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Role of pharmacokinetic and pharmacodynamic parameters in neuroadaptations induced by drugs of abuse, with a focus on opioids and psychostimulants

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ABSTRACT

The purpose of this review is to illustrate the importance of pharmacodynamic and pharmacokinetic factors in the complexity of the behavioral and neurochemical adaptations that occur following chronic treatments with drugs of abuse, with a focus on opioids and psychostimulants. As these neuroadaptations are thought to contribute to the pathogenesis and persistence of addiction, it is important to well understand how they can be modulated. The experimental results clearly show that changes observed are depending on the binding properties of the ligands, drug administration patterns, brain structures considered, and withdrawal periods. Thus, pharmacodynamic and pharmacokinetic factors play a key role, and may highly contribute to the great heterogeneity of the results reported in the literature regarding neuroadaptations observed following repeated treatments with drugs of abuse, each investigator using different protocols and/or different ligands, even if their targets/receptors are the same.

1. Introduction

It is now well admitted that addiction is a brain disease (Leshner, 1997) and that neuroadaptations are a core neurobiological feature of this pathology. The neuroadaptations are complex and may occur not only into the mesocorticolimbic dopamine system, a key neurotransmitter system involved in addictive behaviors, but also in other numerous systems (review in Koob and Volkow, 2016). Addiction is characterized by a compulsive behavior, a continued abuse of drugs despite negative consequences, craving when drugs are not more available and high risk of relapse. Moreover addicts may also be drug tolerant, physically and psychologically dependent. These characteristics involve persistent changes in the brain's structure and function (neuroadaptations). However, not everyone who uses drugs becomes addicted. Thus, depending on the drugs used, between 10–30% of users will develop an addictive behavior (Flórez-Salamanca et al., 2013). No single factor can predict whether a person will become addicted to drugs. But a combination of factors including psycho-biological factors (e.g., genetic factors, personality traits, co-morbidities), environmental factors (e.g., family, peer influence or sociocultural context), and neuroadaptations induce by drugs themselves influence risk for addiction.

Several parameters are directly involved in the pharmacological effects induced by a drug, and consequently in the neuroadaptations that may occur following repeated administrations: i) the bioavailability of the drug itself (importance of the route of administration); ii) the transport across the blood brain barrier (BBB); iii) the rate of delivery to the brain, and iv) the efficacy of the intracellular responses, depending on the interactions (e.g., affinity, partial or full agonist) between the ligand and its target (Fig. 1). This review will summarize the behavioral and neurochemical neuroadaptations observed following repeated administration of drugs of abuse with different routes, speeds and patterns of administration, with a focus on opioid ligands, but also with results obtained following repeated administration of cocaine or other psychostimulants.

In human, drug use is a voluntary act. In rodents, distinct neuroadaptations have been reported in studies comparing active (self-administration) versus passive (experimenter-administered, or yoked animals) drug administrations, suggesting that this parameter is also crucial regarding neuroadaptations induced by drugs of abuse, and development of drug addiction (Jacobs et al., 2004, 2003, 2005; Fernàndez-Castillo et al., 2012). Because self-administration paradigm in rodents involves active drug administration, it mimics some aspects

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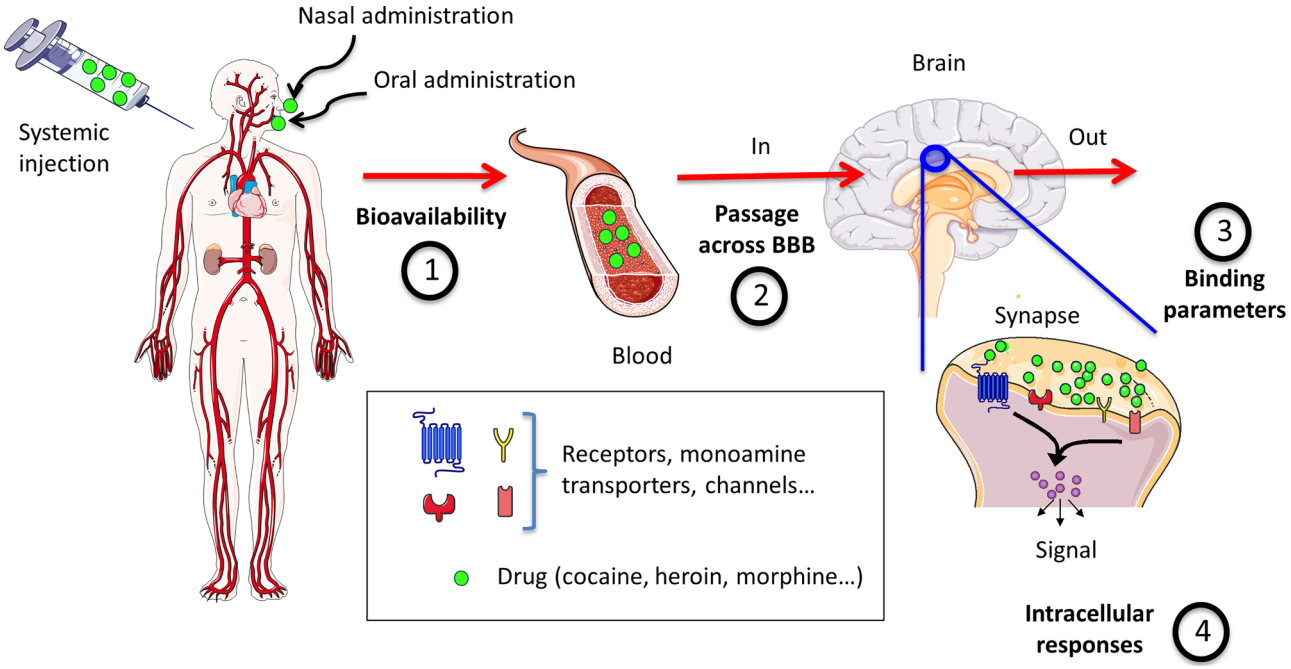


Fig. 1. Schematic representation of the parameters involved in the pharmacological impacts of drugs of abuse.
1) Bioavailability of the drugs depending on the route of administration (systemic, nasal, oral administration); 2) Passage across the blood brain barrier (BBB) that gives the concentration of the drugs that can reach their targets (receptors, monoamine transporters, channels); 3) Binding parameters (affinity and efficacy to activate the signalling cascade); 4) Intracellular responses leading to pharmacological responses (Images are modified from https://smart.servier.com/image-set-download/).

of human addiction behavior with a crucial role of cognitive processes (e.g., reinforcement learning, impulsivity, attention). This model is very helpfull to try to decipher the cellular and molecular mechanisms involved in drug addiction, even if the doses and the frequencies of administration are not controlled, as each animal will have its own behavior, and each animal will decide when pressing a lever or poking its nose into a hole to get drug. However, the main goal of this review is to demonstrate the importance of pharmacodynamic and pharmacokinetic parameters in neuroadapations, and thus only studies reporting results with experimenter-administered drugs of abuse have been considered. From these studies, the routes of administration, the patterns of administration, the pharmacological efficacy of ligands can be directly compared.

2. Importance of the route of administration

The route of administration will define the plasma concentration that can be reached, and thus the amount of compound able to cross the BBB. It is well known that the rewarding effects are dependent on the peak effect. Thus, imaging studies in human, and preclinical studies in animals have demonstrated that the speed with which a drug enters and leaves the brain are important factors in determining its reinforcing effects. Thus when the Cmax and Tmax are reached few minutes after absorption, they are related to the intensity of high (subjective experience of euphoria) that subjects experience. This could be referred to the peak effect that predicts abuse liability, i.e. when the concentration of the drug in the brain increases very rapidly, higher is the risk of dependence (see Volkow et al., 2010; Allain et al., 2015).

Studies investigating the pharmacokinetic properties of morphine have demonstrated that the relative onset of drug effects and the time necessary to reach the peak concentration in the brain are increased from intravenous to intramuscular/subcutaneous, and to oral routes (Upton et al., 1997). After intravenous administration, morphine brain concentration is the result of passage from the blood across the BBB to the brain. After nasal administration, the level of morphine into the brain could be the result of both distribution across the BBB and transfer via direct olfactory pathways. Indeed, it has been demonstrated in rats that morphine is directly and very rapidly transferred from the nose, via olfactory pathways, to the olfactory bulbs and the brain hemispheres (Westin et al., 2006). In a study comparing the effects of intranasal and intravenous heroin self-administration in heroin-dependent patients, it was demonstrated that the reinforcing effects of heroin are similar by the two routes of administrations, but that intranasal heroin is less potent than intravenous heroin when the subjective effects (e.g., “I feel a good drug effect”, “I feel high”) are reported (Comer et al., 1999).

The psychostimulant methylphenidate is used for the treatment of attention-deficit/hyperactivity disorder and narcolepsy but it also has a history of being misused as a ‘smart drug’. Methylphenidate is a blocker of dopamine and noradrenaline transporters (Gatley et al., 1996). Thus, this drug is able to increase the synaptic dopamine concentration. The effects induced by methylphenidate have been compared following either intravenous or oral administration. In the striatum the higher concentration of the psychostimulant was observed 10 min after intravenous administration (Cmax value), and 90 min after oral injection (Volkow and Swanson, 2003). Both routes of administration are able to increase dopamine levels in the striatum with the same magnitude, but the effect is faster following intravenous injection compared to oral administration. The difference in the delivery rate of methylphenidate may explain why the oral route did not induce a « high », whereas for intravenous injection the magnitude of the dopamine increase was associated with the intensity of the « high » (Volkow and Swanson, 2003). This is in good agreement with the “peak effect” theory, which identifies reinforcers with addictive potential as those that have rapid onset and short time to peak effect (Hatsukami and Fischman, 1996; de Wit et al., 1993; Abreu et al., 2001; Allain et al., 2015).

