Neurotensin and Dopamine Interactions

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Abstract——**Interactions between the classical monoamine neurotransmitter dopamine (DA) and the peptide neurotransmitter neurotensin (NT) in the central nervous system (CNS) have now been investigated for over two decades. Interest in this topic has been sustained, primarily because of the potential clinical relevance of these interactions to schizophrenia and drug abuse. In the past five years, important new discoveries in the NT field have markedly expanded our previous database. Additional NT receptors have been cloned, and novel and refined techniques have contributed to a more detailed description of the anatomy of the CNS NT system. Additionally, lipophilic NT receptor antagonists, active in the CNS after peripheral administration, have rendered more facile the investigation of the physiologic importance of endogenous NT at electrophysiologic, neurochemical, and behavioral levels. In the present review, the discussion of NT/DA interactions will progress from a discussion of the anatomical interactions between these two systems, to electrophysiologic and neurochemical interactions, and finally to behavioral implications—always with focus toward the potential clinical relevance of the data. The discussion of interactions between NT and DA systems will be limited to those occurring within the CNS. Moreover, because the DA projections from the midbrain to the striatum account for the bulk of the DA innervation in the CNS, we will focus on NT/DA interactions within these brain regions. Last, because of the extensive literature on NT/DA interactions available in the rat, our discussion will be based primarily on studies using this species.**

I. Introduction

A. Neurotensin Background

Neurotensin (NT[2]) was first isolated in 1973 from bovine hypothalamus by Carraway and Leeman. In 1988, the rat NT gene was isolated and sequenced (Kislauskis et al., 1988) and found to consist of a 10.2-kilobase segment containing 4 exons and 3 introns. The gene encodes a 170-amino acid precursor protein containing both the tridecapeptide NT and a closely related hexapeptide, neuromedin N (NN). The four amino acids at the carboxy terminal of NT and NN are identical, and amino acids 8–13 of NT are essential for biologic activity (Lambert et al., 1995). The NT/neuromedin N (NT/NN) gene is highly conserved between species (Dobner et al., 1987; Bean et al., 1992; Evers et al., 1995).

Elements involved in the regulation of NT/NN mRNA expression are located in the upstream 200-bp flanking region of the rat gene. In this region, several *cis*-regulatory elements function cooperatively to integrate multiple environmental stimuli into a concerted transcriptional response (Kislauskis and Dobner, 1990). In the rat NT/NN gene, these sites include one consensus AP-1 site, two near consensus cyclic AMP response elements,

one near consensus glucocorticoid response element, and a sequence identical to the human *c-jun* gene autoregulatory element. Notably, the glucocorticoid response element is absent in the regulatory sequence of the human NT/NN gene (Vita et al., 1993).

In neurons, NT is stored in dense core vesicles and released in a Ca^{2+}-dependent manner (Bissette and Nemeroff, 1995). NT transmission is terminated primarily by cleavage of NT by several peptidases, including neutral endopeptidase 24.11 (Almenoff et al., 1981), angiotensin-converting enzyme (Skidgel et al., 1984), metalloendopeptidase 24.15 (Orlowski et al., 1983), and metalloendopeptidase 24.16 (Checler et al., 1986b). In brain tissue, the reported half-life of NT is approximately 15 min (Checler et al., 1986a).

There are currently three characterized receptors for NT in the CNS: a receptor with low affinity for NT (NTRL or NT_2) that also binds the histamine H_1 receptor antagonist levocabastine (Chalon et al., 1996; Mazella et al., 1996; Vita et al., 1998), a levocabastine-insensitive receptor with high affinity for NT (NTRH or NT_1) (Tanaka et al., 1990; Vita et al., 1993), and a third NT receptor (NTR; NT_3) that is located intracellularly and has been identified as the previously characterized gp95/sortilin (Mazella et al., 1998; Zsürger et al., 1994). Although there is strong homology and identity between NT_1 and NT_2 across species, there are also significant interspecies differences (see Table 1). Species-selective modified peptide agonists have been identified with over 100-fold higher affinity for the rat over the human NT_1 (Cusack et al., 1995). Additionally, it is unclear whether NT is an agonist or an antagonist at NT_2. When the rat or human NT_2 is expressed in Chinese hamster ovary (CHO) cells, NT acts as an antagonist whereas both levocabastine and SR4869 (a small molecule NT_1 antagonist) act as receptor agonists (Yamada et al., 1998).

TABLE 1
Summary of the characteristics of the NT receptor subtypes

The amino acid sequence of NT and neuromedin N are provided in the top portion of the table. The lower section of the table summarizes the general characteristics, receptor agonists and antagonists for each of the three cloned NTRs (Chabry et al., 1993; Chalon et al., 1996; Gully et al., 1997; Hermans and Maloteaux, 1998; Le et al., 1997a; 1997b; Morris et al., 1998; Munck Petersen et al., 1999; Nouel et al., 1999; Petersen et al., 1997; Vincent, 1995; Vincent et al., 1999; Watson et al., 1993; Yamada et al., 1998).

Neurotensin N-Glu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-C
Neuromedin N N-Lys-Ile-Pro-Tyr-Ile-Leu-C

NT Receptor Subtypes	NT_1 (NTRH)	NT_2 (NTRL)	NT_3 (gp95/sortilin)
Cloned	• rNT_1 (Tanaka et al., 1990) • mNT_1 (Unpublished) • hNT_1 (Vita et al., 1993; Watson et al., 1993)	• rNT_2 (Chalon et al., 1996) • mNT_2 (Mazella et al., 1996) • hNT_2 (Vita et al., 1998)	• hNT_3 (Mazella et al., 1998; Zsürger et al., 1994)
Gene characteristics	• hNT_1 gene localized to long arm (20q13) of chromosome 20 • hNT_1 tetranucleotide repeat polymorphism 3 kb from gene • hNT_1 polymorphism at amino acid 194	• Two splice variants expressed in the CNS (604 and 423 bp). Only the 604 bp splice variant is expressed in glial cultures.	• hNT_3 gene mapped to proximal short arm of chromosome 1 • hNT_3-two NT_3 mRNA transcripts (3.5 and 8.0 kb) expressed
Receptor size and alternative processing	• 50–60 kDa	• mNT_2 = 45 kDa, 417 amino acids, alternative splice sight produces truncated receptor (282 amino acids, 5-transmembrane-spanning regions) expressed in spinal cord	• 100 kDa • Coexpression with furin (prohormone convertase) cleaves receptor to 95 kDa and changes NT affinity from 10–15 nM to 0.1–0.3 nM.
Receptor classification	• G-protein-coupled 7-transmembrane spanning regions	• G-protein-coupled 7-transmembrane-spanning regions	• Type I amino acid receptor single transmembrane-spanning region
Characteristics	• Located on neurons and glia	• Located on neurons and glia	• Expressed in neurons, glia, and adipocytes • Located on intracellular vesicles containing GLUT4 glucose transporter transported to the plasma membrane in response to insulin • NT triggers insertion of the receptor into the membrane from an intracellular compartment in mouse cortical neurons
Agonists	• NT (K_d = 0.1–0.3 nM) • NN • Xenopsin	• NT (K_d = 3–10 nM) • NN • Xenopsin • SR48692 (expressed in oocytes or CHO cells) • SR142948A (expressed in oocytes or CHO cells) • Levocabastine (expressed in oocytes or CHO cells)	• NT (K_d = 0.1–0.3 nM) • Receptor associated protein, a 40-kDa endoplasmic reticulum resident protein • Cleaved sortilin propeptide
Antagonists	SR48692 SR142948A	• NT (expressed in oocytes or CHO cells) • SR142948A • Levocabastine (weak agonist) looks like antagonism of NT effects	• Uncleaved sortilin propeptide functional antagonist blocks agonist binding until cleaved from receptor • SR48692 and SR142948A do not block NT binding in COS-7 cell extracts but block NT effects in cancer cell lines

rNT, rat NTR; mNT, mouse NTR; hNTR, human NTR.

When human NT_2 are expressed in this system, NT, NN, and levocabastine act as antagonists, and the NTR antagonists SR142948A and SR48692 act as agonists (Botto et al., 1998; Vita et al., 1998). In vivo, however, SR142948A has been shown to block the analgesic effects of NT in rodents, an NT effect that has been asso-

ciated with activation of NT_2 (Gully et al., 1997), indicating that the NT effects seen in CHO cells may be expression system-specific.

Both NT_1 and NT_2 are G-protein coupled receptors with the typical 7-transmembrane configuration characteristic of these receptors. Although for the most part it is unclear which second messenger systems the NTRs are associated with in vivo, the NT system has alternately been shown to regulate cyclic AMP (Bozou et al., 1986; Yamada et al., 1993; Slusher et al., 1994), cyclic GMP (Gilbert and Richelson, 1984), phosphatidyl inositol (PI) turnover (Snider et al., 1986; Watson et al., 1992; Erwin and Radcliffe, 1993; Hermans et al., 1994), intracellular Ca^{2+} influx (Memo et al., 1986; Woll and Rozengurt, 1989; Slusher et al., 1994; Trudeau, 2000), phospholipase C (Hermans et al., 1992; Watson et al., 1992; Chabry et al., 1994), and Na^+,K^+-ATPase activity (Lopez Ordieres and Rodriguez de Lores Arnaiz, 2000) in vitro. NTR activation not only leads to an activation of second messenger pathways, but also changes the affinity of DA receptors via allosteric receptor/receptor interactions and modulates gene expression via the internalized NT-NTR complex. NT_3 is a type I amino acid receptor with a single transmembrane-spanning region (Mazella et al., 1998). NT_3 is located in glia, neurons, and adipocytes (Chabry et al., 1993; Morris et al., 1998) and is believed to be involved in the sorting of luminal proteins from the *trans*-Golgi to late endosomes (Petersen et al., 1997). NT_3 may also be involved in modulation of NT signal termination via mediation of NT uptake and degradation (Mazella et al., 1998; Mazella, 2001; Navarro et al., 2001).

The only NTR agonists to date are modified subfragments of the NT peptide itself (Cusack et al., 1993, 2000; Tyler et al., 1999). Conversely, several nonpeptide NTR antagonists have been identified of which SR48692 and SR142948A are the best characterized (Gully et al., 1993, 1997). Both of these antagonists possess nanomolar affinity for NT_1 in different tissues and cells from various species (Gully et al., 1993, 1997). SR142948A, however, has a 90-fold higher affinity for NT_1 than SR48692, and only SR142948A binds NT_2 with nanomolar affinity. Despite the fact that SR4892 has a low binding affinity for NT_3 (Mazella et al., 1998), there is some evidence that in cancer cell lines expressing only NT_3, SR48692 blocks NT-induced cell growth (Dal Farra et al., 2001). Table 1 provides further information on agonists and antagonists of the cloned NTRs.

