NEUROTENSIN: A ROLE IN SUBSTANCE USE DISORDER?

Luca Ferraro[1,2], Laura Tiozzo Fasiolo[1], Sarah Beggiato[3], Andrea Celeste Borelli[3], Lucyna Pomierny-Chamiolo[4], Malgorzata Frankowska[5], Tiziana Antonelli[3], Maria Cristina Tomasini[1], Kjell Fuxe[3], Malgorzata Filip[5]

[1]Department of Life Sciences and Biotechnology and [2]LTTA, University of Ferrara, Italy; [3]Department of Medical Sciences, University of Ferrara, Italy; [4]Department of Toxicology, Faculty of Pharmacy, Jagiellonian University, Medical College, Kraków, Poland; [5]Laboratory of Drug Addiction Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland.

Running Head: Neurotensin and drug addiction

Corresponding author: Prof. Luca Ferraro, Department of Life Sciences and Biotechnology, University of Ferrara, Via Fossato di Mortara 17-19 (Pharmacology), 44121 Ferrara, Italy. Tel 0039-0532 455276; Fax: 0039-0532 455205; e-mail: frl@unife.it

Abstract

Neurotensin is a tridecapetide originally identified in extracts of bovine hypothalamus. This peptide has a close anatomical and functional relationship with the mesocorticolimbic and neostriatal dopamine system. Neural circuits containing neurotensin have been originally proposed to play a role in the mechanism of action of antipsychotic agents. Additionally, neurotensin containing pathways have been demonstrated to mediate some of the rewarding and/or sensitizing properties of drugs of abuse.

This review attempts to contribute to the understanding of the role of neurotensin and its receptors in drug abuse. In particular, the potential relevance of neurotensin, its related compounds and neurotensin receptors in substance use disorders will be summarized by focusing on preclinical research.

General introduction

Neurotensin (NT), a tridecapetide originally identified in extracts of bovine hypothalami by Carraway and Leeman (1973), is widely distributed in the central nervous system (CNS) and in the periphery including the gut, pancreas and adrenal glands (Carraway and Leeman, 1976; Kitabgi et al., 1976). The biological actions of NT are initiated by binding to three different receptor subtypes NTS1, NTS2 and NTS3 (Geisler et al., 2006; Mazella and Vincent, 2006). NTS1 and NTS2 receptors belong to the family of G-protein-coupled receptors (Pelaprat, 2006). These NT receptor subtypes differ in their affinity for NT and their sensitivity to levocabastine, an antihistaminic compound: NTS1 receptor is levocabastine-insensitive with a high affinity for NT, whereas NTS2 receptor is levocabastine-sensitive with a low affinity for NT (Vincent et al., 1999; St-Gelais et al., 2006). NTS1 receptor is the best characterized NT receptor subtype. It is functionally coupled to the phospholipase C and the inositol phosphate signalling cascade, but its activation has been also associated with cyclic guanosine monophosphate, cyclic adenosine monophosphate and arachidonic acid production along with mitogen-activated protein (MAP) kinase phosphorylation. The transduction mechanisms of NTS2 receptor remain a matter of controversy (Mazella and Vincent, 2006). NTS3 is structurally unrelated to these receptors, belongs to the family of sorting receptors and modulates NT intracellular signaling processes (Mazella and Vincent, 2006). By interacting with its receptors, NT is known to exert several effects in mammals, including analgesia, hypothermia, neuroendocrinic control of thyroid hormones, regulation of blood pressure and body weight homeostasis. NT is also deeply involved in immunity and inflammation, but its true role in these events still remains to be elucidated (Katsanos et al., 2008), as well as its relevance in cancer development and progression (Myers et al., 2009). When injected systemically, NT decreases blood pressure, gastric motility, gastric acid secretion and induces hyperglycemia.

The differential regional distribution of NT in the brain, the presence of NT receptors in different brain areas such as cortical, striatal and limbic regions, of sodium and calcium dependent NT release and the involvement of NT in several electrophysiological and behavioural responses (Carraway and Leeman, 1973; Kitabgi et al., 1989; Tanganelli et al., 1994; Vincent et al., 1999; St-Gelais et al., 2006), suggest that this peptide acts as a neurotransmitter or neuromodulator in the mammalian CNS. In this context, the effects of NT include the well-documented interaction of the peptide with dopaminergic (DAergic) systems (von Euler and Fuxe, 1987; Kitabgi et al., 1989; Rostène et al., 1992; Geisler et al., 2006). This is mainly due to an antagonistic action of the activated NTS1 on dopamine (DA) D2 receptor recognition and signaling via an intramembrane NTS1/DA D2 receptor-receptor interaction (von Euler and Fuxe, 1987; von Euler, 1991; von Euler et al., 1991; Fuxe et al., 1992; Antonelli et al., 2007a).

NT also appears to modulate the activity of other neurotransmitter circuits that are innervated by the DA system. Neural circuits containing NT have been originally proposed to play a role in the mechanism of action of antipsychotic agents (Nemeroff, 1980; Kinkead and Nemeroff, 2004; Boules et al., 2007; Boules et al., 2014). In particular, the interaction between NT and DA has been implicated in the pathogenesis and treatment of schizophrenia (Nemeroff et al., 1983; Caceda et al., 2006; LaCrosse and Olive, 2013; Tanganelli et al., 2012; Boules et al., 2014). In fact, it has been reported that NT and NT agonists possess neuroleptic-like properties in DA-mediated animal models of psychosis, such as amphetamine-induced locomotor activity, apomorphine-induced climbing, and drug-induced disruption of prepulse inhibition (PPI) (Nemeroff et al., 1983; Kalivas et al., 1983; 1984; Boules et al., 2001; Shilling et al., 2003).

Besides DA systems, growing evidence suggest that NT may also play an important role in the modulation of aminoacidergic transmission in the basal ganglia and cerebral cortex (Antonelli et al., 2007b; Ferraro et al., 2008; 2009). In particular, NT amplifies glutamate transmission and enhances glutamate-induced excitotoxicity. The hypothesis was therefore introduced that NT may be involved in ischemic brain damage and neurodegenerative disorders (Antonelli et al., 2007b; 2008; Ferraro et al., 2009). Several reviews on the relevance of NT in schizophrenia and neurodegenerative disorders have been published (Kinkead and Nemeroff, 2004; StGelais et al., 2006; Antonelli 2007a; Ferraro et al., 2008; 2009; Tanganelli et al., 2012; LaCrosse and Olive, 2013; Boules et al., 2014), underlining evidence that NT receptor agonists or antagonists may represent novel antipsychotic and neuroprotective drugs, respectively. In contrast, the important role played by central NT receptor mechanisms in drug addiction has only partially been reviewed (Ferraro et al., 2007; Boules et al., 2014), which is true also regarding their relevance for drug abuse treatment. This is probably due to the complex and partially controversial results emerging from the studies in this field. They demonstrate that the effect of NT depends on many parameters such as the dose used, the injection procedure and the NT receptor reached, as well as the experimental model or species used. Nevertheless, the possible implication of NT in drug abuse (StGelais et al., 2006) is supported by substantial experimental evidence and the similarities between certain NT- and psychostimulant drug-induced effects.

This review attempts to contribute to the understanding of the role of NT and its receptors in drug abuse. To this purpose, the potential relevance of NT, its related compounds and NT receptors in substance use disorders will be summarized focusing on preclinical research.

Neurotensin in central nervous system

Biochemistry and localization

Within the CNS, NT is synthesized, stored at specific synapses and asynaptic varicosities and, under appropriate conditions, it may be released or co-released with classical neurotransmitters. NT and its structurally related hexapeptide neuromedin N (NN; Minamino et al., 1988) are products of the same larger precursor, whose cDNA was cloned from bovine brain in 1987 (Dobner et al., 1987). The precursor molecule, a highly conserved polypeptide of 169-170 amino acid length, contains one copy each of NT and NN near the C-terminus and undergoes a differential tissue-specific cleavage at its four dibasic sites by proprotein convertases (PCs). Pro-NT/NN may therefore be processed to generate different sets of peptides. Four biologically active products of pro-NT/NN processing have been described: NT, NN, large NT and large NN (Kitabgi, 2010). In the brain, pro-NT/NN processing mainly depends on PC2 activity and leads to high amounts of NT and NN and small quantities of large NT and large NN (Kitabgi, 2010). Using radioimmunoassay techniques, it has been demonstrated that the regional distribution of NT and NN in brain tissues is, generally, the same (Kitabgi et al., 1992). However, marked differences in the ratio of NT over NN have been observed in different brain areas, NT being generally more abundant in DA-ergic regions such as substantia nigra, pars compacta and ventral tegmental area (VTA). This is in line with the key role of NT in modulating DA transmission.

Once processed as an active peptide in neurons, NT is stored in dense core vesicles and released in a calcium-dependent manner (Iversen et al., 1978). The physiological inactivation of NT is operated by endopeptidases (EPs) belonging to the family of metallopeptidases, which act on primary cleavage sites in the peptide sequence: Arg8-Arg9, Pro10-Tyr11 and Tyr11-Ile12 bonds. Three EPs are responsible of NT degradation: EP 24.11, EP 24.15 and, in particular, EP 24.16 which is ubiquitously expressed (Kitabgi, 2006). Other exo- and endopeptidases further degrade the breakdown products generated by these metallopeptidases. Another mechanism that produces an inactivation of NT transmission is the process of NT internalization (Mazella and Vincent, 2006).

NT pathways

Several NT-containing neuronal circuits have been described in rat. Among others (*see* St-Gelais et al., 2006), these include neurons projecting *a)* from the amygdala to the striae terminalis, the substantia nigra, pars compacta, the substantia nigra, pars reticulata and to the ventromedial nucleus of the hypothalamus; *b)* from the hippocampus through the cingulate cortex to the frontal cortex; *c)* from the hypothalamus, the ventromedial ventral pallidum, the dorsal raphe nucleus and the diagonal band of Broca to the VTA; *d)* from cells in the VTA to the nucleus accumbens (NAC), the amygdala and especially the prefrontal cortex (PFC); from the striatum to the substantia nigra, pars reticulata. High levels of the peptide are present in the hypothalamus, amygdala, bed nucleus of the striae terminalis, lateral septum, NAC, caudate-putamen and VTA (Tyler-McMahon et al., 2000;

Geisler et al., 2006). Such a distribution of the peptide generally matches the distribution of the NT receptors in the brain (Vincent et al., 1999; Geisler et al., 2006).

NT and DA signalling: focus on mesolimbic transmission

Berger et al. (1982) demonstrated that in rat, but not in primates, NT is in part co-localized with DA in mesocortical neurons, but not in nigrostriatal and mesolimbic DA neurons, thus suggesting that NT might play a special role in the regulation of mesocortical DA transmission (Kalivas and Miller, 1984; von Euler et al., 1990). However, the class of mesocortical DA projections that are not co-localized with NT in rat are particularly developed in human, as are the NT projections to the limbic system. These findings strengthen the role of NT corticolimbic innervations in primate brain.

The activation of somatodendritic NTS1 receptors increases the firing rate of mesolimbic ad mesocortical DA-ergic neurons (Werkman et al., 2000) most likely by increasing intracellular Ca^{2+} and reducing K^+ conductances. NT administered to the VTA acutely excites DA neurons (Shi and Bunney, 1990, Werkman et al., 2000) and induces increased turnover and extracellular concentrations of DA in the NAC (Kalivas and Duffy, 1990; Steinberg et al., 1995). Concerning the NAC, NT receptors are co-localized with postjunctional DA receptors on glutamate terminals and on soma-dendrites of striato-pallidal GABA neurons, although this matter is still controversial and inconsistent (Ferraro et al., 2007). Interestingly, NT has been reported to either increase or decrease NAC DA transmission depending on the dose (Ferraro et al., 2007; Boules et al., 2014). It has been suggested that intra-NAC NT application preferentially modulates prejunctional DA-ergic transmission mainly via indirect mechanisms involving other neuronal systems rather than through a direct activation of the few NTS1 receptor located on NAC DA-ergic terminals. In particular, it seems likely that the peptide by activating NTS1 receptors mainly located on NAC glutamate terminals induces an enhancement of glutamate outflow. One of the possible mechanisms underlying this effect may be an antagonistic action of the peptide on glutamate terminal DA D2 receptors (Agnati et al., 1983; Fuxe et al., 1992). The increase in NAC glutamate levels can then activate the inhibitory GABAergic signalling of dendrites and collaterals of the ventral striato-pallidal GABA pathway that could be responsible for the significant reduction of DA release observed in the NAC (Tanganelli et al., 1994). This mechanism can be involved in the neuroleptic-like action of NT. In contrast to the NAC, NT increases DAergic signalling in the dorsal striatum mainly via the activation of a relatively high density of NTS1 receptors located on striatal DA terminals involving inhibition of the DA D2 autoreceptors (Li et al., 1995; Tanganelli et al., 1994).

