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Review

Multitasking with neurotensin in the central nervous system

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Abstract. The 13-amino acid peptide neurotensin (NT) was discovered over 30 years ago and has been implicated in a wide variety of neurotransmitter and endocrine functions. This review focuses on four areas where there has been substantial recent progress in understanding NT signaling and several functions of the endogenous peptide. The first area concerns the functional activation of the high-affinity NT receptor, NTR-1, including the delineation of the NT binding pocket and receptor domains involved in functional coupling to intracellular signaling pathways. The development of NT receptor antagonists and the application of genetic and molecular genetic approaches have accelerated progress in understanding NT function in several areas, including the involvement of NT in antipsychotic drug actions, psychostimulant sensitization and the modulation of pain, and these are reviewed in that order. There is now substantial evidence indicating that NT is required for certain antipsychotic drug actions and that the peptide plays a key role in stress-induced analgesia.

Key words. Antipsychotic drug; amphetamine; neuromedin N; striatum; stress-induced analgesia; pain.

Introduction

The tridecapeptide neurotensin (NT) was discovered by Carraway and Leeman over 30 years ago [1]. Subsequent complementary DNA (cDNA) cloning experiments revealed the structure of the NT precursor that is processed to yield both NT and the related hexapeptide neuromedin N (NMN) [2, 3]. The structure of the predicted 169–170 amino acid precursor has been confirmed in several studies that have also provided evidence that the precursor is differentially processed in the brain and gastrointestinal tract [4–8]. In the brain, the precursor is completely processed to yield both NT and NMN, although there appears to be some regional variation in the molar amounts of the two peptides [9, 10]. In contrast, the precursor is incompletely processed in the gastrointestinal tract to yield principally NT and an amino-terminally extended form of NMN that extends from the signal peptide cleavage site to the carboxyl terminus of NMN [6, 8]. Several lines of evidence indicate that different prohormone convertases (PCs) are responsible for differential processing of the NT precursor. PC2 has been reported to completely process the NT precursor, while PC1 and PC5A incompletely process the precursor to yield amino terminally extended NMN and NT [11, 12].

NT and NMN appear to have largely overlapping functions and bind to a common group of receptors that include two G protein-coupled receptors (NTR-1, NTR-2: also referred to as NTS1, NTS2) and two predominantly intracellular receptors of unknown function (NTR-3/sortilin, NTR-4/SorLA). The first NT receptor to be cloned was NTR-1, corresponding to the high-affinity levocabastine-insensitive NT receptor previously characterized in NT binding studies [13, 14]. This receptor appears to mediate most of the pharmacological and physiological effects of NT based on several lines of evidence that will be covered in this review. The second cloned receptor NTR-2 shares substantial sequence identity with NTR-1 and corresponds

to the low-affinity, levocabastine-sensitive receptor [15, 16]. The physiological functions of NTR-2 remain uncertain, particularly in view of the observation that two non-peptide NT antagonists (SR 48692, SR 142948A) act as agonists for NTR-2 in transfected tissue culture cells, while NT behaves as an antagonist [17–20]. However, there is increasing evidence that NTR-2 may mediate certain analgesic effects of NT, which will be reviewed in detail below. NTR-3 was initially identified as an NT binding protein in detergent solubilized brain membrane preparations and cDNA cloning revealed that this activity corresponds to the primarily intracellular sortilin protein [21]. Both sortilin and the structurally related SorLA are similar to previously identified sorting receptors, and the NT binding domain of these receptors is homologous to the luminal part of the yeast receptor for carboxypeptidase Y, Vsp10p [22–24]. The Vsp10p-related domains appear to comprise multifunctional binding sites containing multiple cysteine residues that form five intertwined disulfide bridges [25]. These receptors appear to function primarily in receptor internalization and ligand degradation, and NT has been shown to stimulate NTR-3/sortilin internalization [24, 26–28]. However, they also bear similarity to the hydra head activator peptide receptor that is required for appropriate development and growth of head structures during hydra development, and there is increasing evidence that NT may stimulate cell growth and migration through NTR-3/sortilin [29–31]. Although NTR-3/sortilin and NTR-4/sorLA may mediate some functions of NT, the available evidence suggests that most of the physiological functions and pharmacological effects of NT are mediated by NTR-1.