B. Dopamine Background

Dopamine (DA), like epinephrine and norepinephrine, is a cathecholamine neurotransmitter [for extensive reviews of the DA system see Cooper et al. (1991) and Wolf et al. (1987)]. The rate-limiting enzyme for DA synthesis, tyrosine hydroxylase (TH) is common for all cathecholamines and its activity is tightly regulated by multiple feedback mechanisms. TH immunoreactivity is a useful marker of DA neurons in brain areas lacking significant adrenergic (epinephrine and norepinephrine) input. The localization of TH in the cell body and along the length of the axon allows the identification of DA perikarya as well as DA-ergic projections.

DA-ergic axons are generally characterized by the presence of multiple varicosities. The number and diameter of these varicosities, as well as the extent of collateral branching varies between terminal regions. Synaptic junctions occur en passant with punctate membrane specializations. DA is stored in synaptic vesicles and released in a Ca^{2+}-dependent manner and signal transduction is terminated by fast reuptake of DA into the terminal by the DA transporter. DA is then converted to dihydroxyphenylacetic acid (DOPAC) by an intraneuronal monoamine oxidase (MAO). Extraneuronally, DA is metabolized to DOPAC and homovanillic acid (HVA) by combined activity of a cathechol-*O*-methyl aminotransferase and an MAO. Increased levels of these metabolites reflect increased DA neurotransmission, and changes in DOPAC and HVA in specific brain regions are closely correlated with changes in impulse flow in the corresponding DA-ergic projections.

Currently, five DA receptors (designated D_1–D_5) have been structurally characterized with elucidation of their gene sequence and corresponding amino acid sequence; all are G-protein coupled receptors (Baldessarini and Tarazi, 1996; Jaber et al., 1996). Historically, two families of DA receptors have been described based on their effect on adenylate cyclase (AC) activity. Activation of D_1-type receptors (D_1 and D_5) increases AC activity via G_s-type G-proteins. In contrast, D_2-type receptors [D_2 (D_2 short and D_2 long isoforms), D_3, and D_4] decrease AC activity via G_i-type G-proteins. It is now clear that DA receptors are also associated with G-proteins other than G_s and G_i and can affect multiple second messenger systems in a brain region-specific manner. In addition to increasing cAMP, D_1 activation increases PI turnover, and D_1 receptors have been found coupled to G_o-type G-proteins in certain systems. D_2-type receptors have been reported to increase PI hydrolysis and may also regulate phospholipase A2, intracellular Ca^{2+} levels, and K^+ currents.

DA receptors are located on DA neurons (DA autoreceptors) as well as postsynaptically on a variety of different neuronal populations including GABA-ergic, glutamatergic, serotonergic, cholinergic, and peptidergic neurons (Baldessarini and Tarazi, 1996; Jaber et al., 1996). Postsynaptic DA receptors consist of all five subtypes whereas only D_2 and D_3 receptors serve as autoreceptors. DA autoreceptors are found on the perikarya, dendrites and axon terminals of DA neurons. Autoreceptor activation tonically inhibits DA transmission by decreasing DA release, firing rate, and TH synthesis in DA neurons. Compared with postsynaptic D_2 receptors, D_2 autoreceptors have a 5- to 10-fold higher affinity for DA and certain DA receptor agonists. Relatively selective

autoreceptor agonists and antagonists are available. At low doses of DA receptor agonists, activation of autoreceptors predominates leading to diminished DA function, whereas at higher doses postsynaptic DA receptors are also activated, resulting in enhanced DA transmission (Wolf et al., 1987).

Several facts indicate that DA-ergic synapses (at least in some brain regions) favor paracrine or volume transmission. First, DA is released from synaptic densities and extrasynaptic sites. Second, although DA terminals form classic symmetric as well as asymmetric synapses, less than 10% of DA receptors are located in postsynaptic densities, and DA transporters are not concentrated solely around synapses (Pickel et al., 1996; Zoli et al., 1998). DA synapses, therefore, appear to be "open" synapses allowing for the diffusion of DA into the extracellular fluid and activation of DA receptors distant from the actual release site.

Pharmacologic manipulation of the DA system is possible at almost every level of DA transmission (Cooper et al., 1991): from modulation of DA synthesis to activity at postsynaptic DA receptors. Relatively selective toxins of DA neurons, including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) allow specific lesions of DA-ergic projections. Vesicular stores of DA can be depleted using reserpine and tetrabenzine. The indirect DA receptor agonists such as cocaine, amphetamine, and nomifensin release DA and/or block its reuptake. These compounds are not completely selective and also bind to other monoamine transporters. Direct DA receptor agonists or antagonists have evolved from nonsubtype-specific drugs to compounds with selective activity at D_1- versus D_2-type receptors. Ligands (especially agonists) that are completely selective for specific members of the D_1 or D_2 receptor families are not yet available.

II. Neurotensin/Dopamine Anatomy

A. Anatomy of the Dopamine System

Within the CNS, DA-containing cells are found in the mesencephalon (cell groups A8–A10), diencephalon (A11–A14), olfactory bulb (A16), and retina (A17) (for extensive review, see Björklund and Lindvall, 1984; Fallon and Loughlin, 1995) (Fig. 1).

Remarkably, 80 to 90% of all DA neurons are found in the midbrain. There are three DA midbrain nuclei; the substantia nigra pars compacta (SNc) and pars lateralis (SNl) (=A9), the ventral tegmental area (VTA) (=A10), and the retrorubral field (RRF) (=A8). These neurons give rise to the nigrostriatal and mesocorticolimbic DA projection systems. The cell bodies of the nigrostriatal DA system are located in the SNc and RRF and project with a medial to lateral topography to the dorsolateral aspects of the caudate/putamen (CPu). DA cell bodies in the SNl project primarily to the amygdala. The mesocorticolimbic DA system has cell bodies primarily in the
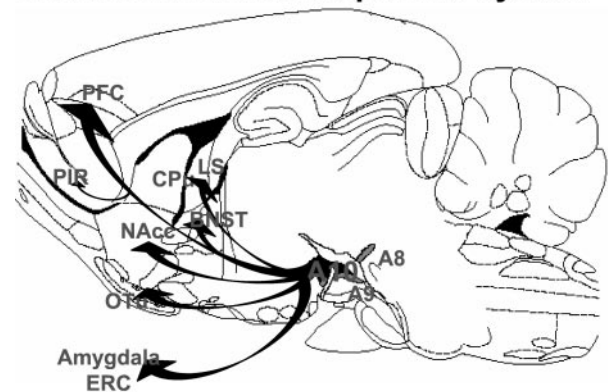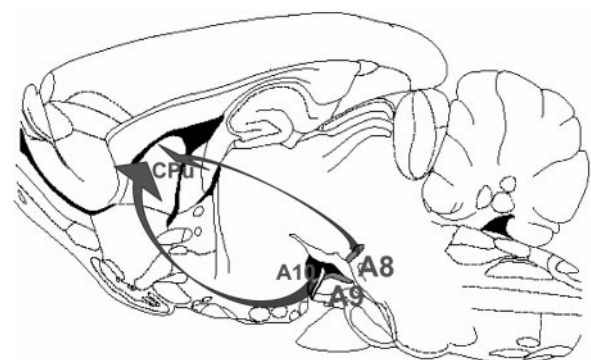
FIG. 1. Origin and major projections of the mesocorticolimbic and nigrostriatal DA systems. There are three DA midbrain nuclei: the SNc and SNl (=A9), the VTA (=A10), and the RRF (=A8). These neurons give rise to the nigrostriatal and mesocorticolimbic DA projection systems. PIR, piriform cortex; OTu, olfactory tubercles.

VTA and terminal fields in the nucleus accumbens (NAcc), olfactory tubercles and ventromedial CPu, bed nucleus of the stria terminalis (BNST), septum, amygdala, and limbic cortical areas such as prefrontal, cingulate, entorhinal, and piriform cortices. In addition to these two major projection systems originating in the SN and VTA, the SNc also innervates the subthalamic nucleus, and the VTA innervates the habenula and the locus coeruleus. Historically the cell bodies of the nigrostriatal and mesocorticolimbic DA system were thought to be strictly segregated to the SNc and RRF or VTA, respectively. It now appears that this segregation is not as strict and that the terminal fields of the A8/A9 and A10 cell groups overlap to a considerable extent. The SNc provides input to limbic and cortical regions such as the amygdala and anterior cingulate cortex; the RRF projects to the amygdala and entorhinal cortex. Midbrain DA neurons differ not only in their projection fields, but also in the inputs they receive, the receptors they express and the neuropeptides they colocalize. For example, the density of DA autoreceptors varies greatly among DA neurons (Fallon and Loughlin, 1995). DA neurons located in the medial VTA that project to prefrontal cortical areas have very few, if any autorecep-

tors. These neurons have a higher spontaneous firing rate, display more burst firing, and are less sensitive to manipulations by DA-ergic drugs than other DA neurons.

Three DA projection systems originate in the diencephalon, the tuberohypophyseal, the incertohypothalamic, and the medullary-periventricular system. The cell bodies of the tuberohypophyseal or tuberoinfundibular systems (A12) are located in the arcuate nucleus and adjacent areas of the periventricular nucleus, and project to the median eminence and the neural and intermediate lobes of the pituitary. In the median eminence, DA released into the hypophyseal portal system inhibits prolactin release from the anterior pituitary. The incertohypothalamic DA system has cell bodies in the posterior hypothalamus (A13 + the periventricular A14 neurons) that innervate the anterior hypothalamus and lateral septal nuclei. The medullary-periventricular system cell bodies (A11) are located periventricularly in the caudal thalamus, posterior dorsal hypothalamus, and periaqueductal gray. A11 neurons project locally as well as to the spinal cord.

Outside these nuclei, DA-containing cells are found in the olfactory bulb and the retina. In the olfactory bulb, periglomerular DA cells (A16) surround the glomerulae, and specialized DA-ergic amacrine cells (A17) are located in the inner portion of the nuclear layer of the retina.

The next section provides a detailed overview of anatomical NT/DA interactions in DA cell body regions and DA terminal areas with an emphasis on midbrain and striatal areas. Most of the electrophysiologic, neurochemical, and behavioral differences in NT/DA interactions between the nigrostriatal and the mesocorticolimbic DA systems can be explained based on prominent anatomical differences between these two projection systems.

B. Neurotensin and Dopamine in the Midbrain

NT cell bodies in the mesencephalon are unequally distributed between the A9 and A10 DA systems (Table 2). In contrast to the significant number of NT-positive cells in the VTA, very few NT-positive cells are detected in the SNc, SNl, and RRF (detectable NT neurons in the SNc are located mostly in its medial aspects) (Uhl et al., 1977; Jennes et al., 1982; Uhl, 1982). Interestingly, the few NT neurons found in the SNc do not colocalize TH (Seroogy et al., 1988). The vast majority of NT-positive cells in the VTA colocalize TH and the neuropeptide cholecystokinin (CCK), however, NT/DA/CCK neurons represent only a small fraction of DA-ergic cells[3] (Hökfelt et al., 1984; Seroogy et al., 1988; Seroogy et al.,

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[3] Because all immunohistochemical studies examining NT-positive neurons in DA cell bodies use colchicine pretreatment (a means to block peptide transport out of the perikarya and thereby facilitate the visualization of NT-like immunoreactivity), it is important to note that colchicine increases NT/NN mRNA expression in this region (Sato et al., 1991). Thus, the number of NT-positive neurons under baseline conditions in this region may be an overestimate.

