as well as their combination at low concentrations (Tizabi et al., 2018). In a preliminary study, we examined the role of PACAP in the crosstalk between nicotine and

alcohol and showed that mice lacking PACAP that showed aversion in the place conditioning paradigm following nicotine conditioning also exhibited a robust aversive response when subsequently conditioned with alcohol. Interestingly, this response was blunted in mice lacking PACAP, suggesting that endogenous PACAP is involved not only in the aversive effect of nicotine (Tseng et al., 2019) but also in the crosstalk between nicotine and alcohol (Marquez, Hamid and Lutfy, in preparation). However, further studies are needed to fully characterize the role of PACAP in this process.

6. The role of the PACAP/PAC1 receptor system in the motivational effects of amphetamine

The role of PACAP in the motor stimulatory action of amphetamine has been reported (Table 1). It was found that amphetamine elicited hyperlocomotion in both Adcyap1$^{-/-}$ mice and their wild type controls (Tanaka et al., 2006) but the acute motor stimulatory action of methamphetamine (1 or 2 mg/kg, i.p.) was not altered in PACAP$-/-$ mice raised on an ICR mouse strain (Fujii et al., 2007). Likewise, mice lacking PACAP and their wild-type controls exhibited comparable locomotor sensitization following repeated administration of methamphetamine (Fujii et al., 2007). Recent studies from our laboratories however showed that PACAP$-/-$ mice fully backcrossed on a C57BL/6 mouse strain express greater locomotor activity following a higher dose (3 mg/kg) of amphetamine (Hamid and Lutfy, unpublished data). Yet, further studies are needed to determine the role of PACAP and its receptors in the rewarding and addictive actions of amphetamine.

7. The role of the PACAP/PAC1 receptor system in the motivational effects of cocaine

PACAP has been implicated in a variety of stress responses through its modulatory action on the hypothalamus and extrahypothalamic structures [reviewed in (Lutfy and Shankar, 2019),]. Miles and colleagues therefore characterized the role of PACAP in stress-mediated reinstatement of cocaine self-administration in adult male Sprague-Dawley rats (Miles et al., 2018). In particular, the role of PACAP in the BNST was determined in this process because high levels of PACAP are found in this brain region. Furthermore, local PACAP administration in this brain region activates the stress response and causes anxiety-like behaviors in rodents [reviewed in (Lutfy and Shankar, 2019),]. To determine the role of endogenous PACAP in the BNST in cocaine relapse, these investigators trained rats to self-administer cocaine and then exposed them to extinction training followed by reinstatement via foot shock, a stressor, in the presence and absence of a PACAP receptor antagonist (Miles et al., 2018). They found animals self-administering cocaine had five-fold higher levels of PACAP transcripts (Table 1). These authors also demonstrated that exposure to foot shock reinstated cocaine-self-administration in rats formerly showed extinction and this stress-induced reinstatement was reduced by PACAP 6–38 (1.0 μg), a PACAP receptor antagonist (Fig. 1). They also injected animals with PACAP-38 (1.0 μg) locally in the BNST and mimicked the effect of stress in reinstating cocaine self-administration in rats (Miles et al., 2018). Given that PACAP could act not only on PAC1 but also VPAC1 and VPAC2 receptors and that PACAP6-38 could activate VPAC2 receptors (Saghy et al., 2015), further studies are needed to characterize the receptor type involved in this process. Also, the role of other brain regions in this process needs to be assessed. Furthermore, additional studies are needed to examine if the level of peptide changes in the BNST during the reinstatement process following exposure to the stressor.

8. Potential mechanisms of regulation of motivational effects of addictive drugs by PACAP

A growing body of literature suggests that PACAP is involved in the stress response as well as in the motivational effects of addictive drugs. PACAP mediates the stress response via acting at the level of the hypothalamus as well as extrahypothalamic brain regions, such as the BNST and CeA. The PACAP/PAC1 receptor system in the BNST was shown to play a significant role in the mediation of stress response as well as in stress-induced anxiety [reviewed in (Lutfy and Shankar, 2019),] and reinstatement of cocaine self-administration in rats (Miles et al., 2018). PACAP may also be involved in the action of nicotine and alcohol and possibly their co-use and co-dependence and may therefore represent a potential target to develop pharmacotherapy to treat drug addiction. Although changes in the level of PACAP gene expression has been reported at least in rats after a sub-chronic alcohol consumption (Gupta et al., 2018) or cocaine self-administration (Miles et al., 2018), further studies are needed to establish the involvement PACAP and its receptors in pathological addictive behaviors. Furthermore, more research is needed to characterize how PACAP may regulate these addictive behaviors, whether PACAP is releasable, where is the origin of PACAP, and whether its release can be altered by pathological conditions including following chronic use of addictive drugs. Below, we provided some possibilities that PACAP could regulate the action of addictive drugs, but further studies are needed to determine the exact mechanism of action of PACAP as well as its network-level action.

The regulatory actions of PACAP on the motivational effects of addictive drugs might be explained through its interaction with the mesolimbic dopaminergic neurons. Along this line, high levels of PACAP-38 have been found in the VTA and NAc (Ghatei et al., 1993). Furthermore, PACAP has been shown to increase the expression of tyrosine hydroxylase (TH) and vesicular monoamine transporter, via the PAC1 receptor (Corbitt et al., 2002; Guillot et al., 2008). Considering that other neuropeptides co-localize with dopamine in the VTA (Hokfelt et al., 1984), it is possible that PACAP and dopamine may be co-released, and PACAP may regulate the activity of the mesolimbic dopaminergic neurons. Alternatively, PACAP is released in the NAc to regulate the activity of these neurons and regulate dopaminergic neurotransmission. Indeed, PACAP has been shown to stimulate tyrosine hydroxylase activity in homogenates of rat NAc (Moser et al., 1999). However, it needs to be proven that endogenous PACAP regulates the synthesis and/or release of dopamine and this response plays a functional role in the motivational effects of addictive drugs.