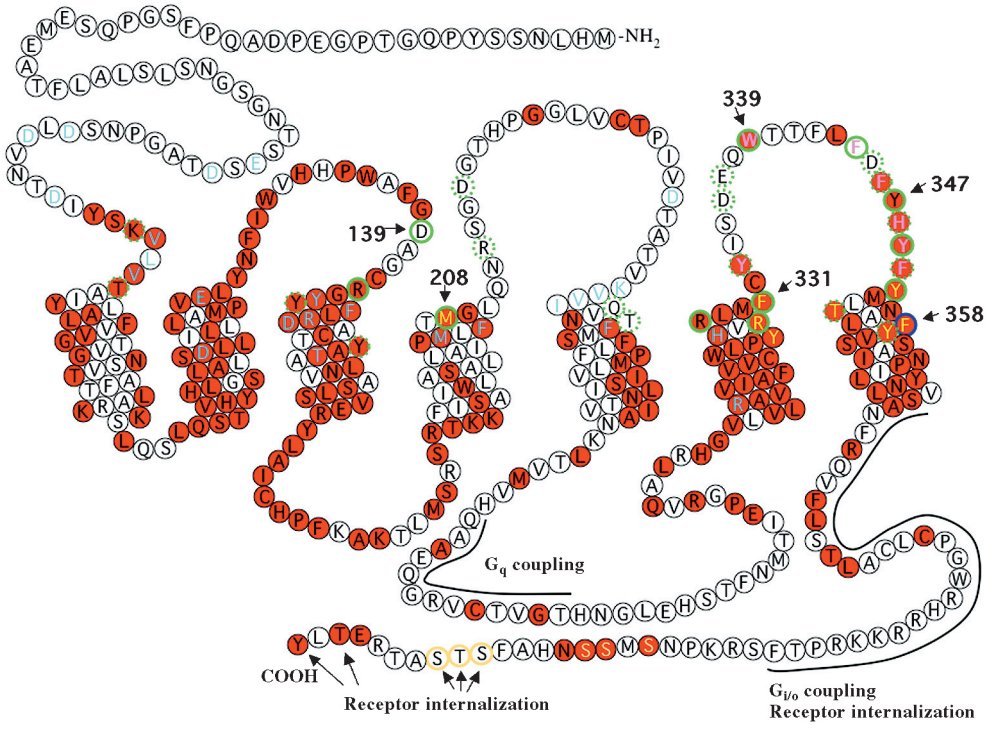

Figure 1. Schematic diagram of rat NTR-1 indicating functional and evolutionarily conserved residues. The amino acid sequences of NTR-1 from species ranging from man to the puffer fish were compared using BLAST (version 2.2.10). Amino acids that are identical in all species examined (human [14], rat [13], mouse [Genbank accession # NM_018766], dog [Genbank accession # XM_543088], chicken [Genbank accession # XM_425707], puffer fish [SINFRUP00000083583 and SINFRUP00000079588]) starting at Tyr^{62} in the rat sequence are indicated by red filled circles, using single-letter amino acid abbreviations. The dog sequence contains an insertion of 334 amino acids (positions 242–575 of the dog sequence) that is located between the amino acids that correspond to Gln^{239} and Val^{240} of the rat sequence and was not included in the analysis). The draft chicken genome NTR-1 sequence is truncated at the amino terminus and begins at the position corresponding to Asp^{230} in the rat sequence. The draft puffer fish NTR-1 sequences were found in two separate incomplete predicted open reading frames. Amino acids that are involved in NT binding are indicated by green circles (broken green circles indicate that NT binding was reduced 2–3-fold following Ala or Gly substitution) [41, 43]. Amino acids that have been implicated in SR 48692 binding are indicated by yellow letters [42]. Positions that were tested but had no effect on either NT or SR 48692 binding are indicated by blue letters. Substitution of Ala for Phe^{358} (blue circle) resulted in constitutive PI turnover in transfected COS cells [59]. Residues that have been implicated in G-protein coupling are designated by pink letters within green or dashed green circles, indicating that these mutations also decrease NT binding at least somewhat [45]. Numbers indicate specific positions in the rat NTR-1 sequence. Regions that have been implicated in coupling to G_q and $G_{i/o}$ are indicated [48, 50]. Amino acid residues that have been shown to be important for receptor internalization are indicated. Potential phosphorylation sites that are involved in interactions with β-arrestin are indicated by light brown circles, and serines that were not found to be important are indicated by light brown letters.

NT has been implicated in an impressive array of neurobiological, endocrine and paracrine functions, and a comprehensive review could easily fill a volume. This review will be focused on four areas where there have been significant recent advances in our understanding of the physiological roles of the peptide and the mechanisms involved in NT signaling. The first area will center on NT binding to NTR-1 and the stimulation of intracellular signaling pathways through this receptor. The second section will highlight recent advances that are consistent with the hypothesis advanced by Nemeroff 25 years ago that NT may constitute an endogenous neuroleptic [32]. Third, the possible role of NT in psychostimulant drug sensitization will be considered. Lastly, recent exciting developments regarding the involvement of NT in stress-induced analgesia will be considered. These advances have been propelled by the development of non-peptide NT antagonists [33, 34] and genetic models [35–38] that in combination have begun to provide a clearer picture of the important physiological functions of the peptide.

NT binding to the high-affinity NT receptor, NTR-1

There has been significant progress made in identifying regions in NTR-1 that are involved in specific receptor functions. For the purposes of this review, sequence comparisons between previously reported NTR-1 sequences from several mammalian species [13, 14, 39, 40] and homologous sequences that have become available from whole genome sequencing projects (dog, chicken and puffer fish) were performed to identify evolutionarily conserved regions of NTR-1. The results are presented schematically in figure 1. Two conserved regions were identified (identical conserved residues are colored red in fig. 1), and perhaps not surprisingly, one conserved region encompasses sequences that have been shown by mutational analysis to comprise at least a portion of the NT binding pocket [41–43]. The second conserved region encompasses extracellular (EC) loop 1 and the two adjacent transmembrane (TM) spanning domains; and although mutation of Asp^{139} or Arg^{143} near the top of TM 3 results in nearly a complete loss of NT binding [41, 43], this region has not been included in published models for the NT binding pocket (note that substitution of Arg^{143} with Gly abolished binding, but substitution with Lys, Gln or Met had no effect) [42, 44].

Systematic mutational analyses centered on either charged [41] or hydrophobic and aromatic residues [42, 43, 45] of rat NTR-1 have provided considerable insight regarding specific residues involved in binding both NT (indicated by green circles in fig. 1) and the relatively NTR-1-selective NT antagonist, SR 48692 (indicated by yellow single-letter amino acid abbreviations in fig. 1). In addition to the conserved charged residues near the junction of EC loop 1 and TM 3 mentioned above, these studies have implicated charged and hydrophobic residues in TM 6 and EC loop 3 in NT or NT-(8-13) binding [42, 43, 45]. Competition binding experiments with ^{125}I-NT-(8-13) and different NT-(8-13) derivatives were used to gain insights regarding specific contacts between NTR-1 residues and the agonist [43]. Ala substitution mutations in NTR-1 at Trp^{339}, Phe^{344} or Tyr^{347} affected binding of NT-(8-13), much more severely than [Ala^{11}]NT-(8-13), indicating that Tyr^{11} likely makes π-π contacts with these residues located in the third EC loop, although slightly different contacts (Phe^{331}, Trp^{339}, Phe^{344}) were suggested earlier based on homologies between EC loop 3 and NT-(8-13) and regions in proteins with known crystal structures [44]. Similar analyses suggest possible interactions between Pro^{10} of NT-(8-13) and Trp^{339}, Ile^{12} and Met^{208}, Arg^{9} and Phe^{331}, and an ionic interaction between Arg^{327} and the carboxyl terminus of NT-(8-13) [43]. In contrast, earlier computer modeling suggested that Ile^{12} and Leu^{13} interact with Phe^{331} and Ile^{334} in NTR-1 and that Arg^{9} in NT-(8-13) makes cation-π contacts with Phe^{331}, Phe^{346} and Tyr^{349} [44]. Interestingly, in the three-dimensional model based on previously determined crystal structures from several different proteins [44], EC loops 1 and 3 are closely juxtaposed, suggesting that residues in EC loop 1 could potentially either make contacts with NT, stabilize the conformation of the NT binding pocket or participate in NT-induced conformational changes.

The SR 48692 binding pocket appears to lie somewhat deeper in the membrane, but several residues have been identified that appear to be important for both SR 48692 and NT binding (yellow letters within green circles in fig. 1) [42]. The mutational data indicate that contacts with hydrophobic residues in TM 6 and 7 are important for SR 48692 binding, including Tyr^{324}, Phe^{331}, Tyr^{351} and Tyr^{359} of rat NTR-1 [42]. Ala substitutions in Trp^{354} and Phe^{358} in TM 7 and Met^{208} in TM 4 had less severe effects. Finally, substitution of Arg^{327} with either Met or Glu displayed greatly reduced SR 48692 and NT binding, most likely because this residue contacts the carboxylic acid functions of both SR 48692 and NT [42, 43]. As noted above, Met^{208}, Phe^{331} and Tyr^{351} also appear to make important NT contacts, suggesting a basis for the ability of SR 48692 to compete for NT binding to the receptor.