1987). These mixed NT/DA neurons have been shown to project to the prefrontal cortex (PFC), entorhinal cortex (ERC), NAcc, basolateral nucleus of the amygdala, and lateral septum (LS) (Fallon, 1988; Febvret et al., 1991). NT/DA projections overlap mesocorticolimbic DA projections with the exception of the central nucleus of the amygdala and the NAcc core where there are no mixed projections (Fallon, 1988; Asan, 1998).

A dense network of NT fibers innervates both the VTA and SNc (Hökfelt et al., 1984; Woulfe and Beaudet, 1989). These fibers do not colocalize TH, suggesting that they originate from outside the midbrain (Bayer et al., 1991; Woulfe and Beaudet, 1992). A recent retrograde labeling study indicates that neurons projecting from the rostral lateral septum, the preoptic area, and the lateral hypothalamus may be the source of NT innervation to the VTA (Zahm et al., 2001).

The vast majority of DA neurons in the VTA and SNc express NTRs, predominantly the NT_1-subtype, and 80 to 95% of midbrain NTRs are expressed on DA-ergic neurons (Palacios and Kuhar, 1981; Uhl, 1982; Quirion, 1983; Quirion et al., 1985; Hervé et al., 1986; Moyse et al., 1987; Szigethy and Beaudet, 1989; Brouard et al., 1992; Nicot et al., 1995; Fassio et al., 2000). The remaining NTRs are found on non-DA-ergic axon terminals (most likely GABA-ergic striatonigral projections) and glial cells (Boudin et al., 1998). NT_1 immunoreactive neurons are also located in the RRF, the SN pars reticulata and to a lesser extent in the SNl (Fassio et al., 2000). In addition to high levels of NT_1 mRNA expression, NT_2 mRNA is also abundant in the midbrain, although the cellular location of NT_2 in the midbrain has not yet been clarified (Walker et al., 1998; Lépée-Lorgeoux et al., 1999). There is also pharmacologic and behavioral evidence for additional NTR subtypes in the midbrain (discussion later in this review).

Of the NT terminals contacting DA-ergic, non-DA-ergic, and mixed DA/NT cells in the midbrain, only a small fraction actually exhibit synaptic specialization (Woulfe and Beaudet, 1992). Less than 10% of these rare synaptic contacts are with TH-positive neurons (Woulfe and Beaudet, 1992). Nonetheless, 60% of NT terminals are within 5 μm of DA cells, which would allow for NT to act on DA cells via paracrine transmission (Woulfe and Beaudet, 1992). Electron microscopic localization of NTRs demonstrates that these receptors are not clustered opposite nerve terminals but are more or less evenly distributed over the perikarya and dendrites of DA cells (Dana et al., 1989; Fassio et al., 2000) supporting paracrine signaling and/or dendritic release as the major mode of NT neurotransmission in the mesencephalon.

C. Neurotensin and Dopamine in the Striatum

Of the neurons in the striatum, 95% are medium spiny GABA-ergic projection neurons that are highly collateralized. The striatum can be divided into distinct subre-

TABLE 2
Anatomical association between the DA system and the NT system
Table 2 summarizes the anatomical association of NT with the mesocorticolimbic, nigrostriatal, and diencephalic DA systems in their origin and projection areas (given in column one). The second column summarizes the presence of NT cell bodies, transmitters colocalized with NT, projection areas of NT-ergic neurons and types of DA receptors expressed by these neurons whenever known. NT cell bodies: (−), not detectable; (+), few; (++), moderate; (+++), high; (ND), not determined. The third column indicates the presence of NT or mixed NT/DA fibers and their origin. NT fibers: NT/DA, NT colocalized with DA; (−), not detectable; (+), sparse; (++), moderate; (+++), dense; (ND), not determined. The last column summarizes the density of NTR binding and the expression of NT_1 or NT_2 mRNA in each of these regions. NT receptors: (−), not detectable; (+), low; (++), moderate; (+++), dense; (ND), not determined. The cellular location of the receptors is given whenever possible.

	NT Cell Bodies	NT Fibers	NT Receptors
Origin			
VTA (A10)	(+/++) NT cell bodies concentrated in dorsolateral VTA Colocalized with: colocalized with TH and CCK, very few NT-only neurons DA receptors: D_2 autoreceptors	(++) NT fibers NT fibers originate outside the midbrain (preoptic nuclei, lateral hypothalamus, others)	(+++) NTR binding; (+++) NT_1 mRNA; (+++) NT_2 mRNA • 80–90% of NT_1 binding is on DA neurons and the majority of DA neurons express NT_1 • NT_1 are distributed evenly over perikarya and dendrites of DA neurons • low NT_2 primarily on non-DA neurons and glia
Projection area			
Preguenual and suprarhinal PFC	(−) NT cell bodies	(−) NT fibers (+++) NT/DA	(+++) NTR binding; (++) NT_1 mRNA; (−) NT_2 mRNA • NT_1 located pre- and postsynaptically
Entorhinal cortex	(−) NT cell bodies	(++) NT: subiculum and VTA (+++) NT/DA	(+++) NTR binding; (++) NT_1 mRNA; (−) NT_2 mRNA • NT_1 located pre- and postsynaptically • High NT_2
Nucleus accumbens shell	(++) NT cell bodies Projections: medial VP, lateral hypothalamus, preoptic area Colocalized with: GABA DA receptors: D_2, D_3, and possibly D_1	(++) NT fibers: local axon collaterals, subiculum and ? (++) NT/DA	(++) NTR binding; (−) NT_1 mRNA; (++) NT_2 mRNA • NT_1 located pre- and postsynaptically, located on neurons and glia • NT_2 moderate
Nucleus accumbens core	(++) NT cell bodies Projections: lateral VP, SNc Colocalized with: GABA DA receptors: D_2 and probably D_1	(++) NT: local axon collaterals, subiculum and (−) NT/DA	(++) NTR binding; (−) NT_1 mRNA; (++) NT_2 mRNA • NT_1 pre- as well as postsynaptically • NT_2 moderate
Olfactory tubercles	(++) NT cell bodies Projections: (ND) Colocalized with: (ND) DA receptors: (ND)	(++) NT fibers: local axon collaterals and ? ? NT/DA	(+++) NTR binding; (+) NT_1 mRNA; (−) NT_2 mRNA • NT_1 located postsynaptically on cell bodies in later II • NT_2 low
Basolateral nucleus of the amygdala	(−) NT cell bodies	(−) NT fibers (+) NT/DA	(+++) NTR binding; (+) NT_1 mRNA; (−) NT_2 mRNA • NT_1 located pre- and postsynaptically
Central nucleus of the amygdala	(+++) NT cell bodies Projections: BNST, dorsal vagal nucleus, parabrachial nucleus, and central grey Colocalized with: (ND) DA receptors: (ND)	(+++) NT fibers: local axon collaterals and ? (−) NT/DA	(+++) NTR binding; (++) NT_1 mRNA; (−) NT_2 mRNA • NT_1 few presynaptically, no postsynaptic NT_1 detected
Lateral septum	(+++) NT cell bodies Projections: Diagonal band of Broca, hypothalamus Colocalized with: (ND) DA receptors: (ND)	(+++) NT: local axon collaterals and ? (++) NT/DA: originate in VTA and diencephalon	(+++) NTR binding; (+++) NT_1 mRNA; (−) NT_2 mRNA • NT_1 located mostly presynaptically • NT_2 low
BNST	(+++) NT cell bodies Projections: dorsal vagal complex, parabrachial nucleus Colocalized with: (ND) DA receptors: (ND)	(+++) NT: CeA, local axon collaterals (ND) NT/DA	(+++) NTR binding; (+++) NT_1 mRNA; (++) NT_2 mRNA • NT_1 located pre- and postsynaptically • NT_2 (ND)
Origin			
Substantia nigra (A9) Retrorubral field (A8)	(−/+) NT cell bodies Very few NT neurons in medial SNc, SNl, and RRF Colocalized with: NT in medial SNc not colocalized with DA or CCK; NT in SNl or RRF colocalized with DA but not CCK DA receptors: D_2 receptors on NT/DA neurons	(+++) NT NT fibers originate outside the midbrain	(+++) NTR; (+++) NT_1 mRNA; (+++) NT_2 mRNA • 95% of NT_1 receptors located on DA neurons • Majority of DA neurons express NT_1 • NTRs evenly distributed over perikarya and dendrites • Some NT_1 located on non-DAergic terminals possibly originating in the striatum or on glial cells • NT_2 low, not on DA neurons

TABLE 2
Continued

	NT Cell Bodies	NT Fibers	NT Receptors
Origin			
Substantia nigra (A9)	$(-/+)$ NT cell bodies	$(+++)$ NT	$(+++)$ NTR; $(+++)$ NT$_1$ mRNA; $(+++)$ NT$_2$ mRNA
Retrorubral field (A8)	Very few NT neurons in medial SNc, SNl, and RRF	NT fibers originate outside the midbrain	• 95% of NT$_1$ receptors located on DA neurons
	Colocalized with: NT in medial SNc not colocalized with DA or CCK; NT in SNl or RRF colocalized with DA but not CCK		• Majority of DA neurons express NT$_1$
			• NTRs evenly distributed over perikarya and dendrites
	DA receptors: D$_2$ receptors on NT/DA neurons		• Some NT$_1$ located on non-DAergic terminals possibly originating in the striatum or on glial cells
			• NT$_2$ low, not on DA neurons
Projection area			
Premotor, retrosplenial, and visual cortex	$(-)$ NT cell bodies	(ND) NT $(-)$ NT/DA	$(-/+)$ NTR; $(-)$ NT$_1$ mRNA; $(-)$ NT$_2$ mRNA
Anterior cingulate cortex	$(-)$ NT cell bodies	(ND) NT $(-)$ NT/DA	$(++)$ NTR; $(++)$ NT$_1$ mRNA; $(-)$ NT$_2$ mRNA
			• NT$_1$ presynaptically
Caudate/putamen	$(-/+)$ NT cell bodies only detectable in ventromedial and ventrolateral aspects	$(-/+)$ NT: local axon collaterals	$(+++)$ NTR; $(-)$ NT$_1$ mRNA; $(-)$ NT$_2$ mRNA
	Projections: globus pallidus and SNr	$(-)$ NT/DA	• NT$_1$ located presynaptically (mostly in DA terminals)
	Colocalized with: GABA, enkephalin, substance P, dynorphin		
	DA receptors: D$_2$ and D$_1$		
Origin			
Arcuate nucleus + periventricular nucleus	$(++)$ NT cell bodies	$(++)$ NT	$(++)$ NTR; $(+++)$ NT$_1$ mRNA; $(+++)$ NT$_2$ mRNA
	Colocalized with: TH, reported extent of colocalization varies from rare to frequent	$(++)$ NT/DA: local axon collaterals	• NT$_1$ locate pre- and postsynaptically
	DA receptors: D$_2$ autoreceptors		• (ND) NT$_2$
Projection area			
Median eminence	$(-)$ NT cell bodies	$(++)$ NT	$(++)$ NTR; $(-)$ NT$_1$ mRNA; $(-)$ NT$_2$ mRNA
		$(++)$ NT/DA: arcuate nucleus, mostly in external layer	• NT$_1$ located on terminals and cell bodies
Pituitary: intermediate lobe	$(-)$ NT cell bodies	$(+)$ NT: arcuate and periventricular nucleus	$(+)$ NTR; (ND) NT$_1$ mRNA; (ND) NT$_2$ mRNA
		(ND) NT/DA	• (ND) NT$_1$
			• (ND) NT$_2$

gions based on several criteria, including DA-ergic innervation, glutamatergic input, projection areas and neurochemical markers. The ventral and dorsal striatum are the two major subdivisions and these two brain regions have distinct functional roles (Fig. 2). The dorsal striatum is part of the basal ganglia and mostly involved in motor coordination. The ventral striatum is part of the limbic system and although it plays a role in motor coordination, its major function is the processing of emotion and cognition (Paxinos and Watson, 1986).