Neurotensin and substance use disorders

Substance use disorder refers to alcohol/drug abuse or alcohol/drug dependence (*American Psychiatric Association, 2013*). Impairments due to drugs of abuse start in the brain reward circuits including the mesolimbic DA system (as all the addictive substances enhance DAergic transmission), while long-term drug intake leads to dysfunctions of brain regions involved in learning and memory, habit forming learning and inhibitory control, being under control of glutamatergic or GABAergic neurotransmissions (Tzschentke and Schmidt, 2003). Wide NT distribution in the brain and its localization to DAergic rich areas as well as its direct or indirect modulation of glutamatergic and GABAergic transmission speak for the interaction of NT with drugs of abuse belonging to different chemical classes. Below we describe and discuss the preclinical behavioural evidence (based on acute and repeated drug treatments) on the role of NT in chemical addictions.

Neurotensin and drug of abuse-evoked hyperlocomotion

Locomotor hyperactivity mainly depends on the stimulation of the meso-accumbens DAergic neurons, projecting from the VTA to NAC, which constitutes the so-called "reward" pathway (Hedou et al., 1999; Filip and Siwanowicz, 2001). Since locomotor hyperactivity has been proposed as an index of the stimulatory and euphorigenic-like effects of drugs of abuse (Wise and Bozarth, 1987; Phillips and Shen, 1996), the effects of NT on spontaneous and drug-induced locomotion will be summarized in the present section.

Several studies have been focussed on the investigation of behavioural effects induced by acute NT administration, leading to somewhat controversial conclusions (Table 1). Considerable pharmacological and electrophysiological evidence indicates that central administration of NT produces some behavioural effects, similar to those induced by antipsychotic drugs (*see* Caceda et al., 2006, for a review). For instance, pioneering behavioural studies demonstrate that microinjection of NT into the NAC leads to a reduction of locomotion (Kalivas et al., 1984; Meisenberg and Simmons, 1985; Tanganelli et al., 2012). Conversely, the non-peptide NT receptor antagonist SR48692 reduces both haloperidol-induced hypolocomotion and haloperidol reversal of amphetamine-induced hyperlocomotion.

More recently, the direct involvement of NT signaling in the psychostimulant properties of drugs of abuse has been extensively explored (Table 1). The intracerebroventricular (i.c.v.) and intracisternal (i.c.) administration of NT attenuated amphetamine-induced hyperlocomotion and reward behaviours induced by DA and cocaine (Skoog et al., 1986; Sarhan et al., 1997). Furthermore, intra-NAC injection of the peptide significantly decreased the cocaine-induced and, at a higher dose, the amphetamine-elicited hyperlocomotion. This suggests the ability of the peptide to modulate the psychostimulants-induced locomotor activation through an interaction with the mesolimbic DA

system (Robledo et al., 1993; Sarhan et al., 1997). The acute systemic administration of the brain-penetrating NT analogue NT69L reduced spontaneous locomotor activity as well as the hyperlocomotion caused by both amphetamine and cocaine (Boules et al., 2001; Hertel et al., 2001; Boules et al., 2003). Hertel et al. (2001) reported that the ability of NT69L to reduce both spontaneous and psychostimulant-induced locomotion disappeared following repeated drug administration, suggesting a desensitisation of NT receptors as a possible mechanism. On the contrary, Boules and colleagues (2001; 2003) demonstrated that tolerance developed to some pharmacological effects of NT69L, but not to the modulation exerted by the compound on amphetamine- and cocaine-induced hyperactivity. This discrepancy seems related to the different dose-regimen used in the two studies (*see* Boules 2003, for details). Other investigations demonstrated that the i.p. injections of NT1, a brain penetrable NT related peptide, decreased the amphetamine-stimulated hyperlocomotion (Sarhan et al., 1997), whereas the systemic administration of PD149163, a selective and potent NTS1 receptor agonist, counteracted the locomotor effects of amphetamine in both acute and subchronic regimen (Feifel et al., 2008). Interestingly, the latter compound was found to reduce mouse spontaneous locomotion when the animals were placed both in a novel environment and in the home-cage, through a negative receptor-receptor interaction between DA D2 receptor and NTS1 receptor (Binder et al., 2001; Vadnie et al., 2014). Moreover, PD149163 abolished locomotion when it was injected into the NAC, but not into the medial PFC. These findings suggest that, although NTS1 receptors are present on medial PFC pyramidal neurons and interneurons, their role is not relevant for the peptide-induced effects on locomotion (Petrie et al., 2005; Vadnie et al., 2014). Although little is known about the precise mechanism underlying these effects, the above studies suggest that NT exerts an inhibitory influence on the stimulatory behavioral effects of psychostimulants (Wagstaff et al., 1994; Chartoff et al., 2004; Feifel et al., 2008). It may take place through an indirect mechanism involving increased striatal GABA activity and release caused by NTS1 mediated reduction of inhibitory DA D2 receptor signalling on glutamate terminals and on the striato-pallidal GABA neurons. This leads to reduced DA release via activation of GABA receptors on the DA terminals via released GABA (Ferraro et al., 1997; *see* above).

Other studies investigated the locomotor effects of NT receptor antagonists. For instance, the oral administration of SR48692 counteracted the behavioral effects induced by intra-VTA NT injection as well as the inhibitory effects of intra-NAC NT injection on amphetamine-induced locomotor hyperactivity (Steinberg et al., 1994). However, SR48692 had no effect on mouse spontaneous motor activity or amphetamine- and cocaine-elicited hyperlocomotion, thus suggesting that endogenous NT does not modulate spontaneous and drug-induced locomotion (Betancur et al., 1998; Casti et al., 2004). These findings have been validated by using another NT receptor

antagonist, SR142948A (Casti et al., 2004; Caceda et al., 2012). On the other hand, repeated systemic injection of SR48692 reduced the behavioural response to acute cocaine, providing additional evidence for the possible involvement of the neuropeptide in behavioural activation induced by psychostimulants (Betancur et al., 1998). Moreover, the acute systemic injection of SR142948A blocked the 3,4-methylenedioxymethamphetamine (MDMA)-elicited hyperlocomotion indicating that endogenous NT might be involved in this effect. In line with this view, systemic administration of MDMA induced the release of endogenous striatal NT (Marie-Claire et al., 2008). The use of transgenic mice recently allowed to obtain further information on the role of NT on drugs of abuse-induced behaviour. Studies that investigated the behavioural effects mediated by NT receptors in response to ethanol, reported that spontaneous locomotion or initial ethanol-induced locomotion did not differ from their respectively control groups in wild-type (WT), NTS1 receptor and NTS2 receptor knockout (KO) mice. However, the acute systemic pre-treatment with NT69L significantly reduced the initial ethanol-induced locomotion in both WT and NTS2 receptor KO mice, but not in NTS1 receptor KO mice, suggesting that motor functions of alcohol are associated with activation of NTS1 receptors. However, according with the previous studies using NT receptor antagonists, these experiments in KO mice seem to validate the lack of involvement of the NT system in spontaneous locomotor activity (Lee et al., 2010; 2011). In a recent study, where different experimental paradigms were used, both spontaneous and acute cocaine-stimulated locomotor activity were similar in WT and NTS1 receptor KO mice. However, in NTS1 receptor KO mice a slight prolongation of some behavioural effects of cocaine has been reported (Hall et al., 2012).

In contrast to the above data, other studies suggested that some behavioural effects of NT are similar to those induced by peripheral administration of psychomotor stimulants (Richelson et al., 2003; Boules et al., 2013). For example, intra-VTA NT microinjection was associated with locomotor hyperactivity. This effect is similar to the psychostimulant-induced increase in exploratory behaviors, being abolished by both i.c.v. injection of haloperidol and the destruction of the meso-NAC DAergic pathway (Kalivas et al., 1983; Kalivas and Taylor, 1985). Interestingly, daily intra-VTA administration of NT enhanced locomotor hyperactivity without affecting the locomotor activation induced by a low dose of amphetamine (Elliott and Nemeroff, 1986). These findings suggest that intra-VTA NT produces behavioral hyperactivity through activation of mesolimbic DA system. Thus, it has been proposed that NT stimulates locomotor activity through activation of DA neurons when it is injected at the VTA DA-ergic cell bodies (Kalivas et al., 1983; Kalivas and Duffy, 1990), while the peptide inhibits locomotion through a post-synaptic modulation of neuronal systems regulated by NAC DA terminals (Kalivas et al., 1984). It was postulated to be due to an antagonistic postjunctional NT-DA D2 receptor-receptor interaction (Fuxe et al., 1992). One mechanism for the VTA results is the existence of NTS1-DA D2 heteroreceptor complexes

(Borroto-Escuela et al., 2013) not only postjunctionally, but also in the VTA DA nerve cells in which NTS1 receptors inhibit DA D2 autoreceptor signaling and thereby increases the firing in the meso-NAC DA neurons (Ferraro et al., 2014).

In conclusion, the above results led to hypothesize that NT analogues or selective NTS1 receptor agonists that cross the brain blood barrier after their systemic administration might be clinically useful in modulating the hyperactivity and certain behavioural responses to drugs of abuse (Boules et al., 2006; Vadnie et al., 2014). However, some of these effects seem to be reachable also by using NT receptor antagonists (Betancur et al., 1998) and other studies argue against the involvement of endogenous NT signalling in the hyperlocomotion elicited by psychostimulant drugs (Hall et al., 2012). Thus, further and more extensive investigations are necessary to possibly clarify the role of the peptide in the drugs of abuse-evoked locomotor behaviours.

Neurotensin and drug of abuse-evoked sensitization

Repeated, intermittent administrations of drugs of abuse induce a strong enhancement in locomotor stimulation that may last for a long time. This phenomenon, also called locomotor sensitization or behavioural sensitization, has been suggested to predict the addictive property of a drug combined with forms of neuronal adaptations linked to an enhancement of the reinforcing and motivational aspects of drugs of abuse. Two separate temporal domains of drug-induced sensitization within neuronal networks have been identified and termed initiation and expression. The initiation of behavioural sensitization to psychostimulants is operationally defined as the transient sequence of cellular and molecular events precipitated by psychostimulant administration that ultimately leads to enduring changes in neural function. Expression is defined as the enduring neural alterations arising from the initiation process that directly mediate the sensitized behavioural response (Robinson and Berridge, 1993; Steketee and Kalivas, 2011). Initiation and expression of locomotor sensitization are reported to have distinct neurochemical mechanisms and different brain structures are involved in the two temporal phases: initiation of behavioural sensitization to psychostimulants is mostly related to DAergic and glutamatergic VTA transmission, while the neuronal changes associated with sensitization expression are mainly localized among the interconnection between VTA, NAC, PFC and amygdala (the so called "motive circuit"), leading to drug-induced increase in DA and glutamate release in the NAC. Moreover, the neuronal adaptations involved in the expression of behavioural sensitization to different drugs of abuse are shown to be distinct into the motive circuit (i.e. cocaine-elicited sensitization appears to involve more descending corticofugal excitatory efferents than amphetamine) and result in an altered balance between the interconnections of several neurotransmitter systems (Pierce and Kalivas, 1997). Numerous studies

have evaluated the possible involvement of NT in psychostimulant sensitization, giving mixed results (Table 2A-C).