NT binding to NTR-1 results in the activation of a number of intracellular signaling cascades, including those involving the generation of inositol 1,4,5-trisphosphate and diacylglycerol, cAMP, cGMP and the activation of mitogen-activated protein kinases (MAPKs) (reviewed in [46]). Interestingly, mutation of Phe^{358} in TM 7 of NTR-1 to Ala (indicated by a blue circle in fig. 1) results in high constitutive stimulation of IP production in transfected Chinese hamster ovary (CHO) cells, without affecting cAMP production, suggesting that this TM segment may be involved in agonist-induced conformational changes

that result in an active receptor conformation that selectively influences coupling to G_q [47]. The third intracellular loop of NTR-1 has been implicated in coupling to the PI pathway, but appears not to be involved in cAMP signaling in CHO cells [48]. Comparison of different internal deletion mutants suggests that the region between amino acids 270 and 282 is important for coupling to G_q and stimulation of PI hydrolysis (see fig. 1). The third intracellular loop has been implicated in G protein interactions for a number of G protein-coupled receptors [49]. In contrast, deletion of the carboxyl terminal tail of NTR-1 disrupted NT-stimulated [^{35}S]GTPγS binding and arachidonic acid production, which are thought to involve interactions with $G_{i/o}$ [50]. Comparisons between different deletion mutants indicated that intracellular C-terminal residues between amino acids 373 and 401 mediate these responses (see fig. 1) [50]. These results provide strong evidence that distinct domains in NTR-1 are required for coupling to different G proteins and thus the activation of different intracellular signaling mechanisms [51], and raise the possibility that distinct receptor conformations are required for coupling to different signaling pathways [52].

The analysis of carboxyl terminal truncation mutants has also provided evidence that this region of the receptor is involved in receptor internalization and desensitization. Thus, deletion of the entire carboxyl terminal intracellular region led to a dramatic reduction in NT-stimulated receptor internalization in transfected CHO cells, while removal of only the last 22 residues had little effect [50, 53, 54]. In contrast, deletion of the third intracellular loop did not affect receptor internalization [48]. In contrast to these results, deletion of the last three residues of NTR-1 nearly abolished receptor internalization in COS cells, and substitution of both Thr^{422} and Tyr^{424} with Gly also dramatically reduced ligand-induced receptor internalization [53]. Although the region required for receptor internalization in CHO cells corresponds to the one required for $G_{i/o}$ coupling, receptor internalization is not blocked by pertussis toxin, suggesting that $G_{i/o}$ and its downstream effectors are not involved in receptor internalization [50]. In addition to the mechanisms involving the membrane proximal region of the carboxyl terminal tail, more distal potential phosphorylation sites have also been implicated in internalization [53, 55]. One group of potential phosphorylation sites near the carboxyl terminus (Ser^{415}, Thr^{416}, Ser^{417}) has recently been shown to mediate interactions with β-arrestin, a scaffolding protein that links G protein coupled receptors to components of the endocytic machinery, although mutation of these sites did not prevent receptor internalization [55]. Curiously, mutation of another evolutionarily conserved group of potential phosphorylation sites (fig. 1, brown letters) did not affect the ability of β-arrestin to associate and internalize with NTR-1 [55]. These results indicate that the carboxyl terminus of NTR-1 is involved in receptor internalization, but suggest that there may be distinct sequence requirements in different cell types.

The low-affinity, levocabastine-sensitive [56] NT receptor, NTR-2, has also been cloned but has not been studied as intensively as NTR-1 [15, 16]. Initial analysis of the mouse receptor in frog oocytes indicated that NT, NMN and levocabastine stimulated Ca^{+2}-activated chloride currents through NTR-2 [15]. However, the functionality of this receptor has been called into question by several studies in transfected cell lines that indicate that NTR-2 is activated by the NT antagonists SR 48692 [33] and SR 142948A [34], and that NT antagonizes these effects [18, 19, 58, 59]. However, NT appears to selectively activate MAPK signaling through NTR-2 in transfected COS cells and cultured cerebellar granule cells [20, 60], although this has not been observed in all studies [18]. The common finding that SR 48692 and SR 142948A stimulate at least some intracellular signaling pathways through NTR-2 should be taken into consideration when interpreting results obtained using these compounds.

NT is required for certain antipsychotic drug actions

NT was formally proposed to be a possible endogenous neuroleptic 25 years ago based on the fact that central NT administration produces a spectrum of effects that are similar to those of antipsychotic drugs (APDs) [32]. Subsequent observations that APD treatment results in significant increases in NT levels and NT gene expression in the striatum suggested that the mechanisms underlying both the therapeutic and side effects of APD treatment might involve increased NT signaling in the striatum (reviewed in [61]). The observation that cerebrospinal fluid NT levels were significantly depressed in a subset of schizophrenic patients displaying more severe symptoms and were normalized following APD treatment suggests that NT deficits may be involved in the etiology of schizophrenia [62–67]. There has been rapid progress over the past several years that reinforces the notion that decreased NT signaling contributes to defects in sensorimotor gating in animal models of schizophrenia and that NT is required for the reversal of these defects by some APDs, but not others [68, 69]. These results suggest that the development of direct NT agonists may provide novel therapeutic approaches toward the treatment of schizophrenia.

All APDs that have been tested increase NT expression in brain regions innervated by midbrain dopamine neurons, but somewhat different patterns of activation have been observed with different APDs. Atypical APDs, like clozapine, display a much lower or absent incidence of extrapyramidal motor side effects (EPSs) than typical APDs, such as haloperidol, and have become the first line treatment for schizophrenia [70]. Initial results suggested

that both typical and atypical APDs increase NT expression in the nucleus accumbens (NAc), while only typical APDs increase expression in the dorsolateral striatum [71–75], although more recent studies indicate that certain atypical APDs increase NT levels in dorsal striatum without increasing levels in the NAc [76]. The propensity of typical APDs to increase NT in a region of the striatum that had been implicated in motor control together with reports that central NT administration produced behavioral catalepsy, suggested that increased NT expression in the dorsolateral striatum might be involved in the production of EPSs. Furthermore, the ability of both typical and certain atypical APDs to increase NT expression in the NAc was suggestive that these increases might underlie the shared therapeutic effects of these drugs. Indeed, treatment with NT antagonists has been shown to block the ability of certain APDs to augment sensorimotor gating in animal models of schizophrenia [68, 69]; however, the ability of the typical APD, haloperidol, to produce catalepsy is unimpaired in NT knockout mice [35].