The distribution of NT cell bodies, NT fibers, and NTRs differs between the dorsal and the ventral striatum. NT/NN mRNA expression, NT-positive neurons and NT axon terminals are primarily restricted to the ventral striatum (olfactory tubercles, the Nacc, and the ventromedial and ventrolateral CPu) (Zahm, 1987, 1992). The number of NT-positive neurons and fibers is extremely low in the dorsal striatum but is dramatically enhanced after specific pharmacologic manipulations (Zahm, 1992). Microdialysis studies also report higher extracellular NT concentrations in the NAcc compared

with the dorsal CPu (Huang and Hanson, 1997; Radke et al., 1998). In contrast to the density of NT terminals, NTR binding is more dense in the CPu than in the NAcc (Uhl, 1982; Quirion et al., 1985; Schotte and Leysen, 1989). One possible explanation for this apparent mismatch between the levels of NT peptide and NT binding is increased basal neuropeptide release resulting in ligand-induced receptor internalization (Dournaud et al., 1998). This hypothesis is supported by a report from Boudin et al. (1998) that compared the distribution of NT$_1$ receptor immunoreactivity and NTR binding as measured by NTR autoradiography in the SNc. This study demonstrated that in dendrites of DA neurons in the SNc, an anti-NT$_1$ receptor antibody detected internalized receptors in the absence of radioligand binding. This would suggest that internalized NTRs are less accessible to the radioligand than cell surface NTRs. Thus, neuropeptide receptor autoradiography may underestimate the number of receptors in areas of high peptide release.
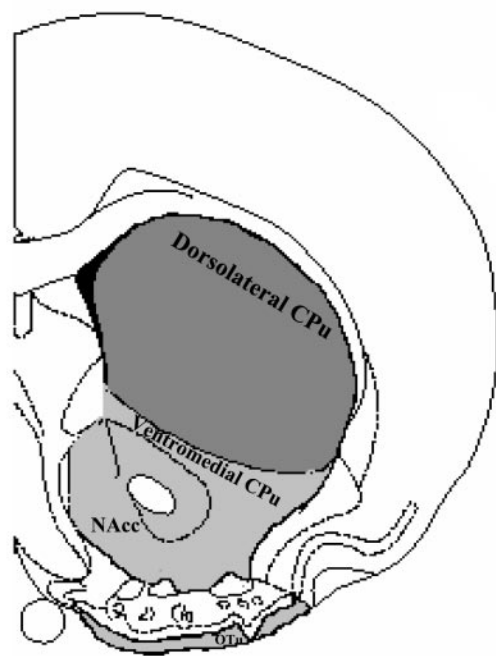
There are discordant results for the cellular location of NTRs in the striatum. A number of in situ and immunohistochemical studies are in agreement that within the ventral striatum, NT_1 receptors are located primarily on medium spiny output neurons as well as aspiny GABA-ergic or cholinergic interneurons and are only rarely detected on nerve terminals (Nicot et al., 1994; Boudin et al., 1996; Delle Donne et al., 1996; Alexander and Leeman, 1998). There is mounting evidence, however, that up to 60% of NT_1 are located on DA-ergic, glutamatergic, and GABA-ergic axons in the ventral striatum (Pickel et al., 2001). In the dorsal striatum, NT_1 receptors are restricted to DA terminals (Boudin et al., 1996). There is a moderate density of NT_2 receptor mRNA in the NAcc and somewhat less in the CPu (Walker et al., 1998). Throughout the striatum, NT_2 receptors appear to be located primarily on glial cells (Schotte et al., 1988). In contrast to in situ hybridization

STRIATUM		
	DORSAL STRIATUM	**VENTRAL STRIATUM**
Regions included	Dorsolateral CPu	Ventromedial CPu Nucleus Accumbens Olfactory tubercles
Glutamate input	Motor and association cortex Motor and association thalamus	Limbic cortex Limbic thalamus Hippocampus Amygdala
Dopamine input	SNc	VTA
Output	Globus Pallidus SNr	Ventral Pallidum VTA Lateral hypothalamus Preoptic area BNST
Function	Motor coordination	Emotion Cognition Motor coordination

FIG. 2. Striatal subdivisions based on the origin of their DA-ergic and glutamatergic input, projection areas, and function.

and immunohistochemical studies, 6-OHDA midbrain DA lesion studies report decreases in NTR binding in the NAcc ranging from 0 to 80%, whereas DA terminal numbers (as determined by DA transporter density) were drastically reduced in all studies. Thus some of these reports indicate that NTRs may be located on DA terminals in the NAcc to some extent (Hervé et al., 1986; Schotte et al., 1988; Schotte and Leysen, 1989; Cadet et al., 1991; Pickel et al., 2001). There are several possible explanations for these conflicting data. First, there may be regional differences in NTR location within subregions of the NAcc. Dilts and Kalivas (1989) reported that 6-OHDA lesioning did not affect NTR binding in the NAcc shell but decreased NTR binding by over 50% in the NAcc core. Second, these discrepancies could be explained by varying extents of DA cell lesions between various studies. This appears unlikely, however, because comparative low levels of DA transporter after 6-OHDA lesions have been associated with both unchanged (Schotte et al., 1988) and reduced (Cadet et al., 1991) NTR binding in the NAcc. Third, unchanged NT binding kinetics in the NAcc after 6-OHDA lesions could be a combination of the loss of NTRs on DA terminals and increases in postsynaptic receptors in the NAcc due to a prolonged reduction in DA-ergic tone. NTRs have been shown to be up-regulated in the NAcc after subchronic D_2 receptor antagonist (haloperidol) administration (Hervé et al., 1986). It is therefore important to consider the time point after 6-OHDA lesions when comparing these studies. Fourth, increased NTR binding could be due to increased glial associated NT_2 binding (Nouel et al., 1999). Under basal conditions, the majority of NT_2 binding in the NAcc is associated with neurons. In response to neuronal injury, there is an increase in the number of astrocytes expressing NT_2 and in the amount of NT_2 mRNA expressed per astrocyte.

Most 6-OHDA lesion studies indicate that the majority of NTRs in the CPu are located on presynaptic DA terminals (Hervé et al., 1986; Dilts and Kalivas, 1989; Schotte and Leysen, 1989; Masuo et al., 1990b; Cadet et al., 1991). Studies lesioning either intrinsic striatal neurons or cortico-striatal projections, however, are not in agreement with an exclusive location of NTRs on DA terminals (Goedert et al., 1984; Masuo et al., 1990b). These studies report that 30% of NTRs may be located on DA terminals, 50% on intrinsic neurons, and 20% on cortico-striatal projections.

The dorsal CPu and the NAcc can be further divided into distinct subregions in which the anatomical interactions of NT and DA vary greatly. The next sections discuss the anatomical compartmentalization of NT/DA interactions in these regions. This regional heterogeneity is of paramount importance for the interpretation of functional and behavioral aspects of NT/DA interactions, discussed in subsequent sections.

1. The Nucleus Accumbens. The NAcc can be divided into three distinct subregions (the cone, the shell, and

the core) based on criteria similar to that used for subdivisions of the striatum. Our review will focus primarily on the shell and core subdivisions of the NAcc. Whereas the NAcc shell is closely related to the limbic system, the NAcc core resembles the CPu and is usually considered part of the basal ganglia (Heimer et al., 1997). The type of anatomical NT/DA interaction varies greatly between, as well as within, these subregions.

In noncolchicine-treated animals, NT-positive cells and NT/NN mRNA expression are detectable only in the shell subdivision of the NAcc (Zahm, 1987; Merchant et al., 1992a; Castel et al., 1994b). When colchicine is used, NT-positive neurons are found in equal quantities in both the shell and core (Zahm, 1992). NT-positive neurons in the shell project to the medial VP, the lateral hypothalamus, and the VTA, whereas NT neurons in the core innervate the lateral VP and possibly the SNc. Dense NTR binding and NT_1 mRNA expression is present in all of these projection areas (Moyse et al., 1987; Nicot et al., 1994; Alexander and Leeman, 1998). The striking overlap between GABA-ergic and NT-ergic projections in the NAcc combined with the fact that 95% of all neurons in the NAcc appear to be GABA-ergic projection neurons, suggests that NT and GABA are colocalized in the NAcc.

NT neurons in the NAcc express D_2, D_3, and possibly D_1 receptors (Diaz et al., 1994; Delle Donne et al., 1996; Le Moine and Bloch, 1996) but marked differences between the shell and the core have been noted. In the NAcc shell, 60% of NT/NN mRNA expressing neurons coexpress D_3 receptor mRNA (Diaz et al., 1995) whereas in the NAcc core, expression of both mRNAs is very low (Diaz et al., 1994; Le Moine and Bloch, 1996). D_3 receptors are also present on terminals in the medial VP and VTA, projection areas of NT neurons in the NAcc shell, suggesting the presence of D_3 receptors on both NT perikarya and axon terminals (Diaz et al., 1995). D_3 receptor activation may therefore be an important regulator of NT transmission in the NAcc shell, but not the core.

Mixed NT/DA fibers from the VTA innervate only the shell subdivision of the NAcc (Kalivas and Miller, 1984; Fallon, 1988). Both the NAcc shell and core, however, receive NT-ergic innervation originating from local NT neurons and possibly limbic areas such as the subiculum. The majority of the NT-ergic synaptic contacts (independent of the type of synapse or postsynaptic neuron) are symmetric (Johansson and Folan, 1984). NT terminals make axo-dendritic contact with accumbal neurons (Johansson and Folan, 1984) and converge with DA terminals onto the same neurons (Delle Donne et al., 1996). Axo-axonic contacts between NT, NT/DA, and DA projections are frequent suggesting that this type of interaction may be of relative importance in the NAcc (Johansson and Folan, 1984).