Development of sensitization

The first evidence indicated that chronic pre-exposure to the NT receptor antagonist SR48692 delayed and attenuated the development of cocaine sensitization, whereas the compound had no effect on cocaine sensitization when administered before each drug injection (Horger et al., 1994; Betancur et al., 1998). Moreover, when co-administered before amphetamine (Rompré and Perron, 2000; Panayi et al., 2002) or morphine (Lévesque et al., 2008), SR48692 dose-dependently attenuated and/or prevented the development of sensitization. However, the other NT receptor antagonist, SR142948A, acutely administrated with amphetamine, failed to effect the acquisition of drug sensitization (Panayi et al., 2005). These discrepancies have been proposed to be due to the different drug administration route and schedule or to other methodological variables (Rompré and Perron, 2000; Panayi et al., 2005). Based on these data, it can be speculated that NT might act on some neural mechanisms that subtend the neuroadaptations underlying psychostimulant drug sensitization. To support this hypothesis, it has been reported that NT is released in the VTA after amphetamine injection and contributes, although not sufficient, to the development of amphetamine behavioral sensitization (Panayi et al., 2005). An increase in ventral midbrain DA release seems to be critical for this NT action. In fact, cocaine and amphetamine sensitization are augmented by compounds that increase extracellular catecholamine levels (Kalivas and Weber, 1988) and the stimulation of ventral midbrain NT receptors enhanced neuronal DA release (Kalivas and Taylor, 1985; Kalivas and Duffy, 1990). Alternatively, NT might stimulate psychostimulant sensitization augmenting ventral midbrain DA release by activating its receptors in the medial PFC, a brain area receiving ventral midbrain efferents (Sesack and Pickel, 1992; Fatigati et al., 2000; Rompré et al., 1998; Petrie et al., 2005).

Controversial results have also been obtained by using NT receptor agonists. The administration of a single dose of the NT analogue NT69L significantly reduced the initiation and expression of nicotine-induced behavioural sensitization (Fredrickson et al., 2003a; 2003b). Furthermore, NT69L was also found to block or attenuate the sensitization to d-amphetamine and cocaine in rats (Fredrickson et al., 2003a) along with nicotine potentiation to cocaine sensitization (Fredrickson et al., 2014). However, central administration of the biologically active NT(8-13) fragment did not alter cocaine sensitization (Torregrossa and Kalivas, 2008).

Expression of sensitization

Opposite to the controversial data obtained in studies on sensitization development, the results concerning the role of NT in the expression of psychostimulant drug sensitization consistently provide evidence that the blockade of NT receptors decreases this process. In fact, the acute administration of SR48692, prior to amphetamine challenge doses, prevented the expression of amphetamine behavioural sensitization in rat pre-exposed to the psychostimulant (Costa et al., 2001). Furthermore, given daily after the amphetamine exposure period necessary to sensitize the animals to the behavioural effects of the drug, SR48692 reverted the expression of amphetamine-induced sensitization (Costa et al., 2007). The same antagonist, chronically administered after cocaine regimen, during the withdrawal period, was effective to attenuate the expression of cocaine-elicited sensitization (Felszeghy et al., 2007). The other NT receptor antagonist, SR142948A, when injected into the VTA, failed to alter the expression of amphetamine sensitization. However, this effect is in line with the accepted notion that the VTA by itself is not an anatomical substrate for expression of the drug sensitization (Panayi et al., 2005). Even though most of the studies focused on the expression of behavioural sensitization to psychostimulant drugs mainly considered the role of DA transmission, the imbalance between some neurotransmitter pathways, such as the glutamatergic and GABAergic ones, could contribute to this process (Pierce and Kalivas, 1997; Vanderschuren and Kalivas, 2000). NT receptors are localized in most of the structures of the motive circuit and the neuropeptide is known to interact with the neuronal pathways involved in drug addiction (Liang et al., 2008; Picciotto and Corrigall, 2002). Thus, the NT-induced modulation of different neurotransmitter systems in these brain regions might be involved into the role that the peptide plays in the expression of psychostimulant sensitization. However, it is worth noting that systemic administration of both NT receptor agonists and antagonists has been reported to produce an attenuation of the expression of drugs-elicited sensitization. This issue needs therefore to be deeply investigated by future studies to better clarify the mechanisms through which the different NT receptor ligands exert these effects.

Finally, cross-sensitization between NT and psychostimulants has been observed. Specifically, repeated, intermittent i.c.v. injections of NT in rats were shown to produce sensitization to the behavioural stimulant effect of systemic amphetamine, while the more potent NT analogue D-Tyr[11]NT, repeatedly i.c.v. administered, increased both cocaine and amphetamine sensitization (Rompré, 1997; Rompré and Bauco, 2006). This action, at least in case of amphetamine sensitization, was demonstrated to be either context-dependent or context-independent based upon the pattern of locomotor activity (Rouibi and Rompré, 2014) and to be prevented by excitotoxic lesions of the PFC (Blackburn et al., 2004). Thus, given these long-lasting changes in responsiveness to psychostimulant drugs after repeated activation of the NT systems, it is reasonable to conclude that NT could act in the same neural mechanisms that induce some

neuroadaptations related to drugs sensitization. However, other investigations are required to better understand the exact role, the anatomical sites and the functional and molecular mechanisms through which NT mediates these effects.

Neurotensin and drug of abuse reward

Some evidence for the rewarding properties of NT and/or its ability to affect the reinforcing behaviours induced by drugs of abuse has been provided by studies using different experimental procedures, such as drug self-administration, drug preference and conditioned place preference (CPP) in rodents (Tables 3-4).

Drug self-administration

Early investigations using the self-administration (SA) paradigm demonstrated that rats performed operant tasks to obtain intra-VTA infusions of NT, thus suggesting that the peptide by itself exerts a primary positive reinforcement in this brain area (Glimcher et al., 1984; Glimcher et al., 1987). These findings are in line with previous results obtained in CPP experiments (*see* the next paragraph). However, when NT was injected into the NAC immediately before cocaine SA in the maintenance phase, no effect of the peptide on cocaine self-infusions was found, whereas the administration of the peptide in the same region attenuated the drug-elicited locomotor activity (Robledo et al., 1993; see above). It is worth noting that, in the latter study, NT was administered into the NAC core that could be more involved in motor than in motivational aspects. In fact, the projections from the NAC core mainly innervate the ventromedial central pallidum, which participates in the indirect pathway to the subthalamic nucleus and the substantia nigra, pars reticulata. Instead, the projections from the NAC shell reach the dorsolateral ventral pallidum, which innervates the medio-dorsal thalamic nucleus sending efferents to the prefrontal cortex (see Fuxe et al., 2008), VTA and the lateral hypothalamus (Kalivas and Miller, 1984; Zahm and Heimer, 1988; 1990; Heimer et al., 1991). The microinjection of NT(8-13) into the ventral pallidum did not affect cocaine self-administration (Torregrossa and Kalivas, 2008).

A systemic (i.p.) pre-treatment with the brain penetrating NT analogue NT69L significantly decreased nicotine i.v. SA in rat (Boules et al., 2011). Moreover, the pre-treatment with the NT receptor agonist, PD149163, inhibited i.v. mephedrone SA (German et al., 2014) and, administered before the day 5 of operant behaviour, blocked lever pressing for i.v. methamphetamine (METH) self-injections (Frankel et al., 2011). In a substitution SA paradigm, PD149163, which was not self-administered by the animals, was found to reduce the lever pressing when used in replacement of METH into the SA session (Hanson et al., 2012). Under these experimental conditions, SR48692 did not significantly alter lever-pressing behaviour in the SA animals. The authors proposed that SA

extinction is associated with increases in NT release which, in turn, participate in the process of extinction of METH SA through a DA D2 receptor mechanism in line with the existence of antagonistic NTS1-DA D2 receptor-receptor interactions (Antonelli et al., 2007a; Borroto-Escuela et al., 2013). Recently, NT receptor KO mice have been used to evaluate the role of the peptide in drug SA. In two bottles choice experiments (ethanol and water) mice lacking NTS1 or NTS2 receptor consumed significantly more ethanol compared to WT animals. NT69L reduced ethanol consumption in both wild type and NTS2 receptor KO mice, but not in NTS1 receptor KO mice (Lee et al., 2010; Lee et al., 2011).

Taken together, the data from combination and substitution SA paradigms provide evidence for the involvement of NT signalling in regulating psychostimulants and ethanol intake and suggest that the activation of NT receptors generally suppresses operant behaviours linked with drugs SA.

It is well-known that the mesolimbic DA system, where NT also exists in its mesocortical component (von Euler et al., 1990; St-Gelais et al., 2006), is the main anatomical substrate for the rewarding effects of drugs of abuse (McBride et al., 1999). NT is associated with inhibitory feedback actions on basal ganglia and limbic DA pathways, and elevated NT levels have been reported in both the NAC and dorsal striatum after treatment with high doses of psychostimulants (Hanson et al., 2012; German et al., 2014). The mechanisms underlying the ability of NT receptor agonists to reduce the reinforcing effects in i.v SA and two drugs choice experiment seem complex, but are possibly related to the antagonistic interaction of the NTS1 receptor with the DA D2 receptor reducing postjunctional DA D2 receptor signaling. It has also been hypothesized that NT69L may modulate the DA neurotransmission implicated in the reinforcing effects of nicotine by modulating tyrosine hydroxylase and DA receptor mRNA levels in the PFC and striatum (Boules et al., 2011). Based on results of these studies, it seems likely that NT systems might be involved in modulating drug SA thus contributing to some elements that influence drug addiction.

Conditioned place preference

CPP is widely used to study the motivational and reinforcing effects of both natural stimuli and drugs of abuse (Tzschentke, 2007). This paradigm is based upon the acquisition of preference for neutral environmental stimuli (conditioned or secondary reward) that were previously combined with a drug administration (primary reward). The CPP comprises an acquisition phase, and an expression phase in which drug-free animals are tested for their preference for the environment previously paired with the drug. It has been reported that the acquisition and expression of this incentive learning are mediated by different neurochemical mechanisms. For example, the neurons involved in the expression and acquisition of CPP in the case of amphetamine and morphine are

anatomically distinct, at least within the NAC (Sellings and Clarke, 2003; Fenu et al., 2006; Marie-Claire et al., 2008).

An early study reported that intra-VTA NT was associated with CPP acquisition and expression, thus suggesting that the peptide acts as a primary reinforce in rats (Glimcher et al., 1984). More recently, it has been demonstrated that NT displayed positive reinforcing actions when microinjected into the central nucleus of amygdala and ventral pallidum, and these effects were mediated by NTS1 receptors because they were prevented by prior administration of selective receptor antagonists (Laszlo et al., 2010; Ollmann et al., 2015). Other studies investigate the role of NT in drugs of abuse-induced CPP. The pre-treatment with SR142948A did not modify the development, but suppressed the expression of MDMA-elicited CPP in mice (Marie-Claire et al., 2008), while chronic treatment with SR48692 blocked cocaine-induced CPP in rats (Felszeghy et al., 2007). These findings suggest that endogenous NT might participate to some behaviours elicited by drugs of abuse and appears to be mainly involved in the expression of psychostimulant-induced CPP. Interestingly, mouse striatal NTS1 receptor mRNA levels were up-regulated when the MDMA-induced CPP expression was tested. Based on these results, it has been proposed that NTS1 receptors may be involved in the behavioural consequences induced by the conditioned environmental reward without directly mediating the reinforcing actions of drugs of abuse. Thus, NT could be a neural target for reward expectation (Marie-Claire et al., 2008). However, the rewarding properties of cocaine, as explored in CPP paradigm, using NT KO mice are reported to be similar to those observed in WT animals, indicating that endogenous NT is not required for the cocaine-induced CPP and for the rewarding effect of the drug (Hall et al., 2012). Nevertheless, the authors did not exclude that NT could be involved in other aspects of cocaine-elicited CPP, such as the retention of CPP following cocaine conditioning (in agreement with Felszeghy et al., 2007), that were not explored in NT KO mice.