A major question concerning NT involvement in APD drug responses concerns the contribution of the peptide to neuronal activation. The induction of immediate early gene expression, most commonly c-Fos, has been used extensively to analyze APD-evoked changes in neuronal activity [77]. Typical and atypical APDs activate Fos expression in distinct patterns, in brain regions innervated by midbrain dopamine neurons, that bear a remarkable similarity to NT gene induction (reviewed in [77, 78]). In addition, atypical – but not typical – APDs increase Fos expression in the prefrontal cortex, suggesting that neuronal activation in this region may be related to the enhanced therapeutic profile of these drugs, particularly with regard to reversal of negative symptoms [79–81]. Several lines of evidence indicate that the NT gene may be directly activated by c-Fos, perhaps explaining the similarities in their patterns of expression following APD treatment [82–86]. Experiments in NT knockout mice and in rats have provided evidence that NT is specifically required for full APD-evoked c-Fos expression in the dorsolateral striatum [35, 87, 88]. Thus, in both NT knockout mice and in rats pre-treated with either the relatively selective NTR-1 antagonist, SR 48692, or the non-selective NT antagonist, SR 142948A, haloperidol-evoked Fos expression was significantly blunted in the dorsolateral striatum but not elsewhere, and was more markedly affected in the striatal patch compartment [87]. The response to clozapine was not affected in any region examined; however, olanzapine-evoked Fos expression in dorsomedial and dorsolateral striatum was augmented by pretreatment with SR 142948A [88]. This difference may reflect the fact that olanzapine binds with relatively high affinities to a variety of receptors that could contribute to neuronal activation in the striatum and that NT may negatively modulate one or more of these [89].

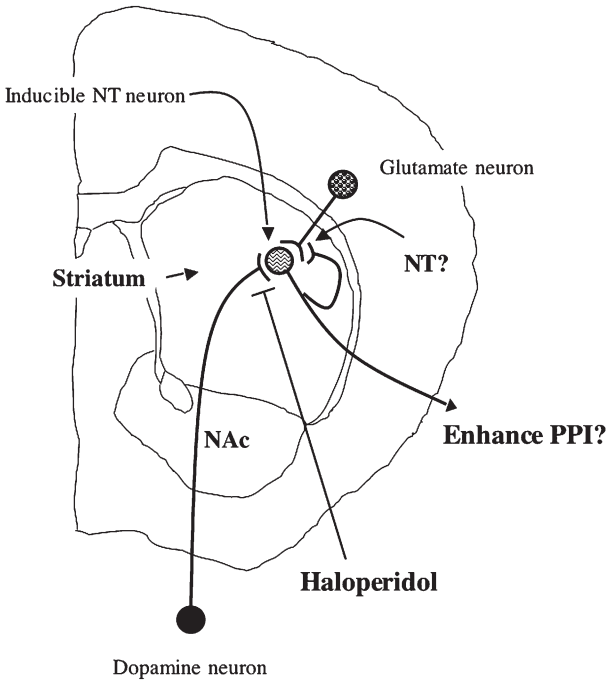

Figure 2. A presynaptic action of NT potentiating glutamate release is required for neuronal activation in the dorsal striatum and increased PPI following haloperidol administration. NT most likely influences neuronal activation through effects on corticostriatal afferents expressing NTR-1 [87], since the available evidence suggests that dorsal striatal neurons do not express this receptor [92, 93]. Recently, treatment with the NT agonist PD149163 has been shown to activate cortical PFC pyramidal neurons and interneurons [238]. Intra-striatal NT administration increases extracellular glutamate levels [100], and glutamate signaling is required for haloperidol-evoked neuronal activation in the striatum [95, 239]. Lesions of the caudodorsal striatum decrease basal PPI in rats, suggesting that this region is required for normal levels of basal PPI and could contribute to haloperidol-evoked increases in PPI [116].

NT most likely influences APD activation of striatal neurons through effects on striatal afferents, since the vast majority of NT receptors are expressed on presynaptic elements in the dorsal striatum (fig. 2) [90–93]. APD-evoked Fos activation involves both dopamine D_2 receptor blockade and glutamate signaling through *N*-methyl-D-aspartate (NMDA) receptors [94–96]. Cortical layer V projection neurons express NTR-1 [92], suggesting that APD-evoked striatal NT release [97–99] could participate in neuronal activation through augmenting glutamate release from corticostriatal afferents (fig. 2). Intrastriatal NT administration has been shown to increase extracellular glutamate levels, and this effect is blocked by SR 48692 [100, 101]. The elucidation of the mechanisms underlying NT involvement in APD-evoked neuronal activation and uncovering the functional consequences of alterations in this activation will undoubtedly yield important clues regarding the mechanisms through which NT mediates certain APD actions.

There is increasing evidence that NT has APD-like effects that are similar to those of atypical APDs. Prepulse inhibition (PPI) of the acoustic startle reflex has been used extensively as a model for sensorimotor gating defects associated with schizophrenia. This test measures reductions in the startle response to a loud acoustic stimulus (pulse) when preceded by a weak acoustic stimulus (prepulse). PPI is disrupted by dopamine agonists, non-competitive NMDA antagonists, α_1-adrenoreceptor agonists and serotonin (5-HT_{2A}) receptor agonists, and can be restored by typical and atypical APDs depending on the mode of disruption [102]. Atypical APDs generally display a broader ability to restore PPI resulting from manipulation of any of these transmitter systems, and NT shares this property. Microinjection experiments in which NT was administered directly into the NAc provided the first evidence that NT can modulate PPI similarly to APDs in that lower doses of NT (0.25, 1.0 µg) reversed amphetamine disruption of PPI without affecting pulse alone startle amplitude [103]. In contrast, a higher dose of NT (5.0 µg) potentiated both amphetamine and apomorphine disruption of PPI [104]. Two recently developed stable NT analogs, PD149163 and NT69L [105], that are capable of producing central nervous system effects following peripheral administration have also been shown to restore PPI following disruption by dopamine, serotonin and α_1 adrenoreceptor agonists [106–109]. The NT agonist PD 149163 and clozapine – but not haloperidol – reversed sensorimotor gating defects in Brattleboro rats, again consistent with the NT agonist having atypical APD-like properties [110]. These results indicate that exogenously administered NT can reverse the disruptive effects of several neurotransmitter systems on PPI and may also augment basal PPI, suggesting that APD-mediated increases in NT signaling might underlie their ability to augment PPI and to reverse the disruption of PPI caused by neurotransmitter agonists or antagonists (fig. 2).