3. Importance of the rate of drug delivery to the brain

Besides the route of administration that plays an important role in

bioavailability of the drug, the speed of administration and the passage across the BBB are also very important factors. They will determine the quantity of drugs reaching the brain which will have a strong impact on the neuroadaptations observed.

The importance of the speed of administration is well illustrated in a paper published by Comer et al. (2009). They clearly demonstrated a relationship between rate of infusion and reinforcing strength of the opioid ligand, oxycodone in humans. Thus, while the same dose of oxycodone was administered intravenously over 2, 15, 30, 60, or 90 min in different groups, it is only when oxycodone was delivered in 2 or 15 min that participants reported reinforcing effects. This is in good agreement with the notion of peak effect, as already evoked above.

The importance of speed of administration was also investigated in a preclinical study using cocaine. The same dose of cocaine was intravenously administered in rats in either 5, 25 or 100 s. In these different conditions, the authors investigated the regulation of c-Fos expression and behavioral sensitization (Samaha et al., 2004). Whatever the time of administration, cocaine is able to induce an increase in c-Fos immunoreactivity particularly in the striatum, but with a much stronger effect when cocaine is injected in 5 s. Then this increase diminishes as the duration of injection lengthens.

The authors have also explored the behavioral consequences of the speed of cocaine administration using the locomotor sensitization model, a behavior usually observed during repeated administration of drugs of abuse. On day 1, administrations of cocaine increased the locomotor activity in the same magnitude whatever the infusion rate. On day 2, a significant behavioral sensitization was observed after intravenous administration of cocaine in 5 s, while the same dose of cocaine administered in 25 or 100 s did not induce this behavioral adaptation (Samaha et al., 2004). Using a different strategy, we highlighted the influence of delivery rate on neuroadaptations with cocaethylene, a psychoactive metabolite produced from a concomitant cocaine and ethanol consumption. Indeed, when cocaethylene was dissolved in an emulsion that is supposed to slow its brain delivery, instead of saline, behavioral sensitization was less robust (Noble et al., 2007). Thus it clearly appears that the rate at which cocaine or its metabolites are delivered influences the development of locomotor sensitization, an expression of neuroadaptations occurring in the brain upon repeated drug administration.

The second important factor, which will define the concentration of the drug at the site of action in the brain, is the permeability of the BBB. This layer protects the brain and is composed of endothelial cells joined together with tight junctions. These cells express transporters that may either prevent intracellular accumulation into the brain of circulating compounds and drugs (efflux pumps), or facilitate their entrance (influx pumps) (review in Theodorakis et al., 2017).

Among the efflux pumps, P-glycoprotein (Pgp ; MDR1 ; ABCB1) significantly contributes to BBB functions, both preventing the influx of agent from the blood into the brain and facilitating the efflux of compounds from the brain into the blood. Using Pgp knockout mice, Xie et al. (1999) nicely demonstrated that this efflux pump participates in regulating the amount of morphine transport across the BBB. Thus, while the brain to plasma morphine concentration ratio was 0.5 for wild-type animals, it was of 1.1 in knockout mice. This has an impact on the pharmacological responses induced by morphine that involved supraspinal structures. In Pgp knockout mice, a leftward shift of the morphine dose-response curve was observed in the tail flick test as compared to wild-type animals (King et al., 2001). All these results suggest that Pgp is able to decrease the permeability of BBB to morphine.

In the same way, using a selective inhibitor of Pgp, PSC833, we have also observed a leftward shift of the dose-response curve of morphine in the hot plate test in mice. Interestingly, no difference was observed in presence or absence of Pgp inhibitor on the analgesic responses obtained with heroin strongly suggesting that while morphine is a Pgp substrate, heroin is not (Seleman et al., 2014). Inhibiting Pgp has consequences not only on the analgesic effects of morphine, but also on regulation of gene expression. We have investigated the regulation of different genes including Rnd3, which is known to regulate actin cytoskeleton, and is an early common effector of several drugs of abuse (Marie-Claire et al., 2007; Seleman et al., 2014). At a dose of morphine unable to regulate Rnd3 expression, co-administration of the Pgp inhibitor PSC833 + morphine, revealed an effect, similar with the one obtained when heroin was administered alone or in association with PSC833 (Seleman et al., 2014). Finally, regarding the rewarding effects of morphine, it clearly appears in the conditioning place preference (CPP) that co-administration of the selective Pgp inhibitor with morphine, potentiated the rewarding effects of this opioid agonist (Seleman et al., 2014).

Very interestingly chronic morphine treatment in rats was able to increase the levels of Pgp in different brain structures, including the cortex and the hippocampus, without modification of the integrity of the BBB (Yousif et al., 2008). This increase could be interpreted as a protective reaction to avoid excessive stimulation by morphine, by preventing entry of large amount of the opioid ligand into the brain.

In human positron-emission tomography (PET) was used to investigate Pgp function in the BBB of patients with depression, schizophrenia or progressive neurodegeneration (de Klerk et al., 2010, 2009; Bartels et al., 2009), but to the best of our knowledge never in addiction field. These investigations could be very interesting as Pgp may modulate the entrance into the brain of different opioid ligands, and thus may also explain variability in the responses to opioid maintenance treatment (Linnet and Ejsing, 2008).

4. Importance of interactions with receptors

Receptors bind drugs (also referred to as ligand), with a relatively high degree of specificity, and after binding of the ligand, initiate a signalling cascade. Membrane receptors, when activated, usually result in activation of secondary enzymes or ion channels via the heterotrimeric G proteins. The pharmacological responses will depend on two main factors: affinity and efficacy. The affinity refers to the ability of a given drug to bind to its receptor by direct chemical interactions with the receptor binding site. It is an intrinsic property of the drug. The efficacy can be defined as the ability of a drug, once bound to its receptor, to activate it and thus initiate cellular signalling pathways that lead to pharmacological responses. A relative efficacy may be defined, as the relative maximum response from the drug. Drugs that produce less than the maximum activation of a given receptor are referred to as partial agonists (in opposite to full agonists, that lead to the maxima responses) (review in Strange, 2008).

Opioid receptors are members of the G protein-coupled receptor (GPCR) superfamily, and several receptors have been cloned : mu opioid receptor (MOR), kappa opioid receptor (KOR), delta opioid receptor (DOR), and ORL1/nociceptin receptor (Dhawan et al., 1996). At the cellular level, opioid receptors are mainly coupled to $G_{i/o}$ and G_q proteins and their activations lead to inhibition of adenylyl cyclase activity and voltage-gated Ca2+ channels, increase in mitogen-activated protein kinase (MAPK) phosphorylation and in the activity of inwardly rectifying K+ channels and phospholipase C beta. In general, studies show that MOR- or DOR-selective agonists can induce both analgesia and reward (Abdallah and Gendron, 2017; Klenowski et al., 2015; Matthes et al., 1996). The use of transgenic mice has provided greater insight into the potential roles of individual opioid receptor subtypes. These studies indicate that the analgesic effects and the rewarding properties of opioids such as morphine are primarily mediated by the activation of MOR (Charbogne et al., 2014). However, DOR has been shown to have a role in the regulation of emotional responses associated with opioid use (Peppin and Raffa, 2015).

Thus, to demonstrate the importance of the binding parameters in the neuroadaptations that may be induced by chronic treatments with opioid agonists, we will review the differences that can be observed

with 3 different opioid agonists : morphine, methadone, and buprenorphine, and we will give results essentially on MOR.

These 3 MOR agonists are largely used in humans, as methadone and buprenorphine are used in the treatment of opioid addiction. It is also important to compare the long-term effects of morphine, methadone and buprenorphine as they show differences in their binding parameters. Buprenorphine has a unique profile, significantly different from morphine, or methadone. It has a high affinity for MOR but low intrinsic activity, with partial agonist properties.

To complexify the picture, most of the compounds administered in animals are subjected to biotransformations that generate active and inactive metabolites. This is well illustrated with heroin which displays a low affinity towards MOR (Inturrisi et al., 1983) and whose action is mediated by its main metabolites produced sequentially : 6-monoacetylmorphine and morphine (review in Rook et al., 2006). Heroin is thereby considered as a prodrug. Morphine is in turn transformed into morphine-3-glucuronide (review in De Gregori et al., 2012), which has a low affinity and activity on MOR (Frölich et al., 2011; Roeckel et al., 2017). In humans, morphine is also transformed in morphine-6-glucuronide (review in De Gregori et al., 2012), an active metabolite (Handal et al., 2002). 6-monoacetylmorphine has an affinity for MOR comparable to morphine (Inturrisi et al., 1983) and behaves as a partial agonist (with an higher efficacy than morphine) (Selley et al., 2001). Methadone is also metabolized, but its main metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, has a poor affinity for MOR (Ki > 1 μM) (Lötsch et al., 2006). Buprenorphine is mainly metabolized in norbuprenorphine, and both ligands have a similar affinity for MOR, DOR and KOR. Norbuprenorphine behaves as a partial agonist toward MOR (but with an higher efficacy than buprenorphine), DOR and KOR (Huang et al., 2001). However, its contribution to buprenorphine effects in vivo is very modest as its passage to brain is limited by the BBB (Ohtani et al., 1995). Buprenorphine and norbuprenorphine are subjected to glucuronidation that generates buprenorphine-3-glucuronide, buprenorphine-6-glucuronide and norbuprenorphine-3-glucuronide, norbuprenorphine-6-glucuronide, respectively (Bruce et al., 2006). Despite the fact that these metabolites display high affinity towards opioid receptors, they have modest pharmacological effects (Brown et al., 2011). In summary, except when the opioid is a prodrug such as heroin, all these metabolites will play a modest role in pharmacological effects and it is more likely the variability in the metabolism that will influence the responses by changing the availability of the active compounds.