Drug-preference

Several studies support the hypothesis for an involvement of NT also in ethanol-mediated physiological and behavioural changes (Luttinger et al., 1982; Widdowson, 1987; Erwin and Su, 1989; Erwin et al., 1997). However, the functional role of NT and its receptors in ethanol preference has not been sufficiently studied. The activation of NTS1 receptor signalling appears to be inversely correlated with ethanol preference (Table 5). In fact, the systemic administration of the NT analogue NT69L significantly reduced ethanol preference in both WT and NTS2 receptor KO mice in a two bottles choice experiment, while NTS1 KO mice were insensitive to this effect (Lee et al., 2010; Lee et al., 2011). In line with these findings, alcohol-preferring rats show a lower concentration of PFC NT in comparison with non-preferring rats (Ehlers et al., 1999). In addition,

either NTS1 or NTS2 KO mice displayed similarly elevated levels of ethanol intake when compared to WT animals, and it has been proposed that NTS1 receptors are involved in the effect of lower, ataxic doses of ethanol, whereas NTS2 receptors might be responsible for the effect of higher, hypnotic doses of ethanol (Lee et al., 2011). Concerning the possible mechanism of action, NT69L might prevent ethanol consumption through the modulation of both DAergic and glutamatergic systems implicated in ethanol addiction (Li et al., 2011). Taken together, these data suggest the potential therapeutic use of NT analogues in alcohol use disorder.

Neurotensin and self-stimulation

Reward stimuli include, among others, electrical stimulations of some brain areas. In the paradigm of brain stimulation reward (BSR), rats rapidly learn an operant task in order to electrically stimulate their own brain in specific sites that are mostly under control of DA neurotransmission. Consistent data show that BSR is modified by the administration of drugs of abuse, whose mechanism of action is known related to a modulation of CNS DA transmission. Experiments using the self-stimulation procedure indicated that NT is involved in the control of behaviours motivated by positive reinforcement (Rompré et al., 1992; Rompré and Boye, 1993; Rompré, 1995; Kempadoo et al., 2013). The evidence is supported by consistent data indicating the anatomical and functional interactions between DA brain reward system and the NT pathways (St-Gelais et al., 2006; Geisler et al., 2006; Boules et al., 2013).

The microinjection of NT into the ventral mesencephalic region, dose-dependently reduced the stimulation frequency necessary to sustain the threshold levels of responding for BSR. The activation of ventral mesencephalon NT receptors induces DA neuron firing and the neurotransmitter release in limbic terminal fields, thus providing evidence that NT enhances reward-related activity in DA cells (Rompré et al., 1992), potentially through antagonistic NTS1-DA D2 autoreceptor interactions (see above). Similarly, the intra-VTA NT, through the DA D2 autoreceptor modulation of a DA neuron subpopulation, produced a long lasting reduction in the stimulation frequency necessary to obtain a half-maximal rate of responding (Rompré and Boye, 1993). Moreover, an augmentation of BRS was found when the peptide was i.c.v. injected, and this effect was associated with a significant time-dependent decrease in frequency threshold in rats. These results provide evidence for psychostimulant-like effects of centrally administered NT. On the other hand, the i.c.v. administration of the peptide was also found to suppress the maximal rate of responding, that is a typical action of neuroleptics. These results can be explained by the fact that i.c.v. injected NT can also reach NAC and produce a reduction of postjunctional DA D2 receptor signalling via an allosteric antagonistic NTS1-DA D2 receptor-receptor interaction (Borroto-Escuela et al., 2013). This proposal can also help explain why the above profiles of action seem to

be related to the dose of NT. In fact, at a low dose NT tended to decrease threshold, whereas at a higher dose this decrease was not larger and a small increase was found immediately after the injection when the i.c.v. injected NT may maximally reach the NAC. It is worth noting that opposite effects of different doses of NT were also observed on spontaneous locomotion (Nouel et., al. 1990; *see* above) which may also be explained according to this proposal.

NT is reported to be one of the most abundant peptides in the lateral hypothalamus (LH) containing VTA projections that are involved in reward-seeking behaviour. Recent work reported that mice displayed robust intracranial self-stimulation to VTA fibres of LH, and this operant behaviour was mediated by NTS1 and NMDA receptors. The NT receptor antagonist SR48692 was found to decrease the amount of reinforced behaviour although maintaining lower levels of stimulation-seeking, suggesting that NT directly mediates reward-related behaviour by enhancing glutamate transmission in midbrain DA neurons and reducing D2 autoreceptor function in VTA (see above). Considering this evidence, it seems likely that NT receptor antagonists might counteract human forms of pathological reward-seeking (Kempadoo et al., 2013).

Neurotensin and drug-seeking behaviour

Recently, the role of NT in drug-seeking behaviour and, specifically, in the relapse to drug-seeking following a prolonged drug-free period, has been investigated by few authors (Table 6). In experimental models of drug-seeking, the animals are trained to self-administer a drug (reinforce); then the reinforcement is removed to extinguish this behaviour and finally the drug-seeking is restored by presentation of a stressor, a drug-associated cue (sound and/or light) or the drug itself (Torregrossa and Kalivas, 2008). Using this paradigm, both NT and its analogue D-TYR[11]NT, injected i.c.v. prior to the reinstatement test in rats, were found to produce a robust reinstatement of cocaine-seeking behaviour and this effect was attenuated by a prior injection of a DA D1/D5 receptor antagonist. Interestingly, the same local pre-treatment with D-TYR[11]NT did not affect the reinstatement of sucrose-seeking in rat. The lack of efficacy of NT in non-drug (sucrose) reinstatement in comparison to the cocaine-reinstatement suggests the hypothesis that during the psychostimulant SA certain neuronal adaptations in some brain regions leads NT to enhance the vulnerability to relapse after a drug-free period (Lopak and Erb, 2005). It has been proposed that the mechanism that sustains the reinstatement process in rats with a previous history of cocaine SA requires the interaction between NT and DA. In particular, the activation of NT receptors at the level of midbrain DA cells, involving a reduction of DA D2 autoreceptor function (see above) that may be enhanced by prior cocaine self-administration, seems to offer a reasonable explanation of this NT/DA interaction (Lopak and Erb, 2005). In fact, as extensively reported above, NT displays anatomical and functional interactions with DA in the midbrain (Nemeroff et al., 1983; Day et al.,

2002) and changes of NT levels in sub-regions of the NAC and PFC occur during the different stages of environmentally-elicited cocaine-seeking behaviour (Ramos-Ortolaza et al., 2009).

Besides DA, NT is known to co-localize with GABA and to increase GABA release in several brain regions (Tanganelli et al., 1994; Ferraro et al., 1997; Ferraro et al., 1998; Rakovska et al., 1998; O'Connor, 2001; Petrie et al., 2005). Because the reduction of GABA transmission in the ventral pallidum (VP) is reported to promote drug-seeking, it seems possible to hypothesize that a putative mechanism through which NT increases the reinstatement of drug-seeking could also be the modulation of VP GABA release, likely from ventral striato-pallidal GABA neurons projecting into the VP representing an anti-reward system (see above). However, the NT peptides are known to activate these GABA neurons through the antagonistic NTS1-DA D2 receptor-receptor interactions and the enhancing NTS1-NMDA receptor-receptor interactions in their glutamate afferents (Tanganelli et al., 2012). Therefore, these interactions would block the reinstatement. In accordance with this view, the active NT fragment NT(8-13), injected intra-VP before the reinstatement test for cocaine-seeking, inhibited cue-induced reinstatement (Torregrossa and Kalivas, 2008). This is likely related to NT fragment induced GABA release from the striato-pallidal GABA terminals via antagonistic NTS1-D2 interactions in these terminals. Unexpectedly augmented cocaine-primed reinstatement was observed (Torregrossa and Kalivas, 2008). This profile of action is surprising since both cue- and cocaine-induced reinstatements are reported to be mediated by VP neurotransmission. At the present, it is difficult to explain these results. It may be speculated that cocaine treatment has reorganized the postjunctional NTS1-DA D2 complexes of the striato-pallidal GABA neurons into producing facilitatory NTS1-DA D2 receptor-receptor interactions which can explain the augmentation of the cocaine induced reinstatement. Finally, only one dose of NT(8-13) was tested in the reinstatement experiments; thus it cannot be excluded that other doses of the NT analogue might have different effects and further experiments will be necessary to clarify this possibility. It is worth noting that when given systemically, but not when directly administrated into the VP, the NT receptor antagonist SR142948 blocked the cocaine-induced reinstatement, indicating that the stimulation of VP NT receptors is not required for this cocaine-mediated behaviour (Torregrossa and Kalivas, 2008). Taken together, these data indicate that NT systems seem to play a role in drug-seeking behaviour, but additional studies are requested to deeply investigate the involvement of the neuropeptide in this model of drug relapse and the exact mechanisms underlying the brain interactions between NT and other neurotransmitter systems during drug-induced seeking behaviour.

Concluding remarks

The mesolimbic and mesocortical DA pathways are highly implicated in the psychomotor stimulant and reinforcing effects of drugs of abuse. The above reported studies strongly suggest that NT signalling is one of the specific neurochemical mechanisms for the modulation of the rewarding activity of cocaine and other drugs of abuse. Nevertheless controversial results exist. At the present, the precise molecular mechanisms by which NT exerts its role in drug addiction remain to be elucidated. In contrast to the case after treatment with typical antipsychotic drugs, psychostimulants enhance NT levels mainly in subpopulations of the striato-nigral GABA pathways (Merchant, 1994) regulated primarily by the DA D1 receptors, although increases in NT levels in other brain regions have been also described (see above). The increase in NT levels and the consequent NTS1 receptor stimulation appear essential for the c-fos expression and thus activation of subpopulations of the striato-nigral GABA pathway (Fadel et al., 2006) that may be part of the reward pathways, especially when originating from the NAC. Furthermore, it could be possible that the psychostimulant induced NT levels in the cell body-dendritic regions of these nerve cells allows the peptide, through extrasynaptic volume transmission, to diffuse and reach the glutamate and DA terminals. Here the NT peptides inhibit DA D2 receptor signalling via the antagonistic NTS1-DA D2 receptor-receptor interaction in the striatal and accumbal glutamate and DA (only dorsal striatal) terminals leading to increased DA and glutamate release (see above). The increased synaptic glutamate and extrasynaptic DA release may contribute to the activation of accumbal-VTA GABA pathways participating in the reward circuits activated by drugs of abuse.

However, increased glutamate release can also activate the ventral striato-pallidal GABA pathways which belong to the anti-reward circuit, where also the inhibitory DA D2 receptors show reduced signalling by being inhibited by released NT peptides via antagonistic NTS1-DA D2 receptor-receptor interactions in these neurons. In this way it becomes possible to understand that the NT induced alterations in the balance of activity in the reward and the anti-reward system will determine how NT mechanisms contribute to the development of psychostimulant sensitization and possibly to cocaine use disorder.

Similar NTS1 receptor mechanisms may also exist in the VTA DA cells leading to the increased activation of the mesolimbic DA neurons through antagonistic NTS1-DA D2 autoreceptor interactions reducing DA D2 autoreceptor signalling and enhancing NTS1-NMDA receptor interactions. These DA neurons represent a key reward system. Thus, also here NTS1 activation may antagonize DA D2 autoreceptor functions and increase glutamate drive. Long-term changes in gene transcription may in this way be triggered and cause plastic changes in the mesolimbic DA reward systems and thus lead to sensitization and addiction development.

Based on the preclinical research it is no doubt that NT has a role in modulation of substance use disorder. However, it is necessary before any significant statements can be made to clarify the

mechanisms underlying the interactions between NT and drugs of abuse. The focus should especially be on the selectivity of the drugs of abuse and on functional activity of the reward/anti-reward neuronal circuitries and their NT heteroreceptor complexes including their allosteric receptor-receptor interactions.

Conflict of interest

The authors declare no conflict of interest.