Recent experiments have provided evidence that endogenous NT signaling through NTR-1 contributes to basal PPI and is required for the augmentation of PPI by certain APDs [68, 69]. Thus, pretreatment of rats with either the relatively NTR-1-selective antagonist SR 48692 or the non-selective antagonist SR 142948A was found to block the acquisition of latent inhibition, a measure of sensorimotor gating involving conditioned associations following multiple neutral pre-exposures to the conditioned stimulus [68, 69]. Similar to PPI, APDs augment the acquisition of latent inhibition and reverse amphetamine-induced disruption of this process. SR 142948A pre-treatment blocked the ability of haloperidol to augment latent inhibition. Interestingly, SR 142948A also blocked the ability of the atypical APD quetiapine to reverse PPI deficits resulting from isolation rearing [68]. Furthermore, isolation reared rats were found to have significantly lower levels of NT messenger RNA (mRNA) and higher levels of NT receptor binding in the NAc, and quetiapine treatment restored striatal NT gene expression in isolation reared, but had no effect on NT mRNA expression in socially reared rats [68]. In view of these results, it is perhaps not surprising that SR 48692 was found to be ineffective in the treatment of schizophrenia [111]. These results indicate that NT signaling is required both for normal basal sensorimotor gating activity and the potentiation of PPI and latent inhibition by certain APDs.

The available evidence suggests that NT influences PPI through actions in the striatum, and important unresolved questions concern the site(s) of NT action, the causal relationship between APD-evoked increases in NT expression and APD effects on PPI, latent inhibition and ultimately the therapeutic benefits of these drugs. The evidence that disruption of NT signaling selectively diminishes the ability of certain APDs to activate Fos expression in the dorsolateral striatum suggests that these changes might contribute to the defects in PPI and latent inhibition caused by NT antagonists (fig. 2). Both direct and indirect dopamine agonists disrupt PPI, and microinjection experiments have implicated several brain regions in this response, including the nucleus accumbens and the anteromedial caudate [112–114]. The ability of the APD haloperidol to restore PPI in apomorphine-treated rats also appears to involve actions that are distributed throughout several brain regions, including the ventral tegmental area, ventral subiculum, medial prefrontal cortex, and the NAc and anteromedial striatum in combination [115]. Lesions of the dorsal posterior striatum have also been reported to reduce PPI, suggesting that activity in this region is required for normal levels of PPI [116]. The demonstration that NT is required for haloperidol-evoked Fos activation throughout the dorsolateral striatum [35, 87, 88] suggests that decreased haloperidol-evoked neuronal activity in this region could account for the observations that NT antagonist pre-treatment blocks haloperidol restoration of PPI and latent inhibition [68, 69]. Thus, endogenous NT appears to contribute to basal PPI and is apparently required for at least certain APDs to enhance or restore PPI (fig. 2); however, the underlying mechanisms remain to be determined.

Finally, there is increasing evidence that the induction of NT in the dorsolateral striatum in response to typical APDs is not related to the production of acute EPSs. The original hypothesis that NT might be involved in EPSs was based on the fact that the dorsolateral striatum is thought to be principally a motor area and on reports that central NT administration produces catalepsy (immobility and increased tolerance of abnormal postures) in mice [117–119]. Catalepsy has been used extensively as a screen for EPSs [120], although a rat model that more closely approximates the uncontrolled orofacial movements associated with conventional APD treatment has also been used to investigate NT involvement in EPSs [121].

NT-induced catalepsy differs from that produced by typical APDs, and is not observed in rats [122] and all strains of mice [123]. Furthermore, haloperidol-induced catalepsy was unaffected in NT knockout mice [35], and NT antagonist treatment potentiated haloperidol-induced catalepsy at suboptimal doses of haloperidol, indicating that NT opposes catalepsy [124]. Consistent with this idea, peripheral administration of a stable NT analog, NT69L, has been shown to block or reverse haloperidol-induced catalepsy in rats [125]. In contrast, SR 48692 microinjection into the striatum, pallidum or substantia nigra attenuated chronic fluphenazine-induced vacuous chewing movements [121]. These results suggest that endogenous NT may differentially modulate APD-induced catalepsy and orofacial EPSs.

The available evidence suggests that NT signaling through NTR-1 is required for the enhancement of PPI by certain APDs. The long-standing hypothesis that NT may serve as an endogenous neuroleptic has prompted genetic linkage studies aimed at determining whether naturally occurring polymorphisms in the NT or NTR-1 genes might be linked to schizophrenia, but these studies have thus far been negative [126, 127], although certain NTR-1 alleles may be protective [128]. The development and testing of NT agonists may lead to the discovery of novel therapeutic approaches and provide further insight into the role of NT in this devastating illness.

NT modulation of psychostimulant responses

In addition to evidence implicating NT in APD effects, several recent reports indicate that NT may also play a key role in psychostimulant sensitization [129–134]. Early microinjection experiments demonstrated that NT can produce psychostimulant-like effects following site-specific microinjection in the ventral tegmental area (VTA) [135–137]. NT microinjection into the VTA increases dopamine release in the NAc and prefrontal cortex (PFC), similar to psychostimulants [137–139]. Furthermore, repeated NT microinjection into the VTA results in a progressive increase in the stimulation of locomotor activity [137, 140, 141], similar to psychostimulant sensitization, and repeated central NT administration results in sensitization of amphetamine (AMP)-induced locomotor activity [142]. NT antagonist treatment has been demonstrated to interfere with psychostimulant sensitization, suggesting that endogenous NT may be involved in this process.

The participation of NT in psychostimulant responses appears paradoxical in view of the evidence supporting its role in APD responses; however, these two actions likely reflect NT signaling in different brain regions or different neuronal populations within a particular brain region. This anatomical separation is perhaps most evident in the differential effects of NT on psychostimulant responses. NT administration in the NAc attenuates amphetamine-stimulated locomotor activity [143, 144] and AMP disruption of PPI [103], similar to APDs, while NT administration in the VTA stimulates locomotor activity, similar to AMP [136, 145]. These different effects most likely reflect differences in the neurons influenced by NT signaling in these different locations. NT has been shown to directly activate dopamine neurons in the VTA and SN [146–149], where the majority of these neurons express high levels of NTR-1 [92, 150], suggesting that NT most likely increases dopamine release in the NAc through direct stimulation of dopamine neuronal firing in the VTA. In contrast, the APD-like actions of NT in the NAc most likely involve effects on neurotransmitter release from striatal afferents and modulation of striatal neurons. Recent immunohistochemical localization experiments have provided conclusive evidence that NTR-1 is expressed predominantly on striatal afferents, but also on a small subpopulation of post-synaptic neurons in the NAc [151, 152]. NT has been shown to antagonize dopamine D_2 receptor-mediated inhibition of GABA, but not dopamine release in the rat NAc [153]. These results indicate that the ability of NT to produce both APD- and psychostimulant-like effects hinges on the differential effects of the peptide in different brain regions.