4.1. Binding parameters and signalling

Whereas morphine and methadone bind to MOR, with high affinities (in the nanomolar range), buprenorphine has an higher affinity (around 0.1 nM) and more importantly, it also binds DOR and KOR contrary to morphine and methadone (Lutfy and Cowan, 2004). On KOR, buprenorphine is usually described as an antagonist that mediates its anti-depressant effects (Falcon et al., 2016), but a recent study also suggests a role of MOR in these effects (Robinson et al., 2017). Buprenorphine is also unique as once bound to the receptor, it slowly dissociates (Rance, 1979). We investigated this characteristic ex vivo by measuring the ability of [^{3}H]-D-Ala2, N-MePhe4, Gly-ol5-enkephalin (DAMGO), a selective MOR ligand to displace buprenorphine on rat brain membranes. We found that in membranes pre-incubated with buprenorphine, [^{3}H]-DAMGO was not able to completely displace buprenorphine. The same results were obtained with [^{3}H]-naltrindole (a DOR ligand) and [^{3}H]-CI977 (a KOR ligand) but to a lesser extent (Mégarbane et al., 2006). This slow dissociation of buprenorphine from the MOR, resulting in a long residence time of the ligand on the receptor, could explain why the intensity of withdrawal signs is lower after chronic buprenorphine treatment as compared to morphine or methadone (Fig. 2) (Marie and Noble, unpublished results). This might have consequences on the ability of buprenorphine to promote

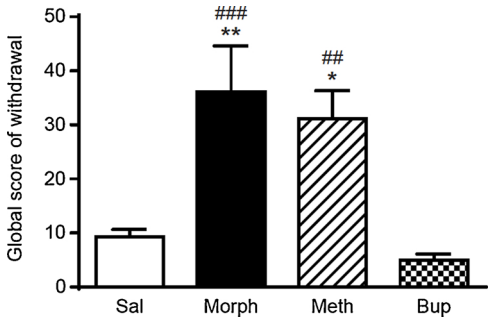


Fig. 2. Naloxone-precipitated withdrawal after opioids chronic treatment. Mice were treated (intraperitoneal route) or not (Sal) with equally effective doses of morphine (10 mg/kg, Morph), methadone (5 mg/kg, Meth) or buprenorphine (0.1 mg/kg, Bup) for 5 days, once a day. The 5th day, all animals received naloxone (1 mg/kg, intraperitoneal route) 90 min after the last injection and withdrawal signs were measured for 20 min and expressed as a global score (mean ± sem). (One-way ANOVA, F (3,75) = 9.123, $p < 0.0001$; * $p < 0.01$, ** $p < 0.05$ vs Sal group; ## $p < 0.01$, ### $p < 0.001$ vs Bup group; Tukey's multiple comparison test; n = 20 animals/group).

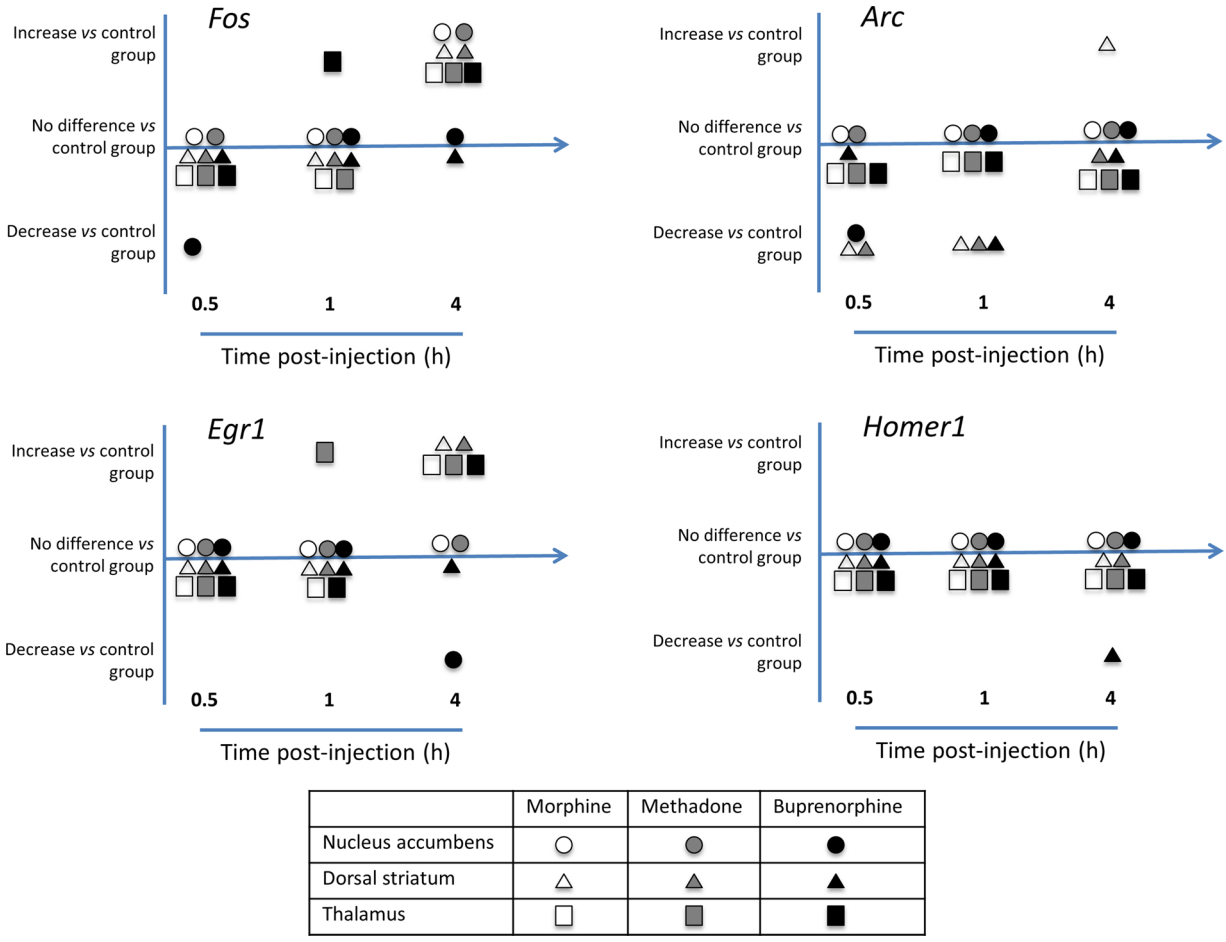
behavioral sensitization (see below 5.1).

Although, morphine, methadone, buprenorphine are MOR agonists, they have different efficacies to couple receptor to G protein and to mobilize intracellular pathways. Indeed, in most of the studies measuring second messengers, morphine and methadone are usually being considered as full agonist with methadone > morphine, whereas buprenorphine is depicted as a partial agonist (Saidak et al., 2006).

4.2. Transcriptional responses

Using morphine, methadone and buprenorphine we investigated changes in gene expression over time (30 min, 1 h and 4 h after drug administration) in three cerebral brain structures, the thalamus involved in analgesic responses observed with opioid ligands (Dong et al., 1999; Yen et al., 1989; Saadé et al., 1997), and the ventral (nucleus accumbens) and dorsal striatum, both implicated in the transition from recreational drug use to compulsive consumption of drugs of abuse (Lesscher and Vanderschuren, 2012). The dose of morphine (10 mg/kg s.c.) used was based on previous studies in the same rat strain showing gene regulations and conditioned place preference (Garcia et al., 1995; Benturquia et al., 2008; Marie-Claire et al., 2003; Gutstein et al., 1998). This dose corresponded to 3 x ED50 value of morphine determined in the tail-flick assay (Belkaï et al., 2013). The corresponding buprenorphine (0.2 mg/kg) and methadone (3.7 mg/kg) doses are within range commonly used in studies investigating their rewarding properties in the conditioned place preference (Rowlett et al., 1994; Steinpreis et al., 1996; Tzschentke, 2004). Regulations of some immediate early genes (Fos, Egr1, Arc and Homer1) (Fig. 3) as non-specific markers of neural activation, and of six opioid system genes (encoding peptides and receptors) (Figs. 4 and 5) were investigated (Belkaï et al., 2013; Belkaï et al., unpublished results). The overview of the results shows that the regulations are opioid ligand-dependent, time-dependent, and brain structure-dependent.