References

Agnati LF, Fuxe K, Benfenati F, Battistini N (1983) Neurotensin in vitro markedly reduces the affinity in subcortical limbic 3H-N-propylnorapomorphine binding sites. Acta Physiol Scand 119: 459-61.

Antonelli T, Tomasini MC, Fuxe K, Agnati LF, Tanganelli S, Ferraro L (2007a) Receptor-receptor interactions as studied with microdialysis. Focus on NTR/D2 interactions in the basal ganglia. J Neural Transm 114: 105-113.

Antonelli T, Fuxe K, Tomasini MC, Mazzoni E, Agnati LF, Tanganelli S, Ferraro L. (2007b) Neurotensin receptor mechanisms and its modulation of glutamate transmission in the brain: relevance for neurodegenerative diseases and their treatment. Prog Neurobiol 83: 92-109.

Antonelli T, Tomasini MC, Fournier J, Mazza R, Tanganelli S, Pirondi S, Fuxe K, Ferraro L (2008) Neurotensin receptor involvement in the rise of extracellular glutamate levels and apoptotic nerve cell death in primary cortical cultures after oxygen and glucose deprivation. Cereb Cortex 18: 1748-1757.

Berger B, Gaspar P, Verney C (1992) Colocalization of neurotensin in the mesocortical dopaminergic system. Restricted regional and laminar distribution in rat, lack of colocalization in human. Ann NY Acad Sci 668: 307-310.

Betancur C, Cabrera R, de Kloet ER, Pélaprat D, Rostène W (1998) Role of endogenous neurotensin in the behavioral and neuroendocrine effects of cocaine. Neuropsychopharmacology 19: 322-332.

Binder EB, Kinkead B, Owens MJ, Nemeroff CB (2001) Neurotensin and dopamine interactions. Pharmacol Rev 53: 453-486.

Blackburn A, Dewar K, Bauco P, Rompré PP (2004) Excitotoxic lesions of the prefrontal cortex attenuate the potentiation of amphetamine-induced locomotion by repeated neurotensin receptor activation. Brain Res 998: 184-193.

Borroto-Escuela DO, Ravani A, Tarakanov AO, Brito I, Narvaez M, Romero-Fernandez W, Corrales F, Agnati LF, Tanganelli S, Ferraro L, Fuxe K (2013) Dopamine D2 receptor

signaling dynamics of dopamine D2-neurotensin 1 receptor heteromers. Biochem Biophys Res Commun 435: 140-146.

Boules M, Warrington L, Fauq A, McCormick D, Richelson E (2001) A novel neurotensin analog blocks cocaine- and D-amphetamine-induced hyperactivity. Eur J Pharmacol 426: 73-76.

Boules M, McMahon B, Wang R, Warrington L, Stewart J, Yerbury S, Fauq A, McCormick D, Richelson E (2003) Selective tolerance to the hypothermic and anticataleptic effects of a neurotensin analog that crosses the blood-brain barrier. Brain Res 987: 39-48.

Boules M, Fredrickson P, Richelson E (2006) Bioactive analogs of neurotensin: focus on CNS effects. Peptides 27: 2523-2533.

Boules M, Shaw A, Fredrickson P, Richelson E (2007) Neurotensin agonists: potential in the treatment of schizophrenia. CNS Drugs 21: 13-23.

Boules M, Oliveros A, Liang Y, Williams K, Shaw A, Robinson J, Fredrickson P, Richelson E (2011) A neurotensin analog, NT69L, attenuates intravenous nicotine self-administration in rats. Neuropeptides 45: 9-16.

Boules M, Li Z, Smith K, Fredrickson P, Richelson E (2013) Diverse roles of neurotensin agonists in the central nervous system. Front Endocrinol (Lausanne). 4: 36.

Boules MM, Fredrickson P, Muehlmann AM, Richelson E (2014) Elucidating the role of neurotensin in the pathophysiology and management of major mental disorders. Behav Sci. (Basel). 4: 125-153.

Cáceda R, Kinkead B, Nemeroff CB (2006) Neurotensin: role in psychiatric and neurological diseases. Peptides 27: 2385-2404.

Cáceda R, Binder EB, Kinkead B, Nemeroff CB (2012) The role of endogenous neurotensin in psychostimulant-induced disruption of prepulse inhibition and locomotion. Schizophr Res 136: 88-95.

Carraway R, Leeman SE (1973) The isolation of a new hypotensive peptide, neurotensin, from bovine hypothalami. J Biol Chem 248: 6854-6861.

Carraway R, Leeman SE (1976) Characterization of radioimmunoassayable neurotensin in the rat. Its differential distribution in the central nervous system, small intestine, and stomach. J Biol Chem 251: 7045-7052.

Casti P, Marchese G, Casu G, Ruiu S, Pani L (2004) Blockade of neurotensin receptors affects differently hypo-locomotion and catalepsy induced by haloperidol in mice. Neuropharmacology 47: 128-135.

Chartoff EH, Szczypka MS, Palmiter RD, Dorsa DM (2004) Endogenous neurotensin attenuates dopamine-dependent locomotion and stereotypy. Brain Res 1022: 71-80.

Costa FG, Frussa-Filho R, Canteras NS, Valera AG, Felicio LF. (2007) Blockade of neurotensin receptors during amphetamine discontinuation indicates individual variability. Neuropeptides 41: 83-91.

Costa FG, Frussa-Filho R, Felicio LF (2001) The neurotensin receptor antagonist, SR48692, attenuates the expression of amphetamine-induced behavioural sensitisation in mice. Eur J Pharmacol 428: 97-103.

Day HE, Vittoz NM, Oates MM, Badiani A, Watson SJ Jr, Robinson TE, Akil H (2002) A 6-hydroxydopamine lesion of the mesostriatal dopamine system decreases the expression of corticotropin releasing hormone and neurotensin mRNAs in the amygdala and bed nucleus of the stria terminalis. Brain Res 945: 151-159.

Dobner PR, Barber DL, Villa-Komaroff L, McKiernan C (1987) Cloning and sequence analysis of cDNA for the canine neurotensin/neuromedin N precursor. Proc Natl Acad Sci USA 84: 3516-3520.

Ehlers CL, Somes C, Li TK, Lumeng L, Kinkead B, Owens MJ, Nemeroff CB (1999) Neurontensin studies in alcohol naive, preferring and non-preferring rats. Neuroscience 93: 227-236.

Elliott PJ, Nemeroff CB (1986) Repeated neurotensin administration in the ventral tegmental area: effects on baseline and D-amphetamine-induced locomotor activity. Neurosci Lett 68: 239-244.

Erwin VG, Markel PD, Johnson TE, Gehle VM, Jones BC (1997) Common quantitative trait loci for alcohol-related behaviors and central nervous system neurotensin measures: hypnotic and hypothermic effects. J Pharmacol Exp Ther 280: 911-918.

Erwin VG, Su NC (1989) Neurotensin and ethanol interactions on hypothermia and locomotor activity in LS and SS mice. Alcohol Clin Exp Res 13: 91-94.

von Euler G, Fuxe K (1987) Neurotensin reduces the affinity of D-2 dopamine receptors in rat striatal membranes. Acta Physiol Scand 131: 625-626.

von Euler G, Meister B, Hökfelt T, Eneroth P, Fuxe K (1990) Intraventricular injection of neurotensin reduces dopamine D2 agonist binding in rat forebrain and intermediate lobe of the pituitary gland. Relationship to serum hormone levels and nerve terminal coexistence. Brain Res 531: 253-262.

von Euler G, van der Ploeg I, Fredholm BB, Fuxe K (1991) Neurotensin decreases the affinity of dopamine D2 agonist binding by a G protein-independent mechanism. J Neurochem 56: 178-183.

von Euler G (1991) Biochemical characterization of the intramembrane interaction between neurotensin and dopamine D2 receptors in the rat brain. Brain Res 561: 93-98.

Fadel J, Dobner PR, Deutch AY (2006) Amphetamine-elicited striatal Fos expression is attenuated in neurotensin null mutant mice. Neurosci Lett 402: 97-101.

Fatigati MD, Anderson RM, Rompré P (2000) Effects of prefrontal cortex microinjection of neurotensin-(8-13) on midbrain dopamine and non-dopamine cell firing. Brain Res 876: 196-200.

Feifel D, Melendez G, Murray RJ, Tina Tran DN, Rullan MA, Shilling PD (2008) The reversal of amphetamine-induced locomotor activation by a selective neurotensin-1 receptor agonist does not exhibit tolerance. Psychopharmacology (Berl) 200: 197-203.

Felszeghy K, Espinosa JM, Scarna H, Bérod A, Rostène W, Pélaprat D (2007) Neurotensin receptor antagonist administered during cocaine withdrawal decreases locomotor sensitization and conditioned place preference. Neuropsychopharmacology 32: 2601-2610.

Fenu S, Spina L, Rivas E, Longoni R, Di Chiara G (2006) Morphine-conditioned single-trial place preference: role of nucleus accumbens shell dopamine receptors in acquisition, but not expression. Psychopharmacology (Berl) 187: 143-153.

Ferraro L, Antonelli T, O'Connor WT, Fuxe K, Soubrié P, Tanganelli S (1998) The striatal neurotensin receptor modulates striatal and pallidal glutamate and GABA release: functional evidence for a pallidal glutamate-GABA interaction via the pallidal-subthalamic nucleus loop. J Neurosci 18: 6977-6989.

Ferraro L, Beggiato S, Borroto-Escuela DO, Ravani L, O'Connor WT, Tomasini MC, Borelli AC, Agnati LF, Antonelli T, Tanganelli S, Fuxe K (2014) Neurotensin NTS1-dopamine D2 receptor-receptor interactions in putative receptor heteromers: relevance for Parkinson's disease and schizophrenia. Curr Protein Pept Sci 15: 681-690.

Ferraro L, O'Connor WT, Antonelli T, Fuxe K, Tanganelli S (1997) Differential effects of intrastriatal neurotensin(1-13) and neurotensin(8-13) on striatal dopamine and pallidal GABA release. A dual-probe microdialysis study in the awake rat. Eur J Neurosci 9: 1838-1846.

Ferraro L, Tomasini MC, Beggiato S, Guerrini R, Salvadori S, Fuxe K, Calzà L, Tanganelli S, Antonelli T (2009) Emerging evidence for neurotensin receptor 1 antagonists as novel pharmaceutics in neurodegenerative disorders. Mini Rev Med Chem 9: 1429-1438.

Ferraro L, Tomasini MC, Mazza R, Fuxe K, Fournier J, Tanganelli S, Antonelli T (2008) Neurotensin receptors as modulators of glutamatergic transmission. Brain Res Rev 58: 365-73.

Filip M, Siwanowicz J (2001) Implication of the nucleus accumbens shell, but not core, in the acute and sensitizing effects of cocaine in rats. Pol J Pharmacol 53: 459-466.

Frankel PS, Hoonakker AJ, Alburges ME, McDougall JW, McFadden LM, Fleckenstein AE, Hanson GR (2011) Effect of methamphetamine self-administration on neurotensin systems of the basal ganglia. J Pharmacol Exp Ther 336: 809-815.

Fredrickson P, Boules M, Stennett B, Richelson E (2014) Neurotensin agonist attenuates nicotine potentiation to cocaine sensitization. Behav Sci (Basel) 4: 42-52.

Fredrickson P, Boules M, Yerbury S, Richelson E (2003a) Novel neurotensin analog blocks the initiation and expression of nicotine-induced locomotor sensitization. Brain Res 979: 245-248.

Fredrickson P, Boules M, Yerbury S, Richelson E (2003b) Blockade of nicotine-induced locomotor sensitization by a novel neurotensin analog in rats. Eur J Pharmacol 458: 111-118.

Fuxe K, Marcellino D, Rivera A, Diaz-Cabiale Z, Filip M, Gago B, Roberts DC, Langel U, Genedani S, Ferraro L, de la Calle A, Narvaez J, Tanganelli S, Woods A, Agnati LF (2008) Receptor-receptor interactions within receptor mosaics. Impact on neuropsychopharmacology. Brain Res Rev 58: 415-452.