Psychostimulants and APDs also produce distinct effects on striatal NT expression. Psychostimulants have been shown previously to produce striking changes in striatal Fos expression, and the pattern of activation changes during repeated drug administration [154, 155]. These drugs also increase NT expression, predominantly in the caudal dorsomedial and ventrolateral striatum [156–160], and these increases require dopamine D_1 receptor signaling [161] and are sustained during chronic treatment [162, 163]. These results suggest that psychostimulants increase NT expression in D_1-positive striatal neurons, in contrast to typical APDs, which increase NT expression in enkephalin-positive (most likely D_2-positive) neurons in the dorsolateral striatum [164].

The distinct pattern of psychostimulant-induced NT expression is mirrored by alterations in neuronal activation in NT knockout mice [165]. AMP-evoked Fos expression is markedly attenuated in the medial striatum of NT knockout compared with wild-type mice and in rats pretreated with SR 48692. Thus, AMP-evoked Fos expression is attenuated in a region where psychostimulants have been shown to increase NT expression, similar to the situation for APDs [35, 87, 88]. SR 48692 similarly attenuated Fos activation in the rostral striatum following cocaine administration [166]. As argued above for typical APDs, NT most likely influences AMP-evoked Fos activation through effects on striatal afferents (fig. 3). Psychostimulants also increase extracellular NT levels in the striatum through a mechanism involving both D_1 and

NMDA receptor signaling, suggesting that NT is released from D_1-positive neurons [167, 168]. NT could influence AMP-stimulated outflow of dopamine through a dampening of D_2 receptor-mediated autoinhibition [169], since this process reportedly modulates AMP-evoked dopamine release [170]. NT microinjection in the striatum also increases glutamate release [100, 171], suggesting that local NT release could augment glutamate signaling, as argued above for APD responses. Finally, there are a small number of immunoreactive NT neurons along the medial border of the dorsal striatum, which could provide a local source of striatal NT [172].

There is somewhat contradictory evidence regarding the involvement of NT in the process of psychostimulant sensitization. Indeed, cocaine sensitization is at best delayed by prior administration of SR 48692 and is not affected at all when SR 48692 is administered just prior to cocaine [129, 130]. In a somewhat complicated protocol in which SR 48692 (1.0 mg/kg) was administered for 5 days prior to cocaine administration, 60 min prior to cocaine (15 mg/kg) on 10 successive days, daily for an additional 7 days and 60 min prior to a final cocaine challenge, SR 48692 was found to attenuate locomotor activity after only the first cocaine administration, but reduced vertical activity significantly after the 1st, 2nd and final cocaine administrations [130]. SR 48692 also failed to influence stereotyped behavior following cocaine challenge in sensitized animals [130]. These results suggest that NTR-1 blockade affects certain cocaine responses, but does not play a major role in cocaine sensitization.

In contrast to the results for cocaine, several groups have reported that SR 48692 (and in one case SR 142948A) blocks the development and expression of AMP sensitization in rats and mice [132, 133, 142]. Interestingly, different doses of SR 48692 had distinct effects on AMP sensitization. Pre-administration of a low dose of SR 48692 (40 μg/kg) 30 min prior to AMP (1.5 mg/kg) every other day for a week increased AMP-induced locomotor and non-ambulatory activity following the final sensitizing dose of AMP, but two higher doses of SR 48692 (80 and 160 μg/kg) blocked sensitization [142]. Similar results were obtained in experiments in which a higher dose of SR 48692 (1.0 mg/kg) was administered once daily for 14 days, including 30 min prior to AMP (0.5 or 1 mg/kg) on days 1, 3, 5, 7 and 14 [133]. SR 48692 treatment blocked or attenuated AMP sensitization, but had no effect on the acute AMP stimulation of locomotor activity [133]. SR 48692 (0.3 mg/kg) administered just prior to AMP challenge (2.0 mg/kg) also blocked the expression of AMP sensitization in mice [132]. These results suggest that NT signaling is important for the development and expression of AMP sensitization.

To examine whether NT is required in the VTA for sensitization, the combined NTR-1/NTR-2 antagonist SR 142948A or vehicle was microinjected into the VTA 1 min prior to AMP (1.0 mg/kg s.c.) in a one-dose sensitization protocol and again just prior to AMP challenge 1 week later [134]. SR 142948A administration prior to the first AMP dose blocked the development of amphetamine sensitization; however, the sensitized response was not affected when SR 142948A was administered only prior to AMP challenge. Curiously, peripheral SR 142948A administration had no effect on sensitization [134]. These data support a role for NT signaling in the VTA for the initiation of AMP sensitization, and suggest that NT signaling in another brain region, for instance the NAc, is most likely involved in the expression of AMP sensitization if the rat is similar to the mouse [132].

There is also preliminary evidence that NT could act to limit psychostimulant sensitization. As described above, a low dose of SR 48692 appeared to augment AMP-stimulated locomotor activity following repeated AMP administration responses [142]. Although seldom considered, the possibility exists that the effects of higher SR 48692 doses might at least in part be due to agonist effects at NTR-2 [17–20]. Furthermore, peripheral administration of the NT derivative NT69L has been shown to suppress both the development and expression of nicotine sensitization and may have similar effects on AMP and cocaine sensitization [174, 175]. Lastly, preliminary results from our laboratory suggest that AMP sensitization is augmented in NT knockout compared with wild-type mice; however, this could be due to compensatory mechanisms [P.R.D., unpublished results]. It will be of considerable interest to determine whether SR 48692 or SR 142948A can influence AMP sensitization in NT knockout mice in view of these discrepancies.

Understanding the mechanisms through which NT might influence AMP sensitization remains an important future objective. AMP sensitization is thought to involve initial alterations in neuronal signaling in the VTA and subsequent changes in the NAc that are important for the expression of sensitization [176]. The initiation of AMP sensitization involves concerted dopamine and glutamate signaling in the VTA and most likely the PFC, where psychostimulants increase NT release [177]. Since NTR-1 is expressed at reasonably high levels in the PFC [92, 93], NT release in this region could influence glutamate transmission, perhaps including transmission to the VTA. Recent work also indicates that there are extensive NT inputs to the VTA [178], and AMP-evoked NT release in this region could also modulate local neurotransmitter release, although such release has not been demonstrated. NT activation of dopamine neurons would seem to be unlikely to be involved in augmenting dopamine release since AMP releases dopamine from non-vesicular stores by promoting reverse transport through the dopamine transporter [179], although as mentioned above NT could augment AMP stimulation of dopamine release through attenuation of D_2 autoreceptor signaling [169, 170, 180].