Regarding Fos mRNA expression, 30 min after acute administration of buprenorphine, a decrease was observed in the nucleus accumbens, while an increase was quantified in the thalamus 1 h after treatment compared to saline-treated rats. With morphine and methadone, a delayed regulation of Fos mRNA was observed, with an increase 4 h after administration of the opioid ligands in the nucleus accumbens, dorsal striatum and thalamus (Fig. 3). For the other immediate early genes investigated, differences in the regulation of Egr1 induced by morphine, methadone and buprenorphine were also observed depending on the brain structure and the withdrawal period after acute administration. In the thalamus, only methadone was able to increase the Egr1 gene



	Morphine	Methadone	Buprenorphine
Nucleus accumbens	○	●	●
Dorsal striatum	△	▲	▲
Thalamus	□	■	■

Fig. 3. Time-course of changes in mRNA encoding immediate early genes.
Sprague-Dawley rats were treated with saline, morphine, methadone or buprenorphine and killed 30 min, 1 h and 4 h after the drug injections. The brains were rapidly removed and the nucleus accumbens, dorsal striatum and thalamus were dissected. Real-time quantitative PCR were performed. (n = 9–12 per group) (modified from Belkaï et al., 2013).

expression 1 h after injection, while 4 h after, the three opioid ligands increased expression of this immediate early gene. Moreover, 4 h after administration morphine and methadone induced an increase of Egr1 in the dorsal striatum, while a decrease was observed with buprenorphine in the nucleus accumbens. Arc was also regulated by acute administration of the opioid agonists, but here again these regulations are ligand-, structure- and time-dependent. A reduction in Homer1 expression was only observed in the dorsal striatum, 4 h after buprenorphine administration. Currently the functional consequences of these complex regulations are not known, but they could be involved in neuroadaptations induced by opioids, as for instance Homer1 as been shown to tune synaptic plasticity in excitatory neurons by regulating the synaptic distribution of GluA2-containing AMPA receptors (Rozov et al., 2012).

Acute injection of the three opioid ligands modulated the expression of the genes encoding endogenous opioid peptides (Pdyn, Penk, POMC) (Fig. 4) and receptors (Oprm1, Oprd1 and Oprk1) (Fig. 5) with different time courses and intensities in the three brain structures studied. The expressions of the genes studied were modulated preferentially in the thalamus and nucleus accumbens at the earliest time point, and in the dorsal striatum at the latest time point studied. Interestingly, methadone and buprenorphine did not produce any common gene expression regulations in the three tested brain structures at any time studied. Moreover the regulations observed suggest that the transcriptional effects of methadone resemble those of morphine more closely than those of buprenorphine in these structures (Belkaï et al., 2013) probably because buprenorphine is not a MOR selective agonist.

5. Importance of administration patterns

5.1. Behavioral and cellular neuroadaptations induced by morphine, methadone and buprenorphine

Very few studies have investigated the influence of the drug administration pattern on both behavioral and neurochemical levels. So, we conducted a series of experiments to explore this factor using two patterns of treatment: one daily repeated injection (ODRI) (one daily injection for 5 or 7 days) or multiple daily repeated injection MDRI (MDRI) (three daily injection for 5 or 7 days) with morphine, methadone or buprenorphine. After the ODRI or MDRI treatment, animals were challenged after different periods of withdrawal either with the same opioid used for the repeated treatment (homologous sensitization) or a different opioid (heterologous sensitization). The three opioids were injected intraperitoneally and except for morphine, equiactive doses of methadone and buprenorphine were used to design the treatment regimen and animals received the same amount of drugs in ODRI and MDRI treatments.

We found that ODRI treatments promoted a more robust behavioral sensitization for all the three opioid agonists as compared to the MDRI patterns. The most important differences were reported with buprenorphine (Allouche et al., 2013; Le Marec et al., 2011). Indeed, no behavioral sensitization was observed with the MDRI treatment that may be due to a lack of withdrawal periods with this pattern of treatment (see above), a state well known to play a key role in the acquisition of sensitization (Rothwell et al., 2010). However, a study

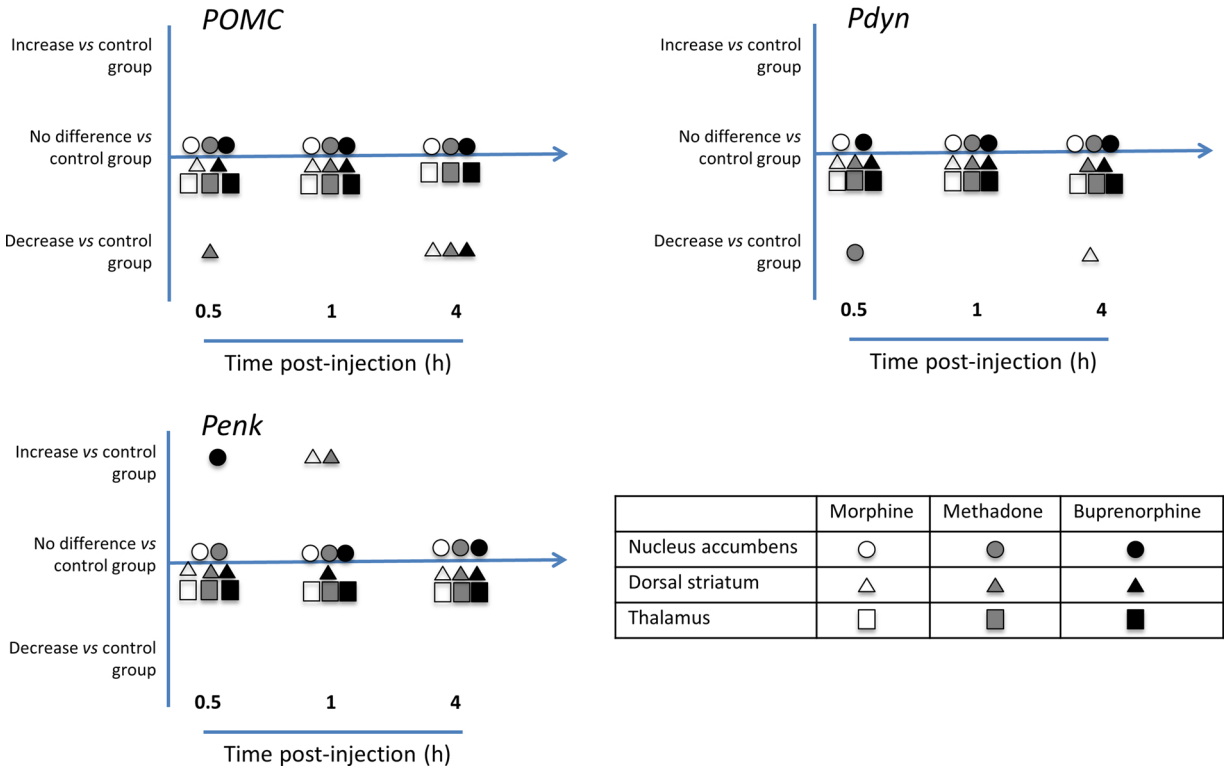


Fig. 4. Time-course of changes in mRNA encoding endogenous opioid peptides.
Sprague-Dawley rats were treated with saline, morphine, methadone or buprenorphine and killed 30 min, 1 h and 4 h after drug injections. The brains were rapidly removed and the nucleus accumbens, dorsal striatum and thalamus were dissected. Real-time quantitative PCR were performed. (n = 9–12 per group) (modified from Belkaï et al., 2013).
Legends: POMC, Pro-opiomelanocortin; Penk; Proenkephalin; Pdyn, prodynorphin.

conducted by Trujillo and co-worked demonstrated that a continuous morphine or fentanyl administration using either osmotic pump or pellets produced locomotor sensitization (Trujillo et al., 2004). Thus, one might argue that the lack of behavioral sensitization with the MDRI buprenorphine treatment is rather due to the partial agonist property of the compound as compared to morphine or fentanyl. Interestingly, the MDRI morphine treatment promoted a transient behavioral sensitization but with a delay (after 14 days of withdrawal), while after one day of withdrawal a reduction of locomotor activity was observed in mice repeatedly treated with morphine. This could be qualified as a tolerance to locomotor effect induced by morphine (Le Marec et al., 2011). This tolerance was probably attributed to the administration pattern, indeed when the same dose of morphine was administered in a ODRI regimen, no tolerance was observed (Le Marec et al., unpublished results).

In order to investigate if some neurochemical modifications could correlate with these behavioral modifications, we measured D1 and D2 dopamine receptor densities in striatum following ODRI and MDRI treatments using radioligand binding assays on brain slices. With morphine, we found that D1 receptors were increased when behavioral sensitization was observed whereas D2 receptors were diminished in the same time. In parallel, when tolerance to locomotor effects of morphine was observed on WD (withdrawal day) 1 after the MDRI treatment, an increase in D2 receptors with a decrease in D1 receptors were measured (Le Marec et al., 2011). These data are in accordance with a role for D1 receptors in acute effects of morphine in locomotion (Serrano et al., 2002). Concerning D2 receptors, our data might be in apparent contradiction with literature where D2 receptor antagonists were found to block morphine sensitization (Serrano et al., 2002). D2 receptors are expressed as two isoforms, D2L mainly described as a post-synaptic receptor and D2S described as a pre-synaptic receptor responsible for the negative feedback on dopamine release (De Mei et al., 2009). One might hypothesize that we detected a decrease of D2S that would reduce the brake on DA release thus facilitating locomotor activity. We also found that MOR was down-regulated in the ventral tegmental area after chronic MDRI morphine treatment. This would reduce inhibitory action of opiates on GABA interneurons, leading to a decrease on dopamine neurons activity, contributing to a lower locomotor activity (tolerance) (Fig. 6).