Fuxe K, O'Connor WT, Antonelli T, Osborne PG, Tanganelli S, Agnati LF, Ungerstedt U (1992) Evidence for a substrate of neuronal plasticity based on pre- and postsynaptic neurotensin-dopamine receptor interactions in the neostriatum. Proc Natl Acad Sci USA 89: 5591-5595.

Geisler S, Bérod A, Zahm DS, Rostène W (2006) Brain neurotensin, psychostimulants, and stress-emphasis on neuroanatomical substrates. Peptides 27: 2364-2384.

German CL, Hoonakker AH, Fleckenstein AE, Hanson GR (2014) Mephedrone alters basal ganglia and limbic neurotensin systems. J Neurochem 130: 402-407.

Glimcher PW, Giovino AA, Hoebel BG (1987) Neurotensin self-injection in the ventral tegmental area. Brain Res. 403: 147-150.

Glimcher PW, Margolin DH, Giovino AA, Hoebel BG (1984) Neurotensin: a new 'reward peptide'. Brain Res. 291: 119-124.

Hall FS, Centeno M, Perona MT, Adair J, Dobner PR, Uhl GR (2012) Effects of neurotensin gene knockout in mice on the behavioral effects of cocaine. Psychopharmacology (Berl) 219: 35-45.

Hanson GR, Hoonakker AJ, Alburges ME, McFadden LM, Robson CM, Frankel PS (2012) Response of limbic neurotensin systems to methamphetamine self-administration. Neuroscience 203: 99-107.

Hanson GR, Hoonakker AJ, Robson CM, McFadden LM, Frankel PS, Alburges ME (2013) Response of neurotensin basal ganglia systems during extinction of methamphetamine self-administration in rat. J Pharmacol Exp Ther 346: 173-181.

Hedou G, Feldon J, Heidbreder CA (1999) Effects of cocaine on dopamine in subregions of the rat prefrontal cortex and their efferents to subterritories of the nucleus accumbens. Eur J Pharmacol 372: 143-155.

Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C (1991) Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 41: 89-125.

Hertel P, Byskov L, Didriksen M, Arnt J (2001) Induction of tolerance to the suppressant effect of the neurotensin analogue NT69L on amphetamine-induced hyperactivity. Eur J Pharmacol 422: 77-81.

Horger BA, Taylor JR, Elsworth JD, Roth RH (1994) Preexposure to, but not cotreatment with, the neurotensin antagonist SR 48692 delays the development of cocaine sensitization. Neuropsychopharmacology 11: 215-222.

Kalivas PW, Burgess SK, Nemeroff CB, Prange AJ Jr (1983) Behavioral and neurochemical effects of neurotensin microinjection into the ventral tegmental area of the rat. Neuroscience 8: 495-505.

Kalivas PW, Duffy P (1990) Effect of acute and daily neurotensin and enkephalin treatments on extracellular dopamine in the nucleus accumbens. J Neurosci 10: 2940-2949.

Kalivas PW, Miller JS (1984) Neurotensin neurons in the ventral tegmental area project to the medial nucleus accumbens. Brain Res 300: 157-160.

Kalivas PW, Nemeroff CB, Prange AJ Jr (1984) Neurotensin microinjection into the nucleus accumbens antagonizes dopamine-induced increase in locomotion and rearing. Neuroscience 11: 919-930.

Kalivas PW, Taylor S (1985) Behavioral and neurochemical effect of daily injection with neurotensin into the ventral tegmental area. Brain Res 358: 70-76.

Kalivas PW, Weber B (1988) Amphetamine injection into the ventral mesencephalon sensitizes rats to peripheral amphetamine and cocaine. J Pharmacol Exp Ther 245: 1095-1102.

Katsanos GS, Anogianaki A, Castellani ML, Ciampoli C, De Amicis D, Orso C, Pollice R, Vecchiet J, Tetè S, Salini V, Caraffa A, Patruno A, Shaik YB, Kempuraj D, Doyle R, Antinolfi PL, Cerulli G, Conti CM, Fulcheri M, Neri G, Sabatino G (2008) Biology of neurotensin: revisited study. Int J Immunopathol Pharmacol 21: 255-259.

Kempadoo KA, Tourino C, Cho SL, Magnani F, Leinninger GM, Stuber GD, Zhang F, Myers MG, Deisseroth K, de Lecea L, Bonci A (2013) Hypothalamic neurotensin projections promote reward by enhancing glutamate transmission in the VTA. J Neurosci 33: 7618-7626.

Kinkead B, Nemeroff CB (2004) Neurotensin, schizophrenia, and antipsychotic drug action. Int Rev Neurobiol 59: 327-349.

Kitabgi P, Carraway R, Leeman SE (1976) Isolation of a tridecapeptide from bovine intestinal tissue and its partial characterization as neurotensin. J Biol Chem. 251: 7053-7058.

Kitabgi P, Hervé D, Studler JM, Tramu G, Rostène W, Tassin JP (1989) Neurotensin/dopamine interactions. Encephale Spec No: 91-4.

Kitabgi P, De Nadai F, Rovère C, Bidard JN (1992) Biosynthesis, maturation, release, and degradation of neurotensin and neuromedin N. Ann NY Acad Sci 668: 30-42.

Kitabgi P (2006) Prohormone convertases differentially process pro-neurotensin/neuromedin N in tissues and cell lines. J Mol Med (Berl) 84: 628-634.

Kitabgi P (2010) Neurotensin and neuromedin N are differentially processed from a common precursor by prohormone convertases in tissues and cell lines. Results Probl Cell Differ 50: 85-96.

LaCrosse AL, Olive MF (2013) Neuropeptide systems and schizophrenia. CNS Neurol Disord Drug Targets 12: 619-632.

László K, Tóth K, Kertes E, Péczely L, Lénárd L (2010) The role of neurotensin in positive reinforcement in the rat central nucleus of amygdala. Behav Brain Res. 208: 430-435.

Lee MR, Hinton DJ, Song JY, Lee KW, Choo C, Johng H, Unal SS, Richelson E, Choi DS (2010) Neurotensin receptor type 1 regulates ethanol intoxication and consumption in mice. Pharmacol Biochem Behav. 95: 235-241.

Lee MR, Hinton DJ, Unal SS, Richelson E, Choi DS (2011) Increased ethanol consumption and preference in mice lacking neurotensin receptor type 2. Alcohol Clin Exp Res. 35: 99-107.

Lévesque K, Lamarche C, Rompré PP (2008) Evidence for a role of endogenous neurotensin in the development of sensitization to the locomotor stimulant effect of morphine. Eur J Pharmacol 594: 132-138.

Li XM, Ferraro L, Tanganelli S, O'Connor WT, Hasselrot U, Ungerstedt U, Fuxe K (1995) Neurotensin peptides antagonistically regulate postsynaptic dopamine D2 receptors in rat nucleus accumbens: a receptor binding and microdialysis study. J Neural Transm Gen Sect 102: 125-137.

Liang Y, Boules M, Shaw AM, Williams K, Fredrickson P, Richelson E (2008) Effect of a novel neurotensin analog, NT69L, on nicotine-induced alterations in monoamine levels in rat brain. Brain Res 1231: 6-15.

Lopak V, Erb S (2005) Activation of central neurotensin receptors reinstates cocaine seeking in the rat: modulation by a D1/D5, but not D2/D3, receptor antagonist. Psychopharmacology (Berl) 182: 297-304.

Luttinger D, Nemeroff CB, Prange AJ Jr (1982) The effects of neuropeptides on discrete-trial conditioned avoidance responding. Brain Res 237: 183-192.

Marie-Claire C, Palminteri S, Romualdi P, Noble F (2008) Effects of the selective neurotensin antagonist SR 142948A on 3,4-methylenedioxymethamphetamine-induced behaviours in mice. Neuropharmacology 54: 1107-1111.

Mazella J, Vincent JP (2006) Functional roles of the NTS2 and NTS3 receptors. Peptides 27: 2469-2475.

McBride WJ, Murphy JM, Ikemoto S (1999) Localization of brain reinforcement mechanisms: intracranial self-administration and intracranial place-conditioning studies. Behav Brain Res 101: 129-152.

Meisenberg G, Simmons WH (1985) Motor hypoactivity induced by neurotensin and related peptides in mice. Pharmacol Biochem Behav 22: 189-193.

Minamino N, Kangawa K, Matsuo H (1984) Neuromedin N: a novel neurotensin-like peptide identified in porcine spinal cord. Biochem Biophys Res Commun 122: 542-549.

Myers RM, Shearman JW, Kitching MO, Ramos-Montoya A, Neal DE, Ley SV (2009) Cancer, chemistry, and the cell: molecules that interact with the neurotensin receptors. ACS Chem Biol 4: 503-525.

Nemeroff CB, Luttinger D, Hernandez DE, Mailman RB, Mason GA, Davis SD, Widerlöv E, Frye GD, Kilts CA, Beaumont K, Breese GR, Prange AJ Jr (1983) Interactions of neurotensin with brain dopamine systems: biochemical and behavioral studies. J Pharmacol Exp Ther 225: 337-345.

Nemeroff CB (1980) Neurotensin: perchance an endogenous neuroleptic? Biol Psychiatry 15: 283-302.

Nouel D, Dubuc I, Kitabgi P, Costentin J (1990) Centrally administered [D-Trp11]neurotensin, as well as neurotensin protected from inactivation by thiorphan, modifies locomotion in rats in a biphasic manner. Peptides 11: 551-555.

O'Connor WT (2001) Functional neuroanatomy of the ventral striopallidal GABA pathway. New sites of intervention in the treatment of schizophrenia. J Neurosci Methods 109: 31-39.

Ollmann T, Péczely L, László K, Kovács A, Gálosi R, Berente E, Karádi Z, Lénárd L (2015) Positive reinforcing effect of neurotensin microinjection into the ventral pallidum in conditioned place preference test. Behav Brain Res 278: 470-475.

Panayi F, Colussi-Mas J, Lambás-Señas L, Renaud B, Scarna H, Bérod A (2005) Endogenous neurotensin in the ventral tegmental area contributes to amphetamine behavioral sensitization. Neuropsychopharmacology. 30: 871-879.

Panayi F, Dorso E, Lambás-Señas L, Renaud B, Scarna H, Bérod A (2002) Chronic blockade of neurotensin receptors strongly reduces sensitized, but not acute, behavioral response to D-amphetamine. Neuropsychopharmacology 26: 64-74.

Pelaprat D (2006) Interactions between neurotensin receptors and G proteins. Peptides 27: 2476-2487.

Petrie KA, Schmidt D, Bubser M, Fadel J, Carraway RE, Deutch AY (2005) Neurotensin activates GABAergic interneurons in the prefrontal cortex. J Neurosci 25: 1629-1636.

Phillips TJ, Shen EH (1996) Neurochemical bases of locomotion and ethanol stimulant effects. Int Rev Neurobiol 39: 243-282.

Picciotto MR, Corrigall WA (2002) Neuronal systems underlying behaviors related to nicotine addiction: neural circuits and molecular genetics. J Neurosci 22: 3338-3341.

Pierce RC, Kalivas PW (1997) A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. Brain Res Brain Res Rev 25: 192-216.

Rakovska A, Giovannini MG, Della Corte L, Kalfin R, Bianchi L, Pepeu G (1998) Neurotensin modulation of acetylcholine and GABA release from the rat hippocampus: an in vivo microdialysis study. Neurochem Int 33: 335-340.

Ramos-Ortolaza DL, Negrón A, Cruz D, Falcón E, Iturbe MC, Cajigas MH, Maldonado-Vlaar CS (2009) Intra-accumbens shell injections of SR48692 enhanced cocaine self-administration intake in rats exposed to an environmentally-elicited reinstatement paradigm. Brain Res 1280: 124-136.

Richelson E, Boules M, Fredrickson P (2003) Neurotensin agonists: possible drugs for treatment of psychostimulant abuse. Life Sci 73: 679-690.

Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive sensitization theory of addiction. Brain Res Brain Res Rev 18: 247-291.