Downstream of dopamine receptor activation is phosphorylation of DARP-32. PACAP has been shown to exert neuromodulatory action through activation of adenylyl cyclase and ultimately cAMP/PKA signaling (Shioda, 2000). Up-regulation of PKA activity leads to phosphorylation of DARPP-32, and therefore PACAP may be implicated in activation of DARPP-32. This could be another potential mechanism through which PACAP could regulate the motivational effects of addictive drugs.

Neuropeptides, such as PACAP may also modulate synaptic output through its action on other neurotransmitters. For example, PACAP has been shown to increase nicotinic neurotransmission in presynaptic nerve terminal (Pugh et al., 2010). Particularly, PACAP was shown to act through PAC1 receptors to selectively increase transmission on nicotinic synapses (Pugh et al., 2010). Considering that the involvement of nicotinic cholinergic inputs in regulation of mesolimbic dopaminergic neurons, PACAP may contribute to the motivational effects of addictive drugs through this mechanism. This may be the case for the role of PACAP in the motivational effect of nicotine and alcohol as well as in the interaction between nicotine and alcohol. PACAP, indeed, has been shown to increase excitatory synaptic responses via the release of acetylcholine (ACh) from the synapses (Roberto and Brunelli, 2000). If ACh release is altered by PACAP in the habenula, for example, this may be a mechanism through which PACAP could mediate the aversive effect of nicotine (Fig. 1). However, further studies are needed to test this possibility.

PACAP is also involved in regulation of synaptic transmission in different brain regions (Cho et al., 2012; Ciranna and Cavallaro, 2003; Roberto and Brunelli, 2000; Roberto et al., 2001; Yang et al., 2010).

PACAP has been shown to influence glutamate signaling in the hippocampus through the processes involving NMDA receptor potentiation via activation of PAC1 receptor and the PLC/PKC/Pyk2/Src signaling pathway (Yang et al., 2010). Interestingly, PACAP and VIP having opposite synaptic effects through cAMP/PKA pathway regulate mossy fibers synapses (Ciranna and Cavallaro, 2003). PACAP even acting on PAC1 vs. VPAC1 and VPAC2 recruit different signaling mechanisms (Yang et al., 2010), which may explain the diversity of PACAP's actions.

PACAP has been shown to modulate NMDA receptor activity through up-regulation of GluN2B subunit and expression of brain-derived neurotrophic factor (BDNF) (Macdonald et al., 2005; Yaka et al., 2003). *In vitro* studies using hippocampal slices, for example, have shown that activation of cAMP/PKA signaling pathway by PACAP induced phosphorylation of GluN2B, leading to increased NMDA channel activity, and expression of BDNF (Yaka et al., 2003). Phosphorylation of GluN2B by PACAP is mediated through the release of inhibitory scaffolding protein C kinase 1 (RACK1) from tyrosine kinase Fyn-RACK1-GluN2B complex, thereby allowing Fyn to phosphorylate GluN2B (Trepanier et al., 2012).

The increase in NMDA receptor-mediated channel activity was abolished in *Fyn* knockout mice, suggesting that PACAP signals through Fyn in order to elevate NMDA receptor activity (Trepanier et al., 2012). This could be another potential mechanism through which PACAP could regulate the motivational effects of addictive drugs. Indeed, the importance of Fyn in regulation of alcohol withdrawal was shown in transgenic mice overexpressing *Fyn*. It is known that Fyn kinase null animals possess acute ethanol behavioral sensitivity and Fyn-centric gene networks influence variance in ethanol loss of righting reflex. More specifically, Fyn transgenic mice did not develop anxiety-like behavior during period of alcohol abstinence, suggesting that PACAP might be involved in regulation of alcohol withdrawal (Stork et al., 2002). However, further studies are needed to directly determine the role of PACAP and its receptors in somatic and affective signs of withdrawal from alcohol.

In summary, a growing body of evidence demonstrates that PACAP is involved in the motivational effects of addictive drugs and may be a potential target to develop novel medications to alter the rewarding and reinforcing actions of nicotine, alcohol, morphine and other addictive drugs. Importantly, this system may be a potential target to develop medications to prevent craving and relapse to cocaine and possibly other addictive drugs. However, more research is needed to assess if this peptide is involved in pathological conditions including addictive behaviors that occur following chronic use of these drugs.

Declaration of competing interest

The authors declare no conflict of interest.

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Abbreviations

aCSF	artificial cerebroventricular fluid
i.c.v.	intracerebroventricularly
s.c.	subcutaneously
i.p.	intraperitoneally
LC	locus coeruleus
EtOH	ethanol
RIIβ$^{-/}$	mice lacking the RII beta subunit of protein kinase A (PKA)
CPA	conditioned place aversion
CPP	conditioned place preference
MLA	mecamylamine
VTA	ventral tegmental area
DA	dopamine
nAChR	nicotinic acetylcholine receptor
FR1	fixed ratio 1 of reinforcement
SA	self-administration

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