With the opioid substitution treatments, we found that both ODRI and MDRI treatments induced regulation of D1 and D2 receptors in the striatum with the ODRI treatment promoting a higher number and long-lasting modifications. For instance, ODRI buprenorphine or methadone regimen promoted an increase of D1 receptors and a decrease of D2 receptors at WD35, respectively (Allouche et al., 2015). Whereas correlations between striatal expression of D1 and D2 receptor and sensitization were found with morphine, no evidences for such links were demonstrated with methadone and buprenorphine. One day after withdrawal, an increase in D1 receptors concomitant to a decrease in D2 receptors were measured following buprenorphine and methadone treatment (except for the ODRI methadone treatment) but no behavioral sensitization was observed suggesting a decoupling between dopamine receptor expression and sensitization.

Overall, our data demonstrated that short term (5 or 7 days) repeated treatments with morphine and more importantly with methadone and buprenorphine were able to promote long-lasting neurochemical and behavioral changes in a dynamic way. It can be speculated that these changes also occur in patients, who are very often treated for many years. Our results also strongly suggest that more than the dose, the administration pattern is crucial to influence these changes. This is emphasized by the pioneer works of Vanderschuren and colleagues where they observed a higher behavioral sensitization in rats after a morphine ODRI regimen as compared to the MDRI treatment despite the fact that the rats received a greater amount of morphine in the MDRI regimen (Vanderschuren et al., 1997).

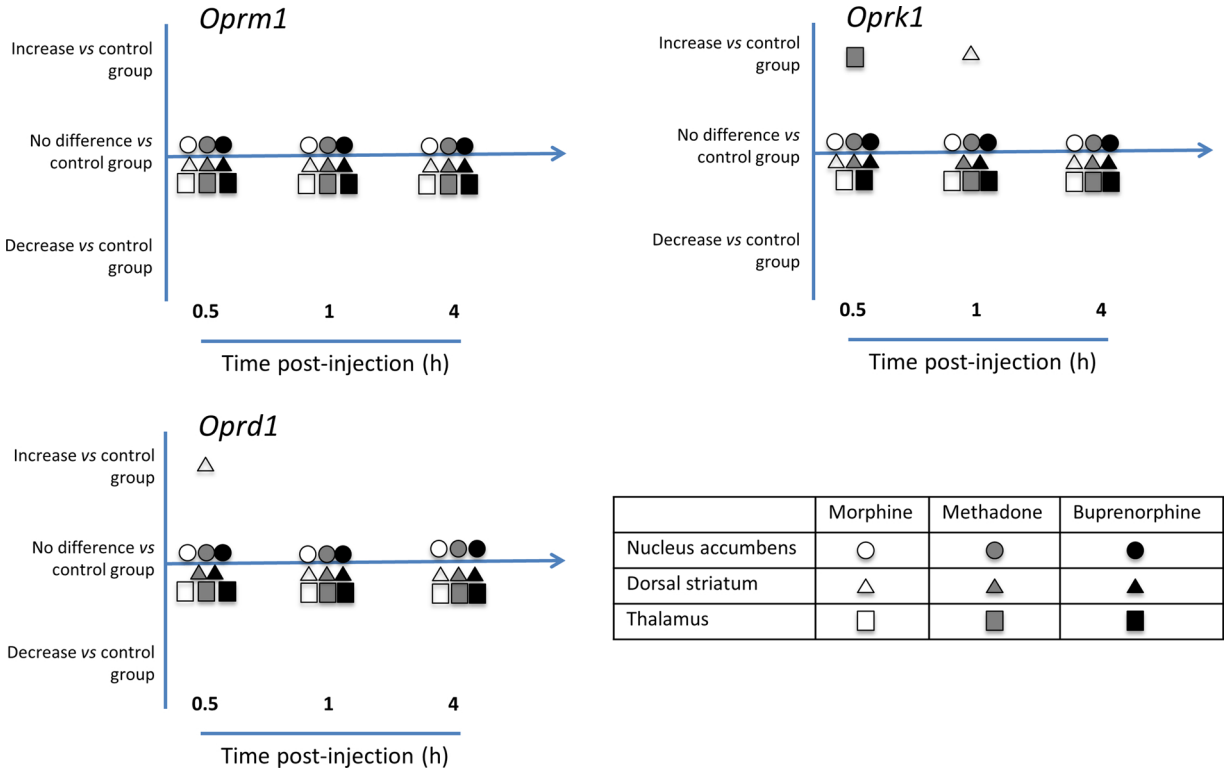


Fig. 5. Time-course of changes in mRNA encoding opioid receptors.
Sprague-Dawley rats were treated with saline, morphine, methadone or buprenorphine and killed 30 min, 1 h and 4 h after drug injections. The brains were rapidly removed and the nucleus accumbens, dorsal striatum and thalamus were dissected. Real-time quantitative PCR were performed. (n = 9–12 per group) (modified from Belkaï et al., 2013).
Legends: Oprm1, mu opioid receptor; Oprd1, delta opioid receptor; Oprk1, kappa opioid receptor.

5.2. Behavioral and cellular neuroadaptations induced by cocaine

Cocaine is a widely abused drug in the world, and addiction to this drug is a major public health problem since there is a lack of specific medication. While the acute effect of this psychostimulant is well characterized (i.e., increases of monoamine levels in the synaptic space by inhibiting their reuptake into presynaptic terminals), the neuroadaptations following a repeated intake remain highly complex. Analysis of literature clearly shows many discrepancies in the results that may be due to distinct experimental procedures. As described above, different patterns of opioid treatment induced distinct behavioral and neurochemical consequences with different time-course (Le Marec et al., 2011; Allouche et al., 2015), thus it could also be speculated that the patterns of cocaine injections play a key role in the development of neuroadaptations observed. To investigate this hypothesis a recent series of experiments have been performed with two different patterns of cocaine treatments. Animals were treated by an ODRI (one administration per day) or a MDRI (three administrations per day) pattern.

As expected, an acute cocaine challenge, one day after the last injection of the chronic treatment (WD1) induced a behavioral sensitization. But more interestingly, the expression of cocaine-induced behavioral sensitization was related to the profile of administration. The MDRI treatment led to sensitization of locomotor effects of cocaine, whereas the ODRI treatment did not (Puig et al., 2012). These results are in good agreement with the literature, showing that the duration and intensity of sensitization are dependent on the administration patterns (Kalivas and Duffy, 1993; Davidson et al., 2002; King et al., 1994b). Interestingly, the locomotor sensitization observed in the MDRI group was associated to a dopamine release sensitization in the nucleus accumbens after a cocaine challenge (Puig et al., 2012). As previous studies showed that D1 and D2 dopamine receptors play a role in the development and expression of behavioral sensitization (Li et al., 2000; McCreary and Marsden, 1993; Nelson et al., 2012; Sim et al., 2013; Tobón and Kuzhikandathil, 2014; Thompson et al., 2010), it was also interesting to evaluate the consequences of the ODRI and MDRI cocaine administration patterns on dopamine receptor regulations, in different brain structures forming the two major dopaminergic pathways in the brain: the ventral tegmental area and the nucleus accumbens for the mesolimbic pathway, and the substantia sigra and the caudate putamen for the nigrostriatal pathway. These two pathways play a key role in the rewarding effects (Hyman, 1996) and the locomotor adaptations (Kalivas et al., 1992) following repeated administrations of cocaine. On WD1, using autoradiography approaches we observed modifications of D1 receptors after the MDRI chronic cocaine treatment pattern in the substantia nigra (increase) and in the caudate putamen and nucleus accumbens (decrease), while no modifications were observed after the ODRI pattern, suggesting that multiple daily injections are needed to induce early D1 receptor modifications (Puig et al., 2014). Regarding regulation of D2 receptors, densities were modified by both cocaine administration patterns, and interestingly they were opposite depending on the administration patterns, in the four brain structures studied (Puig et al., 2014). Regulations of dopamine receptors are long lasting, as on WD14 densities of D1 and D2 receptors were still different in cocaine treated animals as compared to control rats. Surprisingly the modifications observed were different from those observed on WD1 for both cocaine administration patterns, leading to the down-regulations of D1 and D2 receptors in most of the brain structures studied (Puig et al., 2014). Interestingly, these changes in dopamine receptor densities are certainly indirect via modulation of synaptic dopamine concentrations, as cocaine is not a dopamine ligand, but inhibits dopamine reuptake via blockade of the transporter located on the presynaptic neurons.