2. Caudate/Putamen. NT/NN mRNA expression and NT-positive cell bodies are found only in the ventral

CPu, an area that receives mixed innervation from the SNc and VTA (Zahm, 1987; Alexander et al., 1989; Merchant et al., 1992a). These neurons appear to project to the globus pallidus, where a thin strip of NT-positive fibers can be detected in the medial globus pallidus (Eggerman and Zahm, 1988). NTR binding and NT_1 mRNA expression have also been reported in the globus pallidus (Moyse et al., 1987; Alexander and Leeman, 1998). Although very few NT neurons and fibers are detected in the CPu, microdialysis studies report the presence of basal NT release (Huang and Hanson, 1997; Radke et al., 1998). In the absence of prominent NT input (Zahm, 1987), extracellular NT is most likely released from local striatal NT neurons. Numerous NT-positive neurons become detectable in the CPu after pharmacologic manipulation of DA transmission (Zahm, 1992; Castel et al., 1993b). Several regionally distinct NT neuron subpopulations respond differentially after DA-ergic stimuli.

D. Neurotensin and Dopamine in Cortical Areas and the Hippocampus

Cortical areas receive two major types of DA innervation. Mesocortical projections from the VTA innervate deep cortical layers (V and VI) of the PFC, the piriform cortex and the entorhinal cortex. DA-ergic projections from the SNc on the other hand, innervate superficial layers (II and III) of the anterior cingulate cortex and to a lesser extent the premotor, visual, and retrosplenial cortices (Björklund and Lindvall, 1984). Pyramidal as well as nonpyramidal neurons expressing D_1, D_2, and D_4 receptors receive direct DA-ergic input (Gaspar et al., 1995; Vincent et al., 1995; Defagot et al., 1997). Hippocampal areas (including the subiculum) receive a sparse DA-ergic innervation (Björklund and Lindvall, 1984).

In general, NT-positive cell bodies are scarce in cortical and hippocampal areas and are reported in the subiculum, cingulate, and piriform cortices only after colchicine administration (Febvret et al., 1991). High levels of NT/NN mRNA expression are detected in the dorsal subiculum and CA1, and moderate amounts are found in the piriform and the cingulate cortex (Alexander et al., 1989). Despite high levels of NT/NN mRNA expression, no NT-immunoreactive neurons can be detected in CA1, and NT-positive neurons are relatively scarce in the subiculum. NT synthesis and mRNA processing are intact in these neurons and it is therefore likely that the CA1 and subiculum primarily contribute NT innervation to projection areas such as the NAcc A, entorhinal cortex and VTA.

There are dense NT fibers overlapping DA terminal fields in limbic cortical regions (Studler et al., 1988; Febvret et al., 1991). NT is colocalized with DA in all of the mesocortical projections to deep cortical layers, i.e., in DA terminals in the PFC, entorhinal cortex, and piriform cortex (Febvret et al., 1991; von Euler et al.,

1991). In contrast, NT is not colocalized with DA in projections to superficial layers of the anterior cingulate cortex where NT fibers in general are sparse and restricted to layer VI (Febvret et al., 1991). Although all NT-positive fibers in the PFC colocalize DA, NT-only terminals have been reported in the entorhinal cortex, subiculum, and retrosplenial cortex (Febvret et al., 1991). The extent of NT/DA colocalization in afferents to the PFC is somewhat controversial varying from 30 to 100% of all DA terminals (Studler et al., 1988; Febvret et al., 1991).

NTR binding overlaps the distribution of NT terminals in cortical areas. NT_1 mRNA expression is found in layer VI of all neocortical areas, but its expression is highest in the limbic cortex in layers II, III, V, and VI and in the subiculum (Nicot et al., 1994; Alexander and Leeman, 1998). In cortical areas, NTRs are located on terminals (most likely DA-ergic) and on cortical cell bodies and dendrites. In the PFC and entorhinal cortex, NT_1-like immunoreactivity has been described on pyramidal cells in layers II, III, V, and VI. In layer VI of the anterior cingulate cortex on the other hand, NT_1 receptors were detected only on terminals, despite the presence of NT_1 mRNA expression in this brain region (Boudin et al., 1996).

E. Neurotensin and Dopamine in the Amygdala, Bed Nucleus of the Stria Terminalis, and Lateral Septum

One common role of the amygdala, BNST, and LS is the transduction of higher cognitive and emotional processes into peripheral, autonomic responses. All three brain regions receive DA-ergic input from the VTA. DA innervation is the densest in the central nucleus of the amygdala, the dorsal aspect of the lateral segment of the BNST, and the intermediate and ventral parts of the lateral septum (Uhl and Snyder, 1979; Roberts et al., 1982; Björklund and Lindvall, 1984; Kohler and Eriksson, 1984; Asan, 1998). Interestingly, in all these regions, areas with dense DA innervation correspond to the areas with the highest number of NT-positive neurons, and TH-positive fibers contact NT-positive neurons (Uhl and Snyder, 1979; Asan, 1998). Mixed NT/DA neurons project from the VTA to the amygdala, where they terminate in the basolateral nucleus and are only rarely seen in the central nucleus of the amygdala, and the lateral septum (Tay et al., 1989; Bayer et al., 1991; Jakab and Leranth, 1995; Asan, 1998). NT terminals in the amygdala (predominantly local axon collaterals and not extrinsic afferents) make axo-axonic, axo-dendritic, and axo-somatic contacts with mostly NT-positive cells and axons, suggesting NT-ergic autoregulation (Tay et al., 1989; Bayer et al., 1991). In the BNST and lateral septum, the exact relationship between DA and NT has not yet been investigated.

The central nucleus of the amygdala, BNST, and lateral septum all display relatively dense NTR binding (Moyse et al., 1987). NT_1 mRNA is present in all these regions whereas NT_2 mRNA expression is not detectable (Alexander and Leeman, 1998; Walker et al., 1998). Besides providing local axon collaterals, NT neurons in the amygdala, BNST, and lateral septum project to autonomic and endocrine centers in the brainstem and hypothalamus such as the dorsal vagal complex, the parabrachial nucleus, the central gray, and the lateral hypothalamus (Uhl et al., 1979; Moga and Gray, 1985; Gray and Magnuson, 1987, 1992; Moga et al., 1989; Shimada et al., 1989; Jakab and Leranth, 1995). NT could therefore be an important transmitter in the conversion of DA-ergic cognitive and emotional information to peripheral visceral and autonomic responses.

F. Neurotensin and Dopamine in the Diencephalon

We refer the reader to an excellent extensive review by Rosténe and Alexander (1997) for information on NT in the diencephalon. Briefly, of the three diencephalic DA systems, only the tuberoinfundibular DA system originating in the dorsomedial arcuate nucleus and the adjacent periventricular nucleus, appears to be associated with the NT system. The majority of NT neurons in the diencephalon are found in the arcuate nucleus, with some neurons located in the periventricular nucleus and the parvo-cellular paraventricular nucleus (Kahn et al., 1980). NT neurons in the dorsomedial section of the arcuate nucleus colocalize TH and are believed to be part of the tuberoinfundibular DA system. The reported extent of NT and DA colocalization in these neurons varies from extensive to rare (Ibata et al., 1983; Hökfelt et al., 1984).

NT neurons in the arcuate nucleus project to the external zone of the median eminence whereas NT neurons in the periventricular nucleus project to the intermediate lobe of the pituitary. NT neurons within both these nuclei also have dense local axon collaterals (Kahn et al., 1980). NT can therefore be released locally in the hypothalamus, into the portal circulation, or directly into the intermediate lobe of the pituitary.

NTR binding is moderately dense throughout the hypothalamus, including the dorsomedial arcuate nucleus, periventricular nucleus and the intermediate lobe of the pituitary (Goedert et al., 1985). NT_1 receptors are located on cell bodies, dendrites, and terminals in the arcuate nucleus and only on terminals in the median eminence (Boudin et al., 1996). Previous studies suggested that in contrast to mesencephalic DA neurons, TH-positive cells in the hypothalamus do not express NT_1 mRNA (Nicot et al., 1995) and that NT_1 mRNA expression in general is very low in these nuclei (Nicot et al., 1994). Nonetheless, a more recent in situ hybridization study detected abundant NT_1 mRNA throughout the hypothalamus including the arcuate nucleus (Alexander and Leeman, 1998). These same authors reported that NT_1 mRNA is colocalized with TH in tuberoinfundibular DA neurons (Alexander, 1997). The arcuate nucleus also contains one of the highest levels of NT_2

mRNA expression in the rat brain suggesting an important role of NT_2 in NT regulation of tuberoinfundibular DA neurons (Walker et al., 1998).

G. Differences between Interactions of Neurotensin and Dopamine in the Mesolimbic and Nigrostriatal Systems and Interactions with Other Neurotransmitter Systems

The anatomical comparison of NT/DA interactions between the two midbrain DA systems suggests that NT might play a more important role in the physiologic regulation of the mesocorticolimbic than the nigrostriatal DA system. In the latter, NT neurotransmission may only be of importance in pharmacologic or pathologic situations. Figure 3 summarizes the main anatomical differences between the NT and DA systems in mesolimbic, mesocortical, and nigrostriatal DA projections.

It is also important to note that the mesolimbic and nigrostriatal DA systems are not isolated systems but part of larger, heavily interconnected neural circuits (Heimer et al., 1995). Although there is a striking overlap between the anatomical location of NT and DA systems, NT is also associated with other neurotransmitter systems within these interconnected circuits. NT can therefore indirectly effect DA-ergic transmission via other neurotransmitters (see Fig. 4). For example, NT-positive fibers, neurons, and NTRs are present in the dorsal raphe and NT has been shown to have an excitatory effect on these serotonergic neurons (Jolas and

FIG. 3. Representation of the primary anatomical differences in NT and DA interactions in mesocortical (A), mesolimbic (B), and nigrostriatal (C) DA projections. Within the mesocorticolimbic DA system, NT is colocalized within VTA DA neurons projecting to both the nucleus accumbens and the prefrontal cortex. In contrast, NT is not colocalized in DA cell bodies located in the substantia nigra. In addition, the location of the NTRs in the terminal regions of these two DA systems is very different. In the prefrontal cortex, NTR binding is equally distributed pre- and postsynaptically. In the NAcc, studies indicate the NTRs are located both pre- and postsynaptically. In the CPu, the NTRs are located primarily presynaptically on DA terminals.

Aghajanian, 1996). Serotonergic projections originating in the dorsal raphe in turn innervate DA neurons in the midbrain as well as striatal, pallidal, and cortical areas.