Robledo P, Maldonado R, Koob GF (1993) Neurotensin injected into the nucleus accumbens blocks the psychostimulant effects of cocaine but does not attenuate cocaine self-administration in the rat. Brain Res 622: 105-112.

Rompré PP, Bauco P, Gratton A (1992) Facilitation of brain stimulation reward by mesencephalic injections of neurotensin-(1-13). Eur J Pharmacol 211: 295-303.

Rompré PP, Bauco P (2006) Neurotensin receptor activation sensitizes to the locomotor stimulant effect of cocaine: a role for NMDA receptors. Brain Res 1085: 77-86.

Rompré PP, Boye SM, Moisan J (1998) Activation of neurotensin receptors in the prefrontal cortex stimulates midbrain dopamine cell firing. Eur J Pharmacol 341: 169-172.

Rompré PP, Boye SM (1993) Opposite effects of mesencephalic microinjections of cholecystokinin octapeptide and neurotensin-(1-13) on brain stimulation reward. Eur J Pharmacol 232: 299-303.

Rompré PP, Perron S (2000) Evidence for a role of endogenous neurotensin in the initiation of amphetamine sensitization. Neuropharmacology 39: 1880-1892.

Rompré PP (1995) Psychostimulant-like effect of central microinjection of neurotensin on brain stimulation reward. Peptides 16: 1417-1420.

Rompré PP (1997) Repeated activation of neurotensin receptors sensitizes to the stimulant effect of amphetamine. Eur J Pharmacol 328: 131-134.

Rostène W, Brouard A, Dana C, Masuo Y, Agid F, Vial M, Lhiaubet AM, Pelaprat D (1992) Interaction between neurotensin and dopamine in the brain. Morphofunctional and clinical evidence. Ann NY Acad Sci 668: 217-231.

Rouibi K, Rompré PP (2014) Role of context in neurotensin-induced sensitization to the locomotor stimulant effect of amphetamine. Peptides 58: 103-107.

Sarhan S, Hitchcock JM, Grauffel CA, Wettstein JG (1997) Comparative antipsychotic profiles of neurotensin and a related systemically active peptide agonist. Peptides 18: 1223-1227.

Sellings LH1, Clarke PB (2003) Segregation of amphetamine reward and locomotor stimulation between nucleus accumbens medial shell and core. J Neurosci 23: 6295-6303.

Sesack SR, Pickel VM (1992) Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J Comp Neurol. 320: 145-160.

Shi WS, Bunney BS (1990) Neurotensin attenuates dopamine D2 agonist quinpirole-induced inhibition of midbrain dopamine neurons. Neuropharmacology 29: 1095-1097.

Shilling PD, Richelson E, Feifel D (2003) The effects of systemic NT69L, a neurotensin agonist, on baseline and drug-disrupted prepulse inhibition. Behav Brain Res 143: 7-14.

Skoog KM, Cain ST, Nemeroff CB (1986) Centrally administered neurotensin suppresses locomotor hyperactivity induced by d-amphetamine but not by scopolamine or caffeine. Neuropharmacology 25: 777-782.

Steinberg R, Brun P, Fournier M, Souilhac J, Rodier D, Mons G, Terranova JP, Le Fur G, Soubrié P (1994) SR48692, a non-peptide neurotensin receptor antagonist differentially affects neurotensin-induced behaviour and changes in dopaminergic transmission. Neuroscience 59: 921-929.

Steinberg R, Brun P, Souilhac J, Bougault I, Leyris R, Le Fur G, Soubrié P (1995) Neurochemical and behavioural effects of neurotensin vs [D-Tyr11]neurotensin on mesolimbic dopaminergic function. Neuropeptides 28: 43-50.

Steketee JD, Kalivas PW (2011) Drug wanting: behavioral sensitization and relapse to drug-seeking behavior. Pharmacol Rev 63; 348-365.

St-Gelais F, Jomphe C, Trudeau LE (2006) The role of neurotensin in central nervous system pathophysiology: what is the evidence? J Psychiatry Neurosci 31: 229-245.

Tanganelli S, Antonelli T, Tomasini MC, Beggiato S, Fuxe K, Ferraro L (2012) Relevance of dopamine D(2)/neurotensin NTS1 and NMDA/neurotensin NTS1 receptor interaction in psychiatric and neurodegenerative disorders. Curr Med Chem 19: 304-316.

Tanganelli S, O'Connor WT, Ferraro L, Bianchi C, Beani L, Ungerstedt U, Fuxe K (1994) Facilitation of GABA release by neurotensin is associated with a reduction of dopamine release in rat nucleus accumbens. Neuroscience 60: 649-657.

Torregrossa MM, Kalivas PW (2008) Neurotensin in the ventral pallidum increases extracellular gamma-aminobutyric acid and differentially affects cue- and cocaine-primed reinstatement. J Pharmacol Exp Ther 325: 556-566.

Tyler-McMahon BM, Boules M, Richelson E (2000) Neurotensin: peptide for the next millennium. Regul Pept 93: 125-136.

Tzschentke TM (2007) Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addict Biol 12: 227-462.

Tzschentke TM1, Schmidt WJ (2003) Glutamatergic mechanisms in addiction. Mol Psychiatry 8: 373-382.

Vadnie CA, Hinton DJ, Choi S, Choi Y, Ruby CL, Oliveros A, Prieto ML, Park JH, Choi DS (2014) Activation of neurotensin receptor type 1 attenuates locomotor activity. Neuropharmacology 85: 482-492.

Vanderschuren LJ, Kalivas PW (2000) Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. Psychopharmacology (Berl) 151: 99-120.

Vincent JP, Mazella J, Kitabgi P (1999) Neurotensin and neurotensin receptors. Trends Pharmacol Sci 20: 302-309.

Wagstaff JD, Bush LG, Gibb JW, Hanson GR (1994) Endogenous neurotensin antagonizes methamphetamine-enhanced dopaminergic activity. Brain Res 665: 237-244.

Werkman TR, Kruse CG, Nievelstein H, Long SK, Wadman WJ (2000) Neurotensin attenuates the quinpirole-induced inhibition of the firing rate of dopamine neurons in the rat substantia nigra pars compacta and the ventral tegmental area. Neuroscience 95: 417-423.

Widdowson PS (1987) The effect of neurotensin, TRH and the delta-opioid receptor antagonist ICI 174864 on alcohol-induced narcosis in rats. Brain Res. 424: 281-289.

Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psychol Rev 94: 469-492.

Zahm DS, Heimer L (1988) Ventral striatopallidal parts of the basal ganglia in the rat: I. Neurochemical compartmentation as reflected by the distributions of neurotensin and substance P immunoreactivity. J Comp Neurol 272: 516-535.

Zahm DS, Heimer L (1990) Two transpallidal pathways originating in the rat nucleus accumbens. J Comp Neurol 302: 437-446.

TABLE 1. NEUROTENSIN AND DRUG OF ABUSE-EVOKED HYPERLOCOMOTION

Drug (dose range, administration route)	Drug of abuse (dose range, administration route)	Species (sex)	Change	References
NEUROTENSIN				
NT (30 µg; i.c.)	Amph (1-3 mg/kg; i.p.)	SD rats (male)	↓	*Skoog et al., 1986*
NT (30 µg; i.c.v.)	Amph (3 mg/kg; i.p.)	OF1 mice (male)	↓	*Sarhan et al., 1997*
NT (2,5 µg; intra-VTA injection)	Amph (0.5 mg/kg; i.p.)	SD rats (male)	Ø	*Elliott and Nemeroff, 1986*
NT (4.2, 6.7 µg; intra-NAC injection)	Cocaine (15 mg/kg; i.p.)	Wistar rats (male)	↓	*Robledo et al., 1993*
NT (4.2, 16.7 µg; intra-NAC injection)	Amph (0.75 mg/kg; i.p.)	Wistar rats (male)	↓	*Robledo et al., 1993*
NEUROTENSIN ANALOGUES AND AGONISTS				
NT1 (0.3 mg/kg; i.p.)	Amph (3 mg/kg; i.p.)	OF1 mice (male)	↓	*Sarhan et al., 1997*
NT69L (0.10 µmol/kg; s.c.)	Amph (0.5 mg/kg; s.c.)	Wistar rats (male)	↓	*Hertel et al., 2001*
NT69L (1 mg/kg; i.p.)	Amph (0.75 - 5 mg/kg; i.p.)	SD rats (male)	↓	*Boules et al., 2001*
NT69L (1 mg/kg; for 1, 3 or 5 days; i.p.)	Amph (5 mg/kg; i.p.)	SD rats (male)	↓	*Boules et al., 2003*
NT69L (1 mg/kg; i.p.)	Cocaine (4 - 40 mg/kg; i.p.)	SD rats (male)	↓	*Boules et al., 2001*
NT69L (1 mg/kg; for 3 or 5 days; i.p.)	Cocaine (40 mg/kg; i.p.)	SD rats (male)	↓	*Boules et al., 2003*
NT69L (1.0 mg/kg; i.p.)	Ethanol (1.5 g/kg; i.p.)	C57BL/6J mice (male)	↓	*Lee et al., 2010; 2011*
NT69L (0.5, 1.0, 2.0 mg/kg; i.p.)	Ethanol (1.0, 1.5 g/kg; i.p.)	NTS1 null mice (male)	Ø	*Lee et al., 2010*
NT69L (1.0 mg/kg; i.p.)	Ethanol (1.5 g/kg; i.p.)	NTS2 null mice (male)	↓	*Lee et al., 2011*
PD149163 (1 mg/kg; for 8 days; s.c.)	Amph (0.5 mg/kg; s.c.)	SD rats (male)	↓	*Feifel et al., 2008*
NEUROTENSIN ANTAGONISTS				
SR 48692 (0.1–1 mg/kg; i.p.)	Amph (2.5 mg/kg; i.p.)	CD1 Mice (male)	Ø	*Casti et al., 2004*
SR 48692 (1 mg/kg; i.p.)	Cocaine (15 mg/kg; i.p.)	SD rats (male)	Ø	*Betancur et al., 1998*
SR 48692 (1 mg/kg; for 5 days; i.p.)	Cocaine (15 mg/kg; i.p.)	SD rats (male)	↓	*Betancur et al., 1998*
SR 142948A (0.03–0.1 mg/kg; i.p.)	Amph (2.5 mg/kg; i.p.)	CD1 Mice (male)	Ø	*Casti et al., 2004*
SR 142948A (100 µg/kg; i.p.)	Amph (2 mg/kg; i.p.)	SD rats (male)	Ø	*Caceda et al., 2012*
SR 142948A (1 mg/kg; i.p.)	MDMA (9 mg/kg; i.p.)	CD1 Mice (male)	↓	*Marie Claire et al., 2008*

Abbreviations: Amph – Amphetamine; SD - Sprague Dawley; ↓ - decrease; Ø – no change; i.c.-intracisternal; , i.c.v. - intracerebroventricular; i.p. – intraperitoneal; NAC- nucleus acumbens; VTA-ventral tegmental area.