All together, these results show that the behavioral and neurochemical adaptations induced by chronic cocaine treatments are

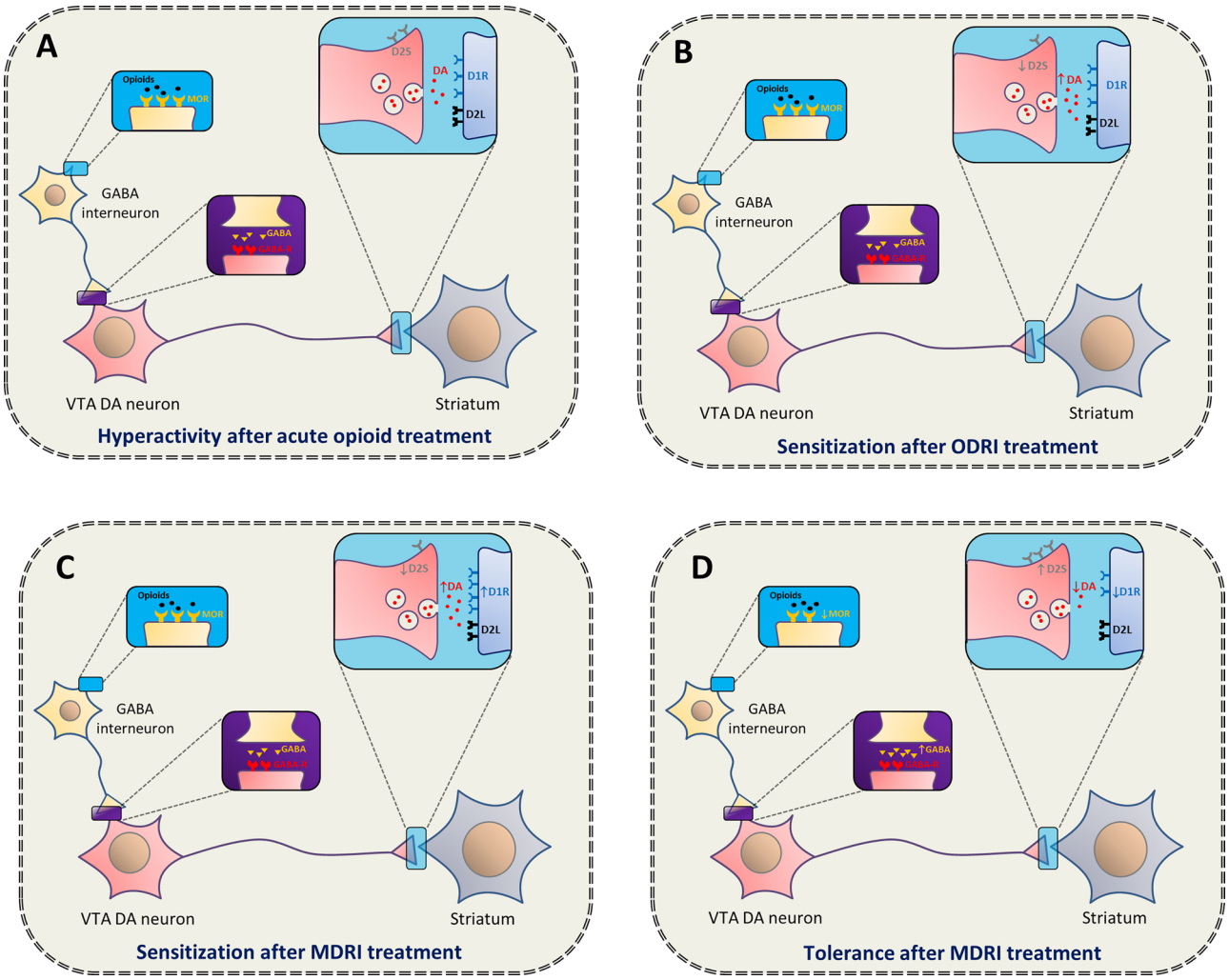


Fig. 6. Mechanisms leading to sensitization or tolerance following different patterns of chronic morphine treatment.
The main mechanism for opioid to increase locomotor activity is through their activation of MOR in GABAergic interneurons in VTA. Indeed, MOR activation will decrease interneurons activity and thereby release the brake on the DA VTA neuron. It will result a dopamine release that will activate striatal D1R to increase locomotor activity (A). The behavioral sensitization following morphine ODRI and MDRI treatments was accompanied by a decrease of D2R in striatum that could be D2S (B, C). This down-regulation would reduce the negative feedback on DA release thus contributing to hyperactivity. Sensitization after MDRI regimen also correlated with a D1R increase that would directly favor hyperlocomotion (C). The transient tolerance to morphine locomotor effect observed after MDRI treatment might be due to (D): a decrease of MOR in VTA that would disinhibit GABAergic interneurons and thus reduce DA neurons activity; an increase of D2R (presumably D2S) in striatum that would increase negative feedback on DA release; a decrease of D1R that reduce directly reduce locomotor activity.
Legends: DA: dopamine; D1R: dopamine D1 receptor; D2S: short isoform of dopamine D2 receptor (presynaptic); D2L: long isoform of dopamine D2 receptor (mostly postsynaptic); GABA: γ-aminobutyric acid; GABA-R: ionotropic GABA receptors; MOR: mu opioid receptor; Opioids: morphine (A, B, C, D), methadone (A) or buprenorphine (A); VTA: ventral tegmental area. ODRI: one daily repeated injection; MDRI: multiple daily repeated injections.

depending on the cocaine administration patterns, the brain structures considered, and the withdrawal periods as described in other studies (King et al., 1994a; Izenwasser and French, 2002; Calipari et al., 2013, 2014; Zhou and Kreek, 2015). As previously described with opioid ligands, the changes observed are dynamic as they develop in a time-dependent manner.

6. Conclusions

The neuroplasticity, both at behavioral and neurochemical levels, observed following chronic opioid or cocaine treatments (even for short period) are dynamic and long lasting, and are dependent on numerous factors. The objectives of this review were to illustrate that the complexity of the neuroadaptations and the divergent results reported in the literature following chronic treatments with drugs of abuse are specific to the agonists used, the patterns of administration, and the withdrawal periods. The behavioral and neurochemical neuroadaptations are different on early, intermediate and protracted abstinence. They develop in a dynamic way, and they are also dependent on several factors, including pharmacodynamic factors (e.g., binding parameters of different ligands on the same target/receptor), and pharmacokinetic factors (e.g., speed and route of administration, transport across the BBB, patterns of administration). This review was focused on the results obtained with experimenter-administered drugs of abuse, the only method to control the exact doses and frequencies of administration. Other data in the literature also report different neuroadaptations depending on the temporal pattern of drug administration in a model of self-administration in rats, with short-, long- and intermittent-access to the drugs (Calipari et al., 2013, 2014; Allain et al., 2015), highlighting the importance of pharmacokinetics in the molecular and cellular mechanisms critical for addiction.

As the same factors of variability are also encountered in drug users, they can certainly largely contribute to the heterogeneity of patients and explain the difficulties encountered by clinicians in the therapeutic

management. The clinical challenge is to stratified the patients with biological and/or behavioral markers, to propose a personnalized treatment adapted to specific neuroadaptation developed, certainly the only way to reduce relapse, and to aid in recovery from addiction. This is a huge challenge, because the full medical history of drug-dependent patients is rarely available. One way to improve this aspect would be to systematically include questionnaires about their drug consumption (e.g., quantities, frequencies) in the interviews.

References

Abdallah, K., Gendron, L., 2017. The delta opioid receptor in pain control. Handb. Exp. Pharmacol Epub ahead of print.

Abreu, M.E., Bigelow, G.E., Fleisher, L., Walsh, S.L., 2001. Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. Psychopharmacology (Berl.) 154, 76–84.

Allain, F., Minogianis, E.-A., Roberts, D.C.S., Samaha, A.-N., 2015. How fast and how often: the pharmacokinetics of drug use are decisive in addiction. Neurosci. Biobehav. Rev. 56, 166–179.

Allouche, S., Le Marec, T., Noble, F., Marie, N., 2013. Different patterns of administration modulate propensity of methadone and buprenorphine to promote locomotor sensitization in mice. Prog. Neuropsychopharmacol. Biol. Psychiatry 40, 286–291.

Allouche, S., Le Marec, T., Coquerel, A., Noble, F., Marie, N., 2015. Striatal dopamine D1 and D2 receptors are differentially regulated following buprenorphine or methadone treatment. Psychopharmacology (Berl.) 232, 1527–1533.

Bartels, A.L., Kortekaas, R., Bart, J., Willemsen, A.T.M., de Klerk, O.L., de Vries, J.J., van Oostrom, J.C.H., Leenders, K.L., 2009. Blood-brain barrier P-glycoprotein function decreases in specific brain regions with aging: a possible role in progressive neurodegeneration. Neurobiol. Aging 30, 1818–1824.

Belkaï, E., Crété, D., Courtin, C., Noble, F., Marie-Claire, C., 2013. Comparison of the transcriptional responses induced by acute morphine, methadone and buprenorphine. Eur. J. Pharmacol. 711, 10–18.

Benturquia, N., Le Marec, T., Scherrmann, J.-M., Noble, F., 2008. Effects of nitrous oxide on dopamine release in the rat nucleus accumbens and expectation of reward. Neuroscience 155, 341–344.

Brown, S.M., Holtzman, M., Kim, T., Kharasch, E.D., 2011. Buprenorphine metabolites, buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, are biologically active. Anesthesiology 115, 1251–1260.

Bruce, R.D., McCance-Katz, E., Kharasch, E.D., Moody, D.E., Morse, G.D., 2006. Pharmacokinetic interactions between buprenorphine and antiretroviral medications. Clin. Infect. Dis. 43 (Suppl. 4), S216–223.

Calipari, E.S., Ferris, M.J., Zimmer, B.A., Roberts, D.C.S., Jones, S.R., 2013. Temporal pattern of cocaine intake determines tolerance vs sensitization of cocaine effects at the dopamine transporter. Neuropsychopharmacol. 38, 2385–2392.

Calipari, E.S., Ferris, M.J., Siciliano, C.A., Zimmer, B.A., Jones, S.R., 2014. Intermittent cocaine self-administration produces sensitization of stimulant effects at the dopamine transporter. J. Pharmacol. Exp. Ther. 349, 192–198.

Charbogne, P., Kieffer, B.L., Befort, K., 2014. 15 years of genetic approaches in vivo for addiction research: opioid receptor and peptide gene knockout in mouse models of drug abuse. Neuropharmacology 76 (Pt. B), 204–217.

Comer, S.D., Collins, E.D., MacArthur, R.B., Fischman, M.W., 1999. Comparison of intravenous and intranasal heroin self-administration by morphine-maintained humans. Psychopharmacology (Berl.) 143, 327–338.