III. Functional Interactions between the Neurotensin and Dopamine Systems

The functional interactions between the NT and DA systems are as complex as the close and interconnected anatomical association between these two systems indicates are possible. The NT and DA systems reciprocally modulate each other in a heterogeneous manner in all brain regions in which these two systems coexist. In this section, we will first discuss the effects of NT on the DA system, followed by the details of how DA transmission affects the NT system.

A. The Neurochemical and Electrophysiologic Effects of Neurotensin on the Dopamine System

This section will first discuss the mechanisms by which NT has been shown to act on DA neurons and then cover the overall neurochemical and electrophysiologic effects of first centrally administered and then endogenous NT in different brain regions. Specific comparisons will be made between the effects of NT on the nigrostriatal versus the mesocorticolimbic DA system. Additionally, because the NT_1 receptor is the primary NTR associated anatomically with DA neurons, our discussion will be limited to the neurochemical and electrophysiologic consequences of NT interactions with the NT_1 receptor.

1. Mechanism of Action of Neurotensin. Once NT binds to the NT_1 receptor, NT has been shown to act via several distinct mechanisms (Fig. 5); 1) internalization of the NT-NTR complex leading to regulation of gene expression, 2) allosteric receptor/receptor interactions between the activated NT receptor and DA D_2-type receptors leading to decreased D_2 receptor agonist binding affinity, and 3) alteration of cell firing via activation of second messenger cascades and ion channels. Although NT_1 receptors are located not only on DA neurons, but also pre- and postsynaptically to them, our discussion will be restricted to the mechanisms by which NT has been shown to act directly on DA neurons.

a. Internalization of the Neurotensin-Neurotensin Receptor Complex and Regulation of Gene Expression. Upon binding of NT to NT_1 receptors, there is rapid ligand-induced receptor internalization (for review, see Hermans and Maloteaux, 1998). This internalization occurs on the axon terminals, perikarya, and dendrites of DA neurons in the midbrain (Beaudet et al., 1994; Faure et al., 1995). In the CPu, NT is internalized exclusively by DA-ergic terminals (Faure et al., 1995) whereas in the midbrain, only 88% of NT is internalized by DA neurons (Beaudet et al., 1994). Once internalized, the NT-NTR complex dissociates and is segregated into separate intracellular trafficking pathways (Hermans et

FIG. 4. Examples of direct and indirect associations between NT projections and the mesocorticolimbic DA system. The cross-hatched lines represent projections colocalizing either NT and DA (black and red) or NT and GABA (yellow and red).

FIG. 5. Mechanisms by which NT modulates DA transmission. ①, once NT binds to the NT_1 receptor, the NT-NT_1 complex is rapidly internalized. The neurochemical consequences of NT-NT_1 complex internalization have been examined in nigrostriatal neurons. The NT-NT_1 complex dissociates after being internalized, and NT and NT_1 segregate to separate intracellular trafficking pathways. Following internalization in a DA axon terminal, NT is retrogradely transported to the cell body. All internalized NT eventually moves to surround the nucleus of the cell, and in DA neurons, this process is followed by up-regulation of TH gene expression. ②, the NT-NT_1 complex decreases the agonist binding affinity of the DA D_2 receptor via allosteric receptor/receptor interactions. ③, binding of NT to NT_1 located on DA cell bodies in the mesencephalon has been shown to decrease the conductance of an inward rectifying K^+ channel (Ih). Decreasing the Ih current leads to a slow depolarization of the neuron, and antagonism of D_2 receptor agonist-induced autoinhibition of DA cell firing. ④, at slightly higher doses of NT than is needed to decrease Ih, NT binding to the NTR increases the conductance of a nonselective cation channel, transduced by activation of $G\alpha q$ and/or $G\alpha$-11 G-protein subtypes and IP_3. An increase in the conductance of the nonselective cation channel leads to cell depolarization, increased firing rate, and eventually depolarization block. ⑤, NT interacts with the extracellular portion of the D_2 receptor via hydrophobic mode matches. This interaction leads to a change in the K_d of D_2 receptor antagonist binding in a manner similar to that of noncompetitive antagonists.

al., 1997; Boudin et al., 1998). The NT_1 receptor is either recycled to the cell surface or degraded in lysosomal compartments (Boudin et al., 1998; Souazé, 2001). The internalized NT eventually moves to surround the nuclei of the cells, potentially regulating gene expression (La-

duron, 1994, 1995). For example, after binding of NT to NT_1 on DA terminals in the CPu, labeled NT is transported retrogradely to cell bodies in the substantia nigra where NT increases TH mRNA expression via a yet unknown mechanism (Castel et al., 1991, 1994a; Burgevin

et al., 1992). The physiologic relevance of this phenomenon is questionable, however, in light of the fact that in most studies a large amount of NT (over 25 μg) was injected into the striatum (Burgevin et al., 1992; Castel et al., 1992a,b).

b. Neurotensin-Induced Changes in Dopamine Receptor Affinity.   In several different preparations NT has been shown to decrease the affinity of D_2 receptors for DA and DA receptor agonists (von Euler et al., 1989; Fuxe et al., 1992; Tanganelli et al., 1993; Li et al., 1995). Pretreatment with NT increases the K_d but not the B_{max} of D_2 and D_3 receptor agonist binding in vitro and in vivo (Agnati et al., 1983; von Euler et al., 1990a,b, 1991; Liu et al., 1994). The increase in K_d of D_2 receptor agonist binding is primarily due to an increased dissociation rate from the high affinity form of D_2 receptors (von Euler et al., 1991). This effect appears to be relatively specific for D_2-type (D_2 and D_3) receptor agonist binding as NT does not affect D_1 receptor agonist or antagonist binding (K_d > 100- to 1000-fold higher concentrations than needed to modify D_2 agonist binding) (von Euler et al., 1991; Fuxe et al., 1995).

The exact mechanism of this effect has not been completely elucidated, however, allosteric receptor/receptor interactions between the NTR and D_2-type receptors, as well as second messenger-dependent receptor alterations such as phosphorylation and dephosphorylation have been implicated (for review, see Fuxe et al., 1992). The fact that NT decreases the affinity of D_2 receptors for DA agonists in crude membrane preparations in the absence of ATP and Ca^{2+} indicates that this effect could be mediated by direct receptor/receptor interactions. Nevertheless, the effects of NT are greater in intact cells than in membrane preparations, indicating that second messenger cascades together with direct allosteric receptor/receptor interactions synergistically influence the agonist affinity of the D_2 receptor. Despite the fact that the NT_1 receptor is to date the only NTR associated with regulation of DA function, the rank order of potency of NT, NN, and NT_{8-13} for decreasing D_2 receptor agonist affinity and their respective K_d for the NT_1 receptor do not coincide, suggesting that this effect may be mediated by an NTR other than NT_1 (Li et al., 1993a,b, 1994, 1995). NT-induced changes in D_2 and D_3 receptor agonist affinity do not appear to be G-protein dependent as the G-protein inhibitors pertussis toxin and *N*-ethylmaleimide do not oppose these NT effects (von Euler et al., 1991; Liu et al., 1994).

NT is not the only neurotransmitter capable of changing the affinity of DA receptors. Similar results have been reported for CCK-8, glutamate, polyethylene carbonate-60, and adenosine (Fuxe et al., 1992). CCK-8 and NT have been shown to synergistically increase the K_d of D_2 receptors, with CCK-8 decreasing the association rate as opposed to NT, which increases the dissociation rate (Li et al., 1993b).

The selective decrease of D_2-type receptor agonist binding over D_1 agonist binding by NT functionally decreases DA autoinhibition and shifts postsynaptic DA transmission to effects mediated by D_1-type receptor activation. Whether these effects actually occur in a specific brain region depends on the colocalization of NTRs with D_2 receptors on DA terminals or postsynaptic neurons. As previously discussed, NTRs and D_2 receptors in the CPu are primarily colocalized on DA terminals, whereas in the NAcc receptor colocalization takes place primarily on postsynaptic neurons.

Contradicting earlier reports that NT does not interfere with D_2 receptor antagonist binding (Nemeroff et al., 1983), a recent study by Mandell et al. (1998) demonstrated that NT can induce changes in the K_d of D_2 receptor antagonist binding similar to the effects of noncompetitive receptor antagonists. This effect was observed in a mouse fibroblastoma cell line transfected with the human D_2 receptor but lacking any NTRs, indicating that this effect was not mediated by NT_1 activation or allosteric receptor/receptor interactions. The authors postulate that NT interacts with the D_2 receptor via hydrophobic mode matches, i.e., similarities in the sequential pattern of relative hydrophobicities in the amino acid chains. This type of interaction could represent a novel mechanism for peptide/receptor modulation; however, the physiologic implications of these data remain to be determined.

To explain the DA receptor antagonist-like properties of NT, some authors have proposed that NT may bind to DA, thus decreasing its synaptic availability. Although electrovoltametry and UV/visible spectroscopy studies support this type of interaction (Adachi et al., 1990), another report did not observe any changes in the nuclear magnetic resonance spectrum of NT by DA or changes in synaptosomal DA uptake in the presence of NT (Nouel et al., 1992).

c. Activation of Neurotensin Receptors.   Activation of NT1 receptors located on midbrain DA neurons has two effects: cell depolarization and opposition of DA receptor agonist-induced autoinhibition of firing frequency, with the net observed effect being an increase in the number of spontaneously active DA neurons (Fig. 6). NT-induced DA cell depolarization can be separated into a fast rising component followed by a slower more prolonged depolarization. These two phases appear to be mediated by two distinct mechanisms (Mercuri et al., 1993; Wu et al., 1995; Wu and Wang, 1995; Chien et al., 1996; Farkas et al., 1996; Cathala and Paupardin-Tritsch, 1997; Nalivaiko et al., 1998). The fast component is mediated by an increase in the conductance of a nonselective cation channel, transduced by activation of $G_{\alpha q}$ and/or $G_{\alpha 11}$ G-protein subtypes and IP_3 (Wu et al., 1995; Wang and Wu, 1996). The slow phase is mediated by a decrease in conductance of an inward rectifying K^+ channel (Ih), and is dependent on protein kinase C (PKC) activation (Wu and Wang, 1995; Wang and Wu, 1996; Cathala and
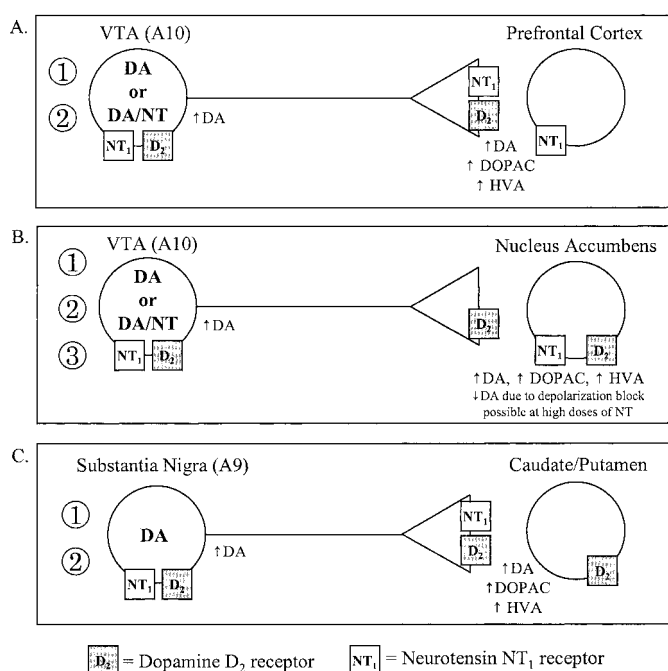
FIG. 6. Summary of the electrophysiologic and neurochemical effects of NT administered into either the ventral tegmental area (A10) or substantia nigra (A9). Effects are shown at the sight of the injection and in the prefrontal cortex (A), nucleus accumbens (B), and caudate/putamen (C). Low dose NT depolarizes midbrain DA neurons without increasing cell firing (①). Intermediate doses of NT increase the number and rate of spontaneously firing DA neurons (②). There is a corresponding increase in DA turnover in the terminal regions of the midbrain DA neurons. At high doses, NT decreases the firing rate of DA neurons in the VTA projecting to the nucleus accumbens (③). This decrease in firing rate is most likely due to depolarization block. There is an associated decrease in DA release in the nucleus accumbens.