TABLE 2A. NEUROTENSIN AND DRUG OF ABUSE-EVOKED SENSITIZATION - DEVELOPMENT

Drug (dose range, administration route)	Drug of abuse (dose range, administration, route)	Species (sex)	Change	References
NEUROTENSIN ANALOGUES AND AGONISTS				
NT69L (1 mg/kg; i.p.; once per week, for 5 weeks)	Nicotine (0.35 mg/kg; s.c.; once per week, for 6 weeks)	SD rats (male)	↓	*Fredrickson et al., 2003a*
NT69L (1 mg/kg; i.p.; for 15 days)	Nicotine (0.35 mg/kg; s.c.; for 15 days)	SD rats (male)	↓	*Fredrickson et al., 2003b*
NEUROTENSIN ANTAGONISTS				
SR 48692 (40, 80, 160 mg/kg; i.p.; day 1, 3, 5, 7)	Amph (1.5 mg/kg; i.p.; day 1, 3, 5, 7) + Amph (0.75 mg/kg; i.p.; day 14)	Long Evans rats (male)	↓	*Rompré and Perron, 2000*
SR 48692 (0.1, 1 mg/kg; i.p.; pretreatment from day 1 to 14)	Amph (0.5 or 1 mg/kg; i.p.; day 1, 3, 5, 7 + day 14)	SD rats (male)	↓	*Panayi et al., 2002*
SR 48692 (80 µg/kg; i.p.or p.o.; for 5 days) *(pre-exposure)*	Cocaine (15 mg/kg; i.p.; every other day, for 6 days after pre-exposure)	SD rats (male)	↓	*Horger et al., 1994*
SR 48692 (80 µg/kg; i.p.; *cotreatment* 2 and 4 days before test)	Cocaine (15 mg/kg; i.p.; *cotreatment* 2 and 4 days before test + *alone* day of test)	SD rats (male)	Ø	*Horger et al., 1994*
SR 48692 (160, 320, 640 µg/kg; i.p.; day 1, 3, 5, 7)	Morphine (5.0 mg/kg; i.p.; day 1, 3, 5, 7) + Morphine (2.5 mg/kg; i.p.; day 14)	Long Evans rats (male)	↓	*Lévesque et al., 2008*
SR 142948A (5 pmol/side; intra-VTA injection; day 1)	Amph (1 mg/kg; s.c.; day 1 + day 8)	SD rats (male)	↓	*Panayi et al., 2005*
SR 142948A (0.03, 0.1, 0.3 mg/kg; i.p.; day 1)	Amph (1 mg/kg; s.c.; day 1 + day 8)	SD rats (male)	Ø	*Panayi et al., 2005*

Abbreviations: Amph – Amphetamine; ↓ - decrease; Ø – no change; i.p. – intraperitoneal; p.o. – per os; s.c. – subcutaneous; VTA- ventral tegmental area.

**TABLE 2B. NEUROTENSIN AND DRUG OF ABUSE-EVOKED SENSITIZATION –
EXPRESSION**

Drug (dose range, administration route)	Drug of abuse (dose range, administration, route)	Species (sex)	Change	References
NEUROTENSIN ANALOGUES AND AGONISTS				
NT69L (1 mg/kg, i.p; on 6th week)	Nicotine (0.35 mg/kg; s.c.; for 6 weeks)	SD rats (male)	↓	*Fredrickson et al., 2003a*
NT69L (1 mg/kg i.p.; pre-treatment to cocaine challenge)	Cocaine (20 mg/kg; i.p.; for 4 days + challenge)	Wistar rats (male)	↓	*Fredrickson et al., 2014*
NT69L (1 mg/kg i.p.; pre-treatment to cocaine challenge)	Nicotine (0.35 mg/kg; s.c.; for 7 days) + Cocaine (20 mg/kg; i.p.; for 4 days) + Cocaine (20 mg/kg; i.p.)	Wistar rats (male)	↓	*Fredrickson et al., 2014*
NEUROTENSIN ANTAGONISTS				
SR 48692 (0.3 mg/kg; i.p; day 2, 9, 16 after pre-treatment period)	Amph (2.0 mg/kg, i.p.; every other day for 13 days + day 2, 9, 16 after pre-treatment period)	Swiss mice (female)	↓	*Costa et al., 2001*
SR 48692 (0.3 mg/kg i.p.; for 7 days after amphetamine discontinuation)	Amph (2.0 mg/kg; i.p.; every other day for 11 days in pre-treatment phase + day 8 after amphetamine discontinuation)	Swiss mice (male)	↓	*Costa et al., 2007*
SR 142948A (5 pmol/side, intra-VTA injection; day 8)	Amph (1 mg/kg; s.c.; day 1 + day 8)	Sprague Dawley rats (male)	Ø	*Panayi et al., 2005*

Abbreviations: Amph – Amphetamine; ↓ - decrease; Ø – no change;; i.p. – intraperitoneal; s.c. – subcutaneous; VTA- ventral tegmental area.

TABLE 2C. NEUROTENSIN AND DRUG OF ABUSE-EVOKED SENSITIZATION – CROSS SENSITIZATION

Drug (dose range, administration route)	Drug of abuse (dose range, administration, route)	Species (sex)	Change	References
NEUROTENSIN AND ANALOGUES				
NT (18 nmol/10 ml; i.c.v.; day 1, 3, 5, 7)	Amph (1 mg/kg; i.p.; day 14)	Long Evans rats (male)	Cross-sensitization	*Rompré, 1997*
(D-Tyr11)-NT (18 nmol/10 ml; i.c.v.; day 1, 3, 5, 7)	Amph (1 mg/kg; i.p.; day 14)	Long Evans rats (male)	Cross-sensitization	*Rompré, 1997*
(D-Tyr11)-NT (18 nmol/10 ml; i.c.v.; day 1, 3, 5, 7)	Cocaine (7.5 mg/kg; i.p.; day 14)	Long Evans rats (male)	Cross-sensitization	*Rompré and Bauco, 2006*
(D-Tyr11)-NT (18 nmol/10 ml; i.c.v.; day 1, 4, 7, 10)	Amph (0.75 mg/kg; i.p.; day 17)	Long Evans rats (male)	Cross-sensitization	*Rouibi and Rompré, 2014*

Abbreviations: Amph – Amphetamine; i.c.v. - intracerebroventricular; i.p. – intraperitoneal.

TABLE 3: NEUROTENSIN AND DRUG OF ABUSE-EVOKED CPP

Drug (dose range, administration route, schedule)	Drug of abuse (dose range, administration route, schedule)	Species (sex)	Change	References
NEUROTENSIN ANTAGONISTS				
DEVELOPEMENT				
SR 142948A (1 mg/kg; i.p; day 1, 3, 5)	MDMA (9 mg/kg; i.p.; for 6 days, alterning with saline)	CD1 mice (male)	Ø	*Marie-Claire et al., 2008*
EXPRESSION				
SR 48692 (1 mg/kg; i.p.; day 9-18)	Cocaine (15 mg/kg; i.p.; day 2, 4, 6, 8 of conditioning phase + day 17)	Sprague Dawley rats (male)	↓	*Felszeghy et al., 2007*
SR 142948A (1 mg/kg; i.p.; day 1, 3, 5 of conditioning phase + day 7)	MDMA (9 mg/kg; i.p.; for 6 days of conditioning phase, alterning with saline)	CD1 mice (male)	↓	*Marie-Claire et al., 2008*

Abbreviations: ↓ - decrease; Ø – no change; i.p. – intraperitoneal.

TABLE 4: NEUROTENSIN AND DRUG OF ABUSE-EVOKED SELF ADMINISTRATION

Drug (dose range, administration route, schedule)	Drug of abuse (training dose range, administration route, schedule of reinforcement)	Species (sex)	Change	References
MAINTENANCE				
NEUROTENSIN				
NT (4.2, 8.4 and 16.7 µg, total bilateral administration; intra-NAC injection)	Cocaine (0.75 mg/kg/infusion i.v.); SA FR5	Wistar rats (male)	Ø	*Robledo et al., 1993*
NEUROTENSIN ANALOGUES AND AGONISTS				
NT69L (1.0 mg/kg; i.p.); every 12 hours	Ethanol (3 to 6 to 10% v/v); two-bottle choice	C57BL/6J mice (male)	↓	*Lee et al., 2010; 2011*
NT69L (1.0 mg/kg; i.p.); every 12 hours	Ethanol (3 to 6 to10% v/v); two-bottles choice	NTS1 null mice (male)	Ø	*Lee et al., 2010*
NT69L (1.0 mg/kg; i.p.); every 12 hours	Ethanol (3 to 6 to 10% v/v); two-bottles choice	NTS2 null mice (male)	↓	*Lee et al., 2011*
NT69L (1 mg/kg; i.p.)	Nicotine (0.03 mg/kg/infusion i.v.); SA FR1-FR5	SD rats (male)	↓	*Boules et al., 2011*
PD 149163 (0.5 mg/kg; s.c.)	METH (0.06 mg/kg/infusion i.v.); SA FR1-FR5	SD rats (male)	↓	*Frankel et al., 2010*
NEUROTENSIN ANTAGONISTS				
SR 48692 (0.3 mg/kg); days 5-7 of SA	METH (0.06 mg/kg/infusion i.v.); SA FR1-FR5	SD rats (male)	Ø	*Frankel et al., 2010*
SUBSTITUTION				
NEUROTENSIN ANALOGUE AND AGONISTS				
PD 149163 (0.1 mg/kg/infusion i.v.)	METH (0.06 mg/kg/ infusion i.v.); SA from FR1 to FR2 to FR3 to FR5	SD rats (male)	↓	*Hanson et al., 2012*

Abbreviations: ↓ - decrease; Ø – no change; FR – fixed ratio; i.c.- intracisternal; , i.c.v. - intracerebroventricular; i.p. – intraperitoneal; i.v. – intravenous; METH- methamphetamine; NAC – nucleus accumbens; SA – self-administration; s.c. – subcutaneous.

TABLE 5: NEUROTENSIN AND DRUG PREFERENCE

Drug (dose range, administration route)	Drug of abuse (dose range, administration route)	Species (sex)	Change	References
NEUROTENSIN ANALOGUE AND AGONISTS				
NT69L (1.0 mg/kg; i.p.)	Ethanol (3 to 6 to 10% v/v); two-bottles choice	C57BL/6J mice (male)	↓	*Lee et al., 2010; 2011*
NT69L (1.0 mg/kg; i.p.)	Ethanol (3 to 6 to 10% v/v); two-bottles choice	NTS1 null mice (male)	Ø	*Lee et al., 2010*
NT69L (1.0 mg/kg; i.p.)	Ethanol (to 6 to 10% v/v); two-bottles choice	NTS2 null mice (male)	↓	*Lee et al., 2011*

Abbreviations: ↓ - decrease; Ø – no change; i.p. – intraperitoneal.

TABLE 6: NEUROTENSIN AND REINSTATEMENT OF DRUG-SEEKING BEHAVIOUR

Drug (dose range, administration route)	Drug of abuse (training dose range, administration route, schedule of reinforcement)	Reinstatement	Species (sex)	Change	References
DRUG-INDUCED					
NEUROTENSIN ANALOGUES					
NT(8–13) (3 nmol; intra-VP)	Cocaine (0.6 mg/kg/infusion i.v.); SA FR1	Cocaine (10, 30 mg/kg; i.p.)	SD rats (male)	↑	*Torregrossa and Kalivas, 2008*
NEUROTENSIN ANTAGONISTS					
SR 142948 (1nmol; intra-VP)	Cocaine (0.6 mg/kg/infusion i.v.); SA FR1	Cocaine (10 mg/kg; i.p.)	SD rats (male)	Ø	*Torregrossa and Kalivas, 2008*
SR 142948 (10 μg/kg; i.p.)	Cocaine (0.6 mg/kg/infusion i.v.); SA FR1	Cocaine (10 mg/kg; i.p.)	SD rats (male)	↓	*Torregrossa and Kalivas, 2008*
CUE-INDUCED					
NEUROTENSIN ANALOGUES					
NT(8–13) (3 nmol; intra-VP)	Cocaine (0.6 mg/kg/infusion i.v.); SA FR1	Light + tone + syringe pump activation cues	SD rats (male)	↓	*Torregrossa and Kalivas, 2008*
OTHER REINSTATEMENTS					
NEUROTENSIN AND ANALOGUES					
NT (15, 30 μg; i.c.v.)	cocaine (1.0 mg/kg/infusion i.v); SA FR1	Lever pressing	Long Evans rats (male)	↑	*Lopak et al., 2005*
D-TYR[11]NT (15, 30 μg; i.c.v.)	cocaine (1.0 mg/kg/infusion i.v); SA FR1	Lever pressing	Long Evans rats (male)	↑	*Lopak et al., 2005*

Abbreviations: ↓ - decrease; Ø – no change; FR- fixed ratio; i.c.v. - intracerebroventricular; i.p. – intraperitoneal; i.v. – intravenous; SA- self-administration; VP – ventral pallidum.