The expression of AMP sensitization is associated with enhanced dopamine release in the NAc and SN [176]. Acute psychostimulant administration has been shown to increase extracellular NT levels in the NAc; however, whether this occurs following sensitization has not been reported [167, 181]. Furthermore, NT attenuates AMP-stimulated locomotor responses following microinjection in the NAc [143], although this has not been tested following sensitization. Finally, NT has also been shown to increase intracellular Ca^{+2} levels in dopamine neurons [182], opening the possibility that NT might be required for the Ca^{+2}-dependent augmentation of dopamine release that occurs in the NAc and dorsal striatum following sensitization [176].

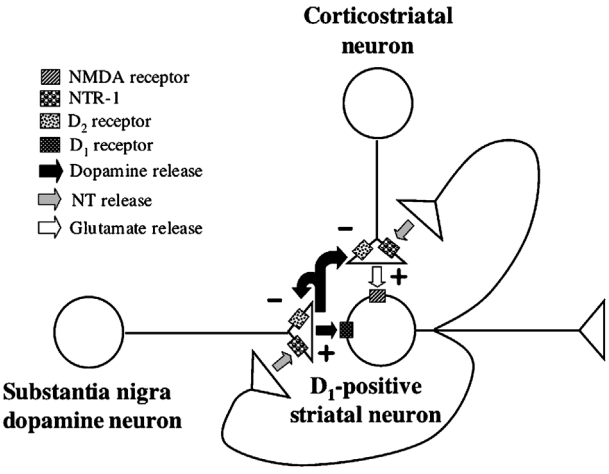

Figure 3. Model for NT involvement in amphetamine activation of D_1-positive striatal neurons. Psychostimulants have been shown to increase extracellular levels of striatal NT, and this release involves signaling through both dopamine D_1 and NMDA receptors [168]. NTR-1 has been localized to both nigral dopamine and cortical projection neurons, but has not been localized to striatal neurons in the dorsal striatum [92]. Amphetamine-evoked c-Fos expression in the medial striatum is markedly attenuated in NT-deficient mice, indicating that NT is required for neuronal activation in this striatal region [165]. These data suggest that NT influences striatal activation principally through effects on either nigral or cortical striatal afferents. NT has been shown to antagonize D_2 autoreceptor function and could enhance amphetamine-evoked increases in extracellular dopamine levels through antagonism of D_2 autoinhibition under certain circumstances [169, 170]. Intrastriatal NT administration has also been shown to increase glutamate release through NTR-1 [100, 101]. Amphetamine-evoked c-Fos expression is attenuated by both D_1 receptor and NMDA receptor antagonists, suggesting that NT-mediated increases in both dopamine and glutamate signaling could be involved in amphetamine activation of D_1-positive striatal neurons [154, 240]. NT augmentation of glutamate and dopamine release (+) and NT antagonism of D_2 receptor-mediated inhibition of dopamine and glutamate release (–) are indicated.

NT facilitates nociceptive responses and is required for stress-induced antinociception

There has also been considerable recent progress in our understanding of the role of endogenous NT in pain responses. Central NT administration has been shown to have a biphasic effect on nociceptive responses, enhancing such responses, at lower doses, but producing a profound analgesia at higher doses [183–188]. The existence of a central descending pain modulatory circuit (diagramed schematically in fig. 4) that includes the periaqueductal gray (PAG) and rostroventral medulla (RVM) was first inferred from electrical stimulation experiments [189]. This circuit is activated by morphine [190] and appears to normally be activated in response to stress [191]. Two forms of stress-induced antinociception (SIAN) have been distinguished based on their sensitivity to μ-opioid receptor antagonists [191]. The production of these two different forms of SIAN is related to stress severity, with more intense stressors typically resulting in μ-opioid receptor-independent SIAN [192]. The observation that centrally administered NT produces a potent analgesia that is resistant to μ-opioid receptor antagonists [184, 193–196] suggests that endogenous NT might play a role in SIAN resulting from severe stress.

NT and NT receptors are well positioned to modulate nociception at several different levels, including the spinal cord, PAG and RVM. Consistent with a possible role in the modulation of pain at the spinal level, numerous NT-immunoreactive (NT-IR) fibers and cell bodies are found to be concentrated in the superficial laminae of the dorsal horn of the spinal cord in the rat [197–200]. Labeled NT binding sites are also located principally in the superficial laminae of the dorsal horn and spinal trigeminal nucleus in the rat [201] and human [202]. Similarly, numerous NT-IR cell bodies and fibers have been described in the rat PAG, and the PAG sends a major NTergic projection to the RVM [203–205]. NTR-1 is expressed at weak to moderate levels in dendrites and cell bodies both dorsal and ventral to the cerebral aqueduct in the PAG, and on serotonin neurons in the nucleus raphe magnus and dorsalis [92, 93, 206]. More recent studies have demonstrated that NTR-2 is also expressed in neuronal cell bodies and processes within the PAG and dorsal raphe nucleus, opening the possibility that both receptors may play a role in nociceptive modulation [207]. These anatomical studies suggest that endogenous NT signaling in the PAG and RVM could influence nociceptive responses.

Site-specific microinjection experiments have provided evidence that that NT produces both antinociceptive and pain facilitatory effects following administration in the PAG, RVM, and brain regions that project to these structures [186–188, 196, 208–213]. Microinjection of NT into the RVM produced a hyperflexive response to noxious heat in the tail flick assay at lower doses, but antinociception at higher doses, and similar results were obtained for visceral pain responses [187, 188, 211]. There is also some evidence that intrathecally adminis-

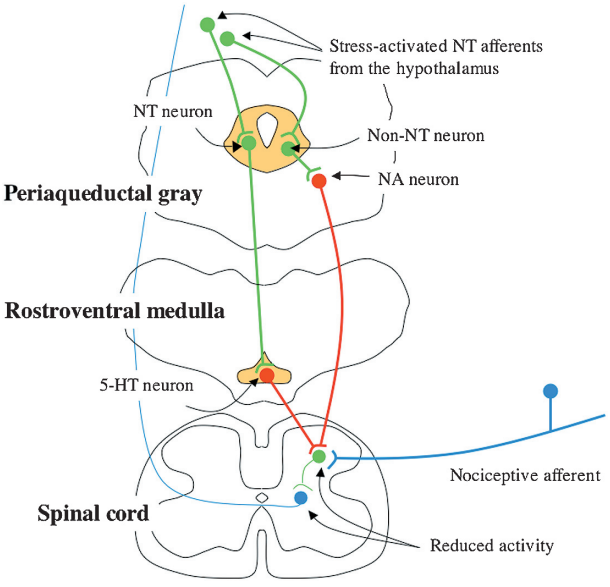

Figure 4. Possible NT functions in stress-induced antinociception. NT and NT receptors are expressed at multiple levels in the central circuits that have been implicated in pain modulation, including the dorsal horn of the spinal cord, the PAG, the RVM and the hypothalamus. Recent evidence suggests that cold water swim stress increases NT expression in areas of the hypothalamus that have been previously demonstrated to project to the PAG, suggesting that increased NT release from hypothalamic afferents may be involved in stress-induced antinociception [221]. Increased NT signaling is proposed to recruit 'off' cells, as has been demonstrated for the RVM [230], leading to increased inhibition of pain responses through the activation of noradrenergic [231] and possibly serotonergic [231] neurons (red) that project to the dorsal horn of the spinal column. The schematic depicts NT and other neurons (green) that are proposed to activate descending noradrenergic and serotonergic neurons (red) that inhibit neurons involved in pain transmission (blue).