Comer, S.D., Ashworth, J.B., Sullivan, M.A., Vosburg, S.K., Saccone, P.A., Foltin, R.W., 2009. Relationship between rate of infusion and reinforcing strength of oxycodone in humans. J. Opioid Manag. 5, 203–212.

Davidson, C., Lazarus, C., Lee, T.H., Ellinwood, E.H., 2002. Behavioral sensitization is greater after repeated versus single chronic cocaine dosing regimens. Eur. J. Pharmacol. 441, 75–78.

De Gregori, S., De Gregori, M., Ranzani, G.N., Allegri, M., Minella, C., Regazzi, M., 2012. Morphine metabolism, transport and brain disposition. Metab. Brain Dis. 27, 1–5.

de Klerk, O.L., Willemsen, A.T.M., Roosink, M., Bartels, A.L., Hendrikse, N.H., Bosker, F.J., den Boer, J.A., 2009. Locally increased P-glycoprotein function in major depression: a PET study with [11C]verapamil as a probe for P-glycoprotein function in the blood-brain barrier. Int. J. Neuropsychopharmacol. 12, 895–904.

de Klerk, O.L., Willemsen, A.T.M., Bosker, F.J., Bartels, A.L., Hendrikse, N.H., den Boer, J.A., Dierckx, R.A., 2010. Regional increase in P-glycoprotein function in the blood-brain barrier of patients with chronic schizophrenia: a PET study with [(11)C]verapamil as a probe for P-glycoprotein function. Psychiatry Res. 183, 151–156.

De Mei, C., Ramos, M., Iitaka, C., Borrelli, E., 2009. Getting specialized: presynaptic and postsynaptic dopamine D2 receptors. Curr. Opin. Pharmacol. 9, 53–58.

de Wit, H., Dudish, S., Ambre, J., 1993. Subjective and behavioral effects of diazepam depend on its rate of onset. Psychopharmacology (Berl.) 112, 324–330.

Dhawan, B.N., Cesselin, F., Raghubir, R., Reisine, T., Bradley, P.B., Portoghese, P.S., Hamon, M., 1996. International Union of Pharmacology. XII. Classification of opioid receptors. Pharmacol. Rev. 48, 567–592.

Dong, Y.F., Tang, J.S., Yuan, B., Jia, H., 1999. Morphine applied to the thalamic nucleus submedius produces a naloxone reversible antinociceptive effect in the rat. Neurosci. Lett. 271, 17–20.

Falcon, E., Browne, C.A., Leon, R.M., Fleites, V.C., Sweeney, R., Kirby, L.G., Lucki, I., 2016. Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors. Neuropsychopharmacology 41, 2344–2351.

Fernàndez-Castillo, N., Orejarena, M.J., Ribasés, M., Blanco, E., Casas, M., Robledo, P., Maldonado, R., Cormand, B., 2012. Active and passive MDMA ('ecstasy') intake induces differential transcriptional changes in the mouse brain. Genes Brain Behav. 11, 38–51.

Flórez-Salamanca, L., Secades-Villa, R., Hasin, D.S., Cottler, L., Wang, S., Grant, B.F., Blanco, C., 2013. Probability and predictors of transition from abuse to dependence on alcohol, cannabis, and cocaine: results from the national epidemiologic survey on alcohol and related conditions. Am. J. Drug Alcohol Abuse 39, 168–179.

Frölich, N., Dees, C., Paetz, C., Ren, X., Lohse, M.J., Nikolaev, V.O., Zenk, M.H., 2011. Distinct pharmacological properties of morphine metabolites at G(i)-protein and β-arrestin signaling pathways activated by the human μ-opioid receptor. Biochem. Pharmacol. 81, 1248–1254.

Garcia, M.M., Brown, H.E., Harlan, R.E., 1995. Alterations in immediate-early gene proteins in the rat forebrain induced by acute morphine injection. Brain Res. 692, 23–40.

Gatley, S.J., Pan, D., Chen, R., Chaturvedi, G., Ding, Y.S., 1996. Affinities of methylphenidate derivatives for dopamine, norepinephrine and serotonin transporters. Life Sci. 58, 231–239.

Gutstein, H.B., Thome, J.L., Fine, J.L., Watson, S.J., Akil, H., 1998. Pattern of c-fos mRNA induction in rat brain by acute morphine. Can. J. Physiol. Pharmacol. 76, 294–303.

Handal, M., Grung, M., Skurtveit, S., Ripel, A., Mørland, J., 2002. Pharmacokinetic differences of morphine and morphine-glucuronides are reflected in locomotor activity. Pharmacol. Biochem. Behav. 73, 883–892.

Hatsukami, D.K., Fischman, M.W., 1996. Crack cocaine and cocaine hydrochloride. Are the differences myth or reality? JAMA 276, 1580–1588.

Huang, P., Kehner, G.B., Cowan, A., Liu-Chen, L.Y., 2001. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. J. Pharmacol. Exp. Ther. 297, 688–695.

Hyman, S.E., 1996. Addiction to cocaine and amphetamine. Neuron 16, 901–904.

Inturrisi, C.E., Schultz, M., Shin, S., Umans, J.G., Angel, L., Simon, E.J., 1983. Evidence from opiate binding studies that heroin acts through its metabolites. Life Sci. 33 (Suppl. 1), 773–776.

Izenwasser, S., French, D., 2002. Tolerance and sensitization to the locomotor-activating effects of cocaine are mediated via independent mechanisms. Pharmacol. Biochem. Behav. 73, 877–882.

Jacobs, E.H., Smit, A.B., de Vries, T.J., Schoffelmeer, A.N.M., 2003. Neuroadaptive effects of active versus passive drug administration in addiction research. Trends Pharmacol. Sci. 24, 566–573.

Jacobs, E.H., de Vries, T.J., Smit, A.B., Schoffelmeer, A.N.M., 2004. Gene transcripts selectively down-regulated in the shell of the nucleus accumbens long after heroin self-administration are up-regulated in the core independent of response contingency. FASEB J. 18, 200–202.

Jacobs, E.H., Smit, A.B., de Vries, T.J., Schoffelmeer, A.N.M., 2005. Long-term gene expression in the nucleus accumbens following heroin administration is subregion-specific and depends on the nature of drug administration. Addict. Biol. 10, 91–100.

Kalivas, P.W., Duffy, P., 1993. Time course of extracellular dopamine and behavioral sensitization to cocaine. II. Dopamine perikarya. J. Neurosci. 13, 276–284.

Kalivas, P.W., Striplin, C.D., Steketee, J.D., Klitenick, M.A., Duffy, P., 1992. Cellular mechanisms of behavioral sensitization to drugs of abuse. Ann. N. Y. Acad. Sci. 654, 128–135.

King, G.R., Ellinwood, E.H., Silvia, C., Joyner, C.M., Xue, Z., Caron, M.G., Lee, T.H., 1994a. Withdrawal from continuous or intermittent cocaine administration: changes in D2 receptor function. J. Pharmacol. Exp. Ther. 269, 743–749.

King, G.R., Joyner, C., Ellinwood, E.H., 1994b. Continuous or intermittent cocaine administration: effects of flupenthixol treatment during withdrawal. Pharmacol. Biochem. Behav. 49, 883–889.

King, M., Su, W., Chang, A., Zuckerman, A., Pasternak, G.W., 2001. Transport of opioids from the brain to the periphery by P-glycoprotein: peripheral actions of central drugs. Nat. Neurosci. 4, 268–274.

Klenowski, P., Morgan, M., Bartlett, S.E., 2015. The role of δ-opioid receptors in learning and memory underlying the development of addiction. Br. J. Pharmacol. 172, 297–310.

Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 3, 760–773.

Le Marec, T., Marie-Claire, C., Noble, F., Marie, N., 2011. Chronic and intermittent morphine treatment differently regulates opioid and dopamine systems: a role in locomotor sensitization. Psychopharmacology (Berl.) 216, 297–303.

Leshner, A.I., 1997. Addiction is a brain disease, and it matters. Science 278, 45–47.

Lesscher, H.M.B., Vanderschuren, L.J.M.J., 2012. Compulsive drug use and its neural substrates. Rev. Neurosci. 23, 731–745.

Li, Y., White, F.J., Wolf, M.E., 2000. Pharmacological reversal of behavioral and cellular indices of cocaine sensitization in the rat. Psychopharmacology (Berl.) 151, 175–183.

Linnet, K., Ejsing, T.B., 2008. A review on the impact of P-glycoprotein on the penetration of drugs into the brain. Focus on psychotropic drugs. Eur. Neuropsychopharmacol. 18, 157–169.

Lötsch, J., Skarke, C., Wieting, J., Oertel, B.G., Schmidt, H., Brockmöller, J., Geisslinger, G., 2006. Modulation of the central nervous effects of levomethadone by genetic polymorphisms potentially affecting its metabolism, distribution, and drug action. Clin. Pharmacol. Ther. 79, 72–89.

Lutfy, K., Cowan, A., 2004. Buprenorphine: a unique drug with complex pharmacology. Curr. Neuropharmacol. 2, 395–402.

Marie-Claire, C., Laurendeau, I., Canestrelli, C., Courtin, C., Vidaud, M., Roques, B., Noble, F., 2003. Fos but not Cart (cocaine and amphetamine regulated transcript) is overexpressed by several drugs of abuse: a comparative study using real-time quantitative polymerase chain reaction in rat brain. Neurosci. Lett. 345, 77–80.