Paupardin-Tritsch, 1997). The concomitant regulation of a nonselective cation channels and Ih responsible for the NT-induced excitation, is recognized as a general intracellular mechanism for the mediation of slow excitation and has been reported to mediate slow depolarization after muscarinic, Substance P, and luteinizing hormone releasing hormone receptor activation (Tsuji and Kuba, 1988; Koyano et al., 1993; Shen and Surprenant, 1993). Higher, potentially nonphysiologic doses of NT might also promote burst firing (Mercuri et al., 1993; Sotty et al., 1998) and eventually, at very high doses, a cessation of spontaneous activity that resembles the depolarization inactivation of DA neurons seen after antipsychotic drug administration (Pozza et al., 1988; Seutin et al., 1989).

D_2 autoreceptor activation decreases DA cell firing by increasing a G-protein-coupled inward rectifying K^+ conductance via a G_o-type G-protein. At much lower doses than needed to increase DA cell firing, NT antagonizes D_2 receptor agonist-induced autoinhibition of DA cell firing (Shi and Bunney, 1992a). This neuromodulatory effect of NT appears to be independent of receptor/receptor interactions (implicated as a regulatory mechanism in other brain regions) and interactions at the G-protein level (Shi and Bunney, 1992b). In fact, the

second messenger transduction pathways for NTRs and D_2 receptors most likely converge farther downstream at the level of the actual effector molecule, the G-protein-coupled inward rectifying K^+ channel (Farkas et al., 1997). Intracellular cAMP and protein kinase A appear to be involved in this modulatory NT effect (Shi and Bunney, 1992a). The neuromodulatory effects of NT are specific for NTR activation and not due to a general opposition of excitation, as neither glutamate nor CCK (neurotransmitters that also increase DA cell firing) mimic these effects (Shi and Bunney, 1991b).

2. The Neurochemical and Electrophysiologic Effects of Centrally Administered Neurotensin. In accordance with the fact that NT acts via several different mechanisms in the brain, central administration of NT has both dose- and region-specific effects. This next section details the electrophysiologic and neurochemical effects of administration of NT into the midbrain and in the terminal regions of the DA neurons. All of the mechanisms by which NT has been demonstrated to act combine in a brain region-specific manner to directly modulate DA-ergic neurotransmission. The net effect of NT appears to be opposition of the functional consequences of DA release.

a. The Effect of Neurotensin in the Midbrain. Within physiologic concentrations, NT opposes DA autoinhibition and induces a slow, long-lasting depolarization (Mercuri et al., 1993; Wu et al., 1995; Wu and Wang, 1995; Chien et al., 1996; Farkas et al., 1996; Cathala and Paupardin-Tritsch, 1997; Nalivaiko et al., 1998). At slightly higher concentrations, NT increases both the number and rate of spontaneously firing midbrain DA neurons. NT therefore increases the general excitability of DA neurons. At even higher, potentially pathologic or therapeutic concentrations, NT induces depolarization inactivation. Physiologically, NT may therefore act predominantly as a neuromodulator, facilitating the effects of other neurotransmitters with excitatory effects on DA neurons (e.g., glutamate and CCK) and opposing DA autoinhibition. In fact, data from in vitro and in vivo studies suggests that the NT response is dependent on the influence of external afferents. Nonetheless, NT-induced excitation of midbrain cells in vitro is not affected by coapplication of GABA (Shi and Bunney, 1991b), CCK receptor antagonist proglamide (Chiodo et al., 1987), substance P (Chiodo et al., 1987), or *N*-methyl-D-aspartate (NMDA) (Seutin et al., 1989).

DA neurons in the VTA and SN display different thresholds for NT-induced depolarization (Seutin et al., 1989; Shi and Bunney, 1990; Werkman et al., 2000) and depolarization inactivation (Shi and Bunney, 1991a); NT has a greater effect in the VTA than in the substantia nigra, and within the VTA, projections to the rostral nucleus accumbens are more sensitive to NT than VTA projections to the caudal nucleus accumbens (Myers and Lee, 1983; Seutin et al., 1989; Pinnock and Woodruff, 1994).

These electrophysiologic effects eventually translate into increased DA release in the terminal fields. The differential sensitivity of the midbrain DA projections to NT may be reflected in differences in the amount of DA release in subregions of the NAcc. In general, however, intra-VTA NT increases DA release and/or the concentrations of the major DA metabolites HVA and DOPAC in the NAcc, prefrontal cortex, septum, amygdala, olfactory tubercles, and diagonal band of Broca (Kalivas and Miller, 1984; Kalivas and Taylor, 1985; Cador et al., 1989; Ford and Marsden, 1990; Laitinen et al., 1990; Steinberg et al., 1994; Sotty et al., 1998, 2000). NT injected into the SN has alternately been reported to either increase DA, DOPAC, and HVA in both caudate nucleus and the globus pallidus (Napier et al., 1985) or to have no effect on striatal DOPAC (Myers and Lee, 1983; Ford and Marsden, 1990). These conflicting results may be explained by a similar regional gradient of response to NT in the SNc (Myers and Lee, 1983; Sotty et al., 1998).

b. Neurotensin in the Terminal Regions of Dopamine Neurons. Within the terminal fields, NT opposes the effects of DA both pre- and postsynaptically, leading to

either an increase or a decrease in DA transmission depending on the intrinsic anatomical location of NTRs in the brain region examined (Fig. 7). As in the midbrain, NT acts as both a neuromodulator and a neurotransmitter on DA-responsive neurons. In general, however, NT is more effective at modulating the effects of DA on cell firing than changing cell firing on its own. For reviews of the effects of NT on cell firing see Stowe and Nemeroff, 1991, Shi and Bunney, 1992, and Lu et al., 1996. Conflicting results reported in these reviews may be explained by the criteria used in these studies for reporting changes in firing rate. Although some studies report the percent change in firing rate for all cells examined (e.g., Z. N. Stowe, J. C. Landry, Z. Tang, M. J. Owens, and C. B. Nemeroff, manuscript submitted for publication), others only report the number of responding cells, a response being defined as a change in firing rate greater than 20 to 30% (Audinat et al., 1989; Beauregard et al., 1992).

i. Neurotensin in the Prefrontal Cortex. In vivo NT alone has no effect on the firing frequency of DA-responsive cells in the PFC (Beauregard et al., 1992). When administered in combination with DA, NT attenuates
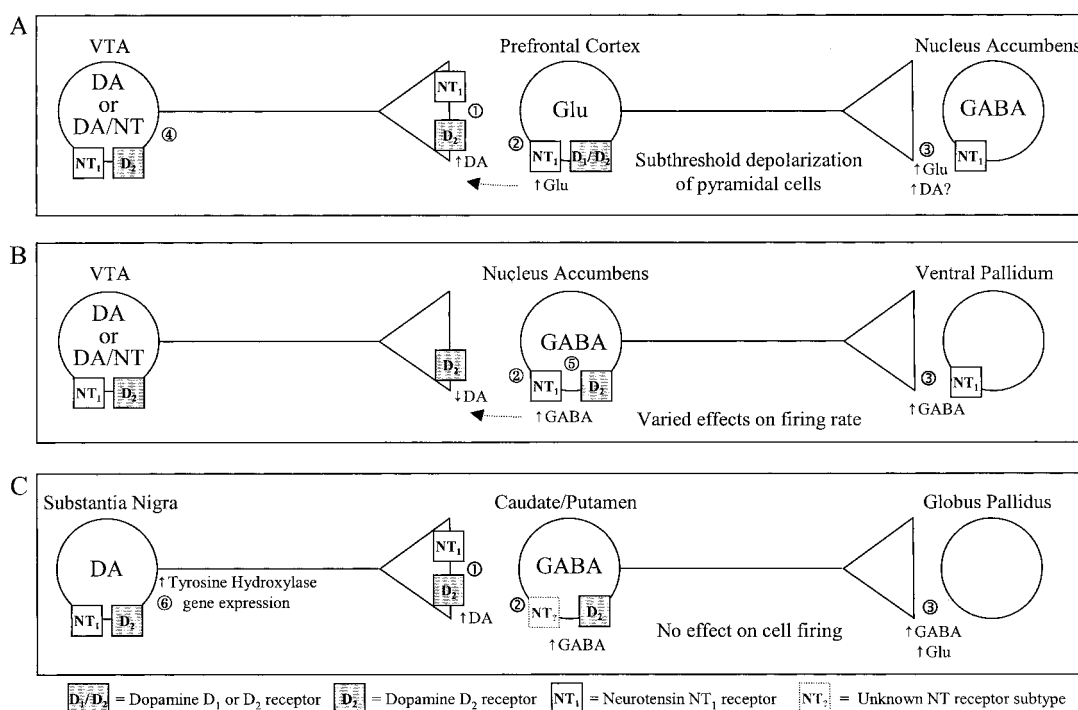
FIG. 7. Summary of the electrophysiologic and neurochemical effects of NT administered directly into the prefrontal cortex (A), nucleus accumbens (B), or caudate/putamen (C). Prefrontal cortex (A): NT administered directly into the prefrontal cortex increases DA release via a presynaptic decrease in DA autoinhibition (①) and increases glutamate release via a direct postsynaptic effect (②). NT also blocks the inhibitory effects of DA on prefrontal cortical cell firing, leading to an increase in glutamate release and a consequent increase in DA release in terminal regions of the prefrontal pyramidal neurons such as the nucleus accumbens (③). Microinjection of NT into the prefrontal cortex increases the firing rate of DA-ergic neurons in the VTA (④). Nucleus accumbens (B): Low dose NT injected directly into the nucleus accumbens increases GABA release via either a direct postsynaptic effect (②) or a decrease in postsynaptic D_2 receptor-mediated inhibition (⑤) leading to a decrease in DA release via activation of presynaptic GABA receptors. NT stimulation of GABA-ergic neurons in the nucleus accumbens through direct stimulation and decreased D_2 receptor-mediated inhibition, leading to an increase in GABA release in accumbal terminal areas such as the ventral pallidum (③). Caudate/putamen (C): NT injected directly into the CPu increases the release of DA by decreasing presynaptic D_2 autoinhibition (①). Interestingly, GABA release is also increased and this effect has been attributed to a novel postsynaptic NTR (②). GABA release is also increased in the projection area of D_2 positive GABA-ergic neurons (③), indicating that intra-CPu administration of NT stimulated striatopallidal neurons. The NT-NT_1 complex is also internalized by DA terminals in the CPu and retrogradely transported to the cell body in the SNc where tyrosine hydroxylase expression is increased ( ).