tered NT increases both hot plate and aversive response latencies, although these increases were attenuated by naloxone, indicating that these effects are dependent on opioid signaling [214, 215]. In contrast, spinal NT administration had no effect on response latencies in the tail flick assay [215, 216]. More recent experiments have provided compelling evidence that endogenous NT normally facilitates nociceptive responses, but also plays a key role in SIAN.

Several different lines of evidence support a role for endogenous NT in basal nociception. Thus, blockade of NT signaling with either a neutralizing antiserum or the NT antagonist SR 48692 was found to produce analgesia under certain circumstances [188, 217, 218] and to augment morphine-induced analgesia [186, 211]. More recently, the analysis of both NT and NTR-2 knockout mice has provided further evidence for an involvement of NT in basal pain responses. Perhaps the most convincing evidence comes from the analysis of NT knockout mice where visceral nociception was significantly reduced under basal conditions compared with wild-type mice [218]. A subtle defect was detected in NTR-2 knockout mice, which displayed increased jump latency in the hot plate test, although the latency to the first hind paw lick was similar to wild type [38]. However, reflex pain responses were largely unaffected in both NTR-1 and NTR-2 knockout mice [36, 38]. Thus, there may be some functional redundancy between NTR-1 and NTR-2 receptors in this regard.

Endogenous NT also appears to play a key role in SIAN. NT knockout mice were found to be completely defective in SIAN resulting from cold water swim/water avoidance stress as measured by the visceromotor response to colorectal distension, and peripheral SR 48692 administration produced the same effect in rats [218]. Instead, stress produced a hyperalgesic response in these animals that was significantly greater in female than in male rats, perhaps explaining previous observations that female rats exhibit lower levels of SIAN than males [219, 220]. The stress-induced hyperalgesia uncovered in these experiments appears to differ from the hyperalgesia caused by noxious irritants, since acetic acid-induced hyperalgesia was blocked by SR 48692 pre-treatment [218]. The transition from NT pain facilitation to antinociception could involve stress-induced increases in NT signaling within the PAG or RVM, possibly through hypothalamic afferents, as depicted in figure 4 [221].

Although a number of studies have implicated NTR-2 in NT modulation of pain responses, there is now substantial evidence that NTR-1 is also involved. Several lines of evidence point toward an important involvement of NTR-2 in the suppression of chemical irritant-induced writhing by NT, including the correlation between analgesia potency and NTR-2 binding affinity for a series of NT analogs [222], the ability of NTR-2, but not NTR-1, antagonists to block NT-induced analgesia [34, 223–225], and the observation that antisense inhibition of NTR-2, but not NTR-1, attenuates NT-induced analgesia [222]. In contrast, antisense inhibition of NTR-1 attenuated NT-induced analgesia in the hot plate test, but had no effect on morphine analgesia [226, 227]. Intra-RVM administration of the relatively selective NTR-1 antagonist SR 48692 also blocked NT-induced analgesia in the tail flick assay, although with complex dose-response characteristics [186]. Finally, NT fails to increase response latencies in the hot plate test in NTR-1 knockout mice [36], but NT suppression of acetic acid-induced writhing was not affected in another independently derived NTR-1 knockout line [37].

There is only limited information available regarding the mechanisms underlying the antinociceptive actions of NT; however, electrophysiological studies have demonstrated that NT has mainly an excitatory effect on neuronal activity in both the PAG and the RVM. NT has been shown to excite PAG neurons in vivo [209], in slice preparations [228] and in dissociated cell culture [229].

NT administration in the PAG also resulted in neuronal excitation in the nucleus raphe magnus, and NT excited PAG neurons that project to the RVM in dissociated cell culture [209, 229]. NT also dose-dependently activates different populations of neurons following infusion in the RVM in a manner that is consistent with NT facilitating pain at low doses and producing analgesia at higher doses [230]. These results suggest that NT is capable of activating substantial numbers of neurons in both the PAG and RVM and that differences in the intensity of NT signaling underlie pain facilitation and analgesia.

The mechanisms underlying NT modulation of pain responses remain unclear; however, there is limited evidence that NT produces analgesia through the activation of descending noradrenergic and serotonergic spinal afferents (fig. 4). Thus, depletion of spinal noradrenaline abolished NT-induced analgesia without affecting basal responsiveness in the tail flick test in mice, and similar results were obtained 1 week, but not 15 days, following depletion of spinal serotonin by 5,7-dihydroxytryptamine [231]. Recently, both SR 48692 and intrathecal adminstration of the non-selective serotonin receptor antagonist methysergide have been shown to block NT-induced analgesia following focal administration in the RVM [206]. In contrast, repeated administration of *p*-chlorophenylalanine, which inhibits serotonin synthesis, had no effect on NT-induced analgesia in mice [231] and potentiated the response in rats [232]. Interestingly, NT excites large numbers of serotonin neurons in both the nucleus raphe dorsalis and magnus most likely through NTR-1 [206, 233–235]. Finally, spinal cholecystokinin (CCK) signaling through the CCK_B receptor has been implicated in the pain facilitatory effects of NT, and signaling through CCK_A and CCK_B receptors appears to be required for the suppressive effects of NT on morphine analgesia [236, 237]. Collectively these results indicate that noradrenergic and possibly serotonergic mechanisms are involved in NT-induced analgesia, while CCK is likely to play a role in NT pain facilitation.

Conclusions

This review has centered on several important recent advances in understanding the functions of endogenous NT. There is increasing evidence that NT may truly represent an endogenous neuroleptic. The situation is less clear for NT involvement in amphetamine sensitization; nevertheless, the evidence supports the hypothesis that NT is involved in striatal activation in response to amphetamine. The evidence is perhaps most clear for an important involvement of NT in stress-induced antinociception. However, there is much work to be done to elucidate the underlying mechanisms and to uncover the full range of tasks that are juggled by this multitasking peptide.

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