Marie-Claire, C., Salzmann, J., David, A., Courtin, C., Canestrelli, C., Noble, F., 2007. Rnd

family genes are differentially regulated by 3,4-methylenedioxymethamphetamine and cocaine acute treatment in mice brain. Brain Res. 1134, 12–17.
Matthes, H.W., Maldonado, R., Simonin, F., Valverde, O., Slowe, S., Kitchen, I., Befort, K., Dierich, A., Le Meur, M., Dollé, P., Tzavara, E., Hanoune, J., Roques, B.P., Kieffer, B.L., 1996. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. Nature 383, 819–823.
McCreary, A.C., Marsden, C.A., 1993. Cocaine-induced behaviour: dopamine D1 receptor antagonism by SCH 23390 prevents expression of conditioned sensitisation following repeated administration of cocaine. Neuropharmacology 32, 387–391.
Mégarbane, B., Marie, N., Pirnay, S., Borron, S.W., Gueye, P.N., Risède, P., Monier, C., Noble, F., Baud, F.J., 2006. Buprenorphine is protective against the depressive effects of norbuprenorphine on ventilation. Toxicol. Appl. Pharmacol. 212, 256–267.
Nelson, A.B., Hang, G.B., Grueter, B.A., Pascoli, V., Luscher, C., Malenka, R.C., Kreitzer, A.C., 2012. A comparison of striatal-dependent behaviors in wild-type and hemizygous Drd1a and Drd2 BAC transgenic mice. J. Neurosci. 32, 9119–9123.
Noble, F., Sanchez, M., Lowenstein, W., 2007. Interest for delivery of cocaethylene in a sustained release emulsion vs saline evaluated on behavioral sensitization in naive and cocaine-sensitized mice. Psychopharmacology (Berl.) 193, 415–421.
Ohtani, M., Kotaki, H., Sawada, Y., Iga, T., 1995. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. J. Pharmacol. Exp. Ther. 272, 505–510.
Peppin, J.F., Raffa, R.B., 2015. Delta opioid agonists: a concise update on potential therapeutic applications. J. Clin. Pharm. Ther. 40, 155–166.
Puig, S., Noble, F., Benturquia, N., 2012. Short- and long-lasting behavioral and neurochemical adaptations: relationship with patterns of cocaine administration and expectation of drug effects in rats. Transl. Psychiatry 2, e175.
Puig, S., Marie, N., Benturquia, N., Noble, F., 2014. Influence of cocaine administration patterns on dopamine receptor regulation. Psychopharmacology (Berl.) 231, 3131–3137.
Rance, M.J., 1979. Animal and molecular pharmacology of mixed agonist-antagonist analgesic drugs. Br. J. Clin. Pharmacol. 7 (Suppl. 3), 281S–286S.
Robinson, S.A., Erickson, R.L., Browne, C.A., Lucki, I., 2017. A role for the mu opioid receptor in the antidepressant effects of buprenorphine. Behav. Brain Res. 319, 96–103.
Roeckel, L.-A., Utard, V., Reiss, D., Mouheiche, J., Maurin, H., Robé, A., Audouard, E., Wood, J.N., Goumon, Y., Simonin, F., Gaveriaux-Ruff, C., 2017. Morphine-induced hyperalgesia involves mu opioid receptors and the metabolite morphine-3-glucuronide. Sci. Rep. 7, 10406.
Rook, E.J., Huitema, A.D.R., van den Brink, W., van Ree, J.M., Beijnen, J.H., 2006. Pharmacokinetics and pharmacokinetic variability of heroin and its metabolites: review of the literature. Curr. Clin. Pharmacol. 1, 109–118.
Rothwell, P.E., Gewirtz, J.C., Thomas, M.J., 2010. Episodic withdrawal promotes psychomotor sensitization to morphine. Neuropsychopharmacol. 35, 2579–2589.
Rowlett, J.K., Gibson, T.R., Bardo, M.T., 1994. Dissociation of buprenorphine-induced locomotor sensitization and conditioned place preference in rats. Pharmacol. Biochem. Behav. 49, 241–245.
Rozov, A., Zivkovic, A.R., Schwarz, M.K., 2012. Homer1 gene products orchestrate Ca (2+)-permeable AMPA receptor distribution and LTP expression. Front. Synaptic Neurosci. 4, 4.
Saadé, N.E., Atweh, S.F., Bahuth, N.B., Jabbur, S.J., 1997. Augmentation of nociceptive reflexes and chronic deafferentation pain by chemical lesions of either dopaminergic terminals or midbrain dopaminergic neurons. Brain Res. 751, 1–12.
Saidak, Z., Blake-Palmer, K., Hay, D.L., Northup, J.K., Glass, M., 2006. Differential activation of G-proteins by mu-opioid receptor agonists. Br. J. Pharmacol. 147, 671–680.
Samaha, A.-N., Mallet, N., Ferguson, S.M., Gonon, F., Robinson, T.E., 2004. The rate of cocaine administration alters gene regulation and behavioral plasticity: implications for addiction. J. Neurosci. 24, 6362–6370.
Seleman, M., Chapy, H., Cisternino, S., Courtin, C., Smirnova, M., Schlatter, J., Chiadmi, F., Scherrmann, J.-M., Noble, F., Marie-Claire, C., 2014. Impact of P-glycoprotein at the blood-brain barrier on the uptake of heroin and its main metabolites: behavioral effects and consequences on the transcriptional responses and reinforcing properties. Psychopharmacology (Berl.) 231, 3139–3149.
Selley, D.E., Cao, C.C., Sexton, T., Schwegel, J.A., Martin, T.J., Childers, S.R., 2001. mu opioid receptor-mediated G-protein activation by heroin metabolites: evidence for greater efficacy of 6-monoacetylmorphine compared with morphine. Biochem. Pharmacol. 62, 447–455.
Serrano, A., Aguilar, M.A., Manzanedo, C., Rodríguez-Arias, M., Miñarro, J., 2002. Effects of DA D1 and D2 antagonists on the sensitisation to the motor effects of morphine in mice. Prog. Neuropsychopharmacol. Biol. Psychiatry 26, 1263–1271.
Sim, H.-R., Choi, T.-Y., Lee, H.J., Kang, E.Y., Yoon, S., Han, P.-L., Choi, S.-Y., Baik, J.-H., 2013. Role of dopamine D2 receptors in plasticity of stress-induced addictive behaviours. Nat. Commun. 4, 1579.
Steinpreis, R.E., Rutell, A.L., Parrett, F.A., 1996. Methadone produces conditioned place preference in the rat. Pharmacol. Biochem. Behav. 54, 339–341.
Strange, P.G., 2008. Agonist binding, agonist affinity and agonist efficacy at G protein-coupled receptors. Br. J. Pharmacol. 153, 1353–1363.
Thompson, D., Martini, L., Whistler, J.L., 2010. Altered ratio of D1 and D2 dopamine receptors in mouse striatum is associated with behavioral sensitization to cocaine. PLoS One 5, e11038.
Tobón, K.E., Kuzhikandathil, E.V., 2014. Preadolescent drd1-EGFP mice exhibit cocaine-induced behavioral sensitization. Neurosci. Lett. 558, 20–25.
Trujillo, K.A., Kubota, K.S., Warmoth, K.P., 2004. Continuous administration of opioids produces locomotor sensitization. Pharmacol. Biochem. Behav. 79, 661–669.
Tzschentke, T.M., 2004. Reassessment of buprenorphine in conditioned place preference: temporal and pharmacological considerations. Psychopharmacology (Berl.) 172, 58–67.
Upton, R.N., Semple, T.J., Macintyre, P.E., 1997. Pharmacokinetic optimisation of opioid treatment in acute pain therapy. Clin. Pharmacokinet. 33, 225–244.
Vanderschuren, L.J., Tjon, G.H., Nestby, P., Mulder, A.H., Schoffelmeer, A.N., De Vries, T.J., 1997. Morphine-induced long-term sensitization to the locomotor effects of morphine and amphetamine depends on the temporal pattern of the pretreatment regimen. Psychopharmacology (Berl.) 131, 115–122.
Volkow, N.D., Swanson, J.M., 2003. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. Am. J. Psychiatry 160, 1909–1918.
Volkow, N.D., Wang, G.-J., Fowler, J.S., Tomasi, D., Telang, F., Baler, R., 2010. Addiction: decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. BioEssays 32, 748–755.
Westin, U.E., Boström, E., Gråsjö, J., Hammarlund-Udenaes, M., Björk, E., 2006. Direct nose-to-brain transfer of morphine after nasal administration to rats. Pharm. Res. 23, 565–572.
Xie, R., Hammarlund-Udenaes, M., de Boer, A.G., de Lange, E.C., 1999. The role of P-glycoprotein in blood-brain barrier transport of morphine: transcortical microdialysis studies in mdr1a (-/-) and mdr1a (+/+) mice. Br. J. Pharmacol. 128, 563–568.
Yen, C.T., Fu, T.C., Chen, R.C., 1989. Distribution of thalamic nociceptive neurons activated from the tail of the rat. Brain Res. 498, 118–122.
Yousif, S., Saubaméa, B., Cisternino, S., Marie-Claire, C., Dauchy, S., Scherrmann, J.-M., Declèves, X., 2008. Effect of chronic exposure to morphine on the rat blood-brain barrier: focus on the P-glycoprotein. J. Neurochem. 107, 647–657.
Zhou, Y., Kreek, M.J., 2015. Persistent increases in rat hypothalamic POMC gene expression following chronic withdrawal from chronic "binge" pattern escalating-dose, but not steady-dose, cocaine. Neuroscience 289, 63–70.