the inhibitory effects of DA in 50 to 100% of the cells examined in the prefrontal and anterior cingulate cortices. In this same study, a D_1 receptor agonist inhibited 100% of the cells examined, whereas a D_2 receptor agonist inhibited only 27% of the cells examined. NT blocked the D_1 receptor agonist-induced inhibition 100% of the time and the D_2 receptor agonist effect only half of the time, providing a functional shift to D_2 receptor-mediated effects. The antagonism of direct DA receptor agonist effects suggests that NT is acting primarily at postsynaptic NTRs. In slice preparations of the PFC, bath application of NT depolarized pyramidal cells but did not lead to spike generation (Audinat et al., 1989). In a similar preparation, NT potentiated spontaneous and K^+-induced glutamate release (Ferraro et al., 2000). These effects were not due to a decrease in the post spike after hyperpolarization (an effect seen after administration of NT into the midbrain) or due to an increase in the K+ current responsible for spike maintenance in pyramidal cells. These findings suggest that NT plays a role in the regulation of DA-responsive cortical glutamate release.

Neurons in the PFC send efferent projections to the midbrain, synapsing with both DA-ergic and non-DA-ergic neurons. Microinjection of NT into the PFC increased the firing rate of approximately 50% of DA cells in the VTA (Rompré et al., 1998; Fatigati et al., 2000). In contrast, the firing rate of a majority of non-DA-ergic cells in the midbrain was inhibited by slightly higher doses of intra-PFC NT (Fatigati et al., 2000).

ii. Neurotensin in the Nucleus Accumbens. Within the NAcc (recording from spontaneously active, DA-responsive cells classified as type II neurons), NT alone had no effect on the firing rate in 60 to 80% of cells, inhibited 20% of cells, and increased the firing rate in 20% cells (McCarthy et al., 1979; Beauregard et al., 1992; Stowe et al., 2000). NT blocked DA-induced inhibition of cell firing in 100% of the cells examined. In vivo, local application of low doses of NT into the NAcc decreases DA release and increases GABA release in a tetrodotoxin (TTX)-sensitive manner (O'Connor et al., 1992). Coadministration of the GABA$_A$ receptor antagonist bicuculline prevented NT-induced decrease in DA release suggesting that this effect is mediated by NTRs located postsynaptically on GABA-ergic neurons (see Fig. 7). At higher doses, intra-NAcc NT increased DA release in the NAcc (Chapman et al., 1992; Ferraro et al., 1997). Assuming that NTRs are located postsynaptically in the NAcc, these effects were proposed to be due to nonspecific ion channel effects of NT (Ferraro et al., 1997). There is some anatomical evidence, however, for NTRs located presynaptically on DA terminals, especially in the NAcc core (Dilts and Kalivas, 1989), and also within the NAcc shell (Pickel et al., 2001). Increases in DA release could therefore be due to the effects of an NT at a presynaptically located NTR with a lower affinity for NT than the postsynaptic receptor. This is sup-

ported by data from slice preparations showing that NT potentiates K^+-evoked DA release in slices of the NAcc in a Ca^{2+}-dependent and TTX-independent and thus presynaptic manner (Hetier et al., 1988; Reyneke et al., 1990).

iii. Effects of Neurotensin in the Caudate/Putamen. In accordance with the reported lack of postsynaptic NTRs in the CPu, NT has no effect on spontaneously active cells when administered alone in the CPu (Beauregard et al., 1992). On the other hand, NT potentiated the inhibitory effects of DA in 60% of the cells examined (Audinat et al., 1989), an effect not in accordance with the predominantly presynaptic location of NTRs in this brain region. Despite the fact that the majority of anatomical data demonstrates an exclusively presynaptic location of NTRs in the CPu, there is anatomical as well as functional evidence for the existence of postsynaptic NTRs (Goedert et al., 1984; Masuo et al., 1990a). Local administration of either NT_{1-13} or NT_{8-13} increased extracellular GABA concentrations, but only NT_{1-13} increased DA release (Ferraro et al., 1997). The authors therefore propose the existence of two NTRs in this brain region: one located presynaptically involved in increasing DA release, and the other located postsynaptically, mediating GABA release. Both receptors recognize NT_{1-13} whereas only the postsynaptic receptor recognizes NT_{8-13}. In this preparation, potentiation of DA release in CPu slices was blocked by the NTR antagonist SR142948A (antagonist at both NT_1 and NT_2) but not SR48692 (antagonist at NT_1 only) indicating that this effect may be mediated by activation of a pharmacologically distinct NT receptor other than NT_1. In contrast to the NAcc, low dose application of NT in the CPu has no effect on DA release on its own, but blocks apomorphine-induced decreases in DA release (Tanganelli et al., 1989, 1994). These effects may be mediated via a decrease in the agonist affinity for the presynaptic D_2 receptor due to allosteric D_2/NT_1 interactions.

3. Implications for the Role of Endogenous Neurotensin. Exogenously applied NT has been shown to oppose the effects of DA. The more relevant question, however, is whether this is also the role of endogenous NT. As mentioned in the anatomy section, NT and DA are colocalized in projections from the VTA to the medial NAcc, lateral septum, PFC, entorhinal cortex, and basolateral amygdala. This anatomical association allows for corelease of NT and DA from the same terminals. The corelease of NT/DA has been studied mostly in the PFC due to the lack of postsynaptic NT neurons, simplifying interpretation of the data. The extent of NT/DA corelease in the PFC is dependent on the firing frequency, firing pattern, and the level of DA autoinhibition at the DA terminal. NT and DA release in the PFC was increased by electrical stimulation of mesocortical projections in the median forebrain bundle, with burst stimulation being more effective than tonic stimulation (Bean and Roth, 1991). Increasing firing rate and burst firing

increased the ratio of NT to DA release at the cortical terminal. This preferential release of NT at higher firing frequencies may be explained by progressive depletion of the readily releasable DA but not NT pool (Bean et al., 1990; During et al., 1992). Activation of DA autoreceptors differentially regulated DA and NT release (Bean et al., 1990; During et al., 1992). Intracortical application of DA receptor agonists decreased extracellular DA and simultaneously increased NT release, arguing for different storage pools for DA and NT within the same terminal.[4] In summary, NT/DA corelease in general may serve as a limiting factor for DA transmission.

Although it is not known whether NT and DA are coreleased in all VTA projection areas that receive mixed NT/DA afferents, two studies provide evidence for corelease of DA and NT in the NAcc after electrical stimulation of the median forebrain bundle (Brun et al., 1995, 2001). Peripheral administration of the NTR antagonist SR48692 was found to have no effect on electrically evoked DA release on its own, but potentiated the effect of haloperidol on electrically evoked DA release in the NAcc. For any given dose of haloperidol, increases in electrical stimulation rate lead to a greater potentiation of DA release when the NTR antagonist SR48692 was administered, possibly due to blockade of DA inhibition by coreleased NT. In contrast to the effects in the NAcc, SR48692 did not potentiate the effects of haloperidol on electrically evoked DA release in the CPu, a brain region that does not receive mixed DA/NT afferents.

Intriguingly, acute administration of both NT and NTR antagonists increase the number of spontaneously active midbrain DA neurons (Shi and Bunney, 1992a; Gully et al., 1997; Santucci et al., 1997). Unlike the NTR antagonists, however, NT is also capable of increasing the firing rate and inducing burst firing (Shi and Bunney, 1992a). Similar to the effects of intracerebroventricular (i.c.v.) NT in the midbrain (where DA neurons in the VTA are more sensitive to NT application than DA neurons in the SN) the NTR antagonists also have relatively limbic selective effects. Both SR48692 and SR142948A selectively increase the number of spontaneously active cells in the VTA whereas DA neurons in the SN only respond at the highest doses tested (Gully et al., 1997; Santucci et al., 1997). In contrast to NT, which selectively increases DA-ergic cell firing via activation of NTRs within the midbrain (Werkman et al., 2000), the

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[4] The main caveat associated with studies examining NT/DA corelease in the PFC is assumption of 100% colocalization of NT and DA in this brain region. This assumption is supported by Studler et al. (1988) but not by Febvret et al. (1991) who report only 30 to 55% NT/DA colocalization in the PFC. At less than 100% colocalization, discrete responses to electrical as well as autoreceptor stimulation of DA alone versus mixed NT/DA projections have to be taken into account. It is also important to note that NT/DA colocalization in mesocortical projections appears to be restricted to rodents. NT/TH colocalization has not been found in human mesocortical projections although NT and DA project in parallel to the same cortical regions (Gaspar et al., 1990).

NTR antagonists are most likely acting outside the midbrain, as direct injections of SR48692 into the PFC mimic the effects of peripherally administered NTR antagonist (Santucci et al., 1997).

Chronic peripheral administration of NTR antagonists has effects similar to those of high doses of intramidbrain NT. After chronic administration of SR48692, there is a selective depolarization block-type of inactivation of DA neurons in the VTA (Gully et al., 1997; Santucci et al., 1997). Similar to the depolarization block seen after antipsychotic drug administration, this effect can be reversed by administration of apomorphine (Santucci et al., 1997). In addition, the NTR antagonist most likely selectively induces depolarization block in mesolimbic and not mesocortical projections, as DA release is decreased in the NAcc shell but not the PFC (Azzi et al., 1998). Studies using the NTR antagonists suggest a complex balance of regionally and qualitatively different effects of endogenous NT on DA-ergic transmission.

B. Effects of Dopamine on the Neurotensin System

Decreasing as well as increasing DA neurotransmission has consistently been shown to alter NT neurotransmission in ventral and dorsal striatal areas and in striatal output regions the globus pallidus, ventral pallidum and SN pars reticulata (SNr). DA-ergic modulation of the NT system has been observed in the midbrain, hypothalamus, preoptic area, PFC, olfactory bulbs, BNST, endopiriform cortex, and the amygdala (Govoni et al., 1980; Eggerman and Zahm, 1988; Kilts et al., 1988; Merchant et al., 1988; Hanson et al., 1989, 1992; Radke et al., 1989). This next section focuses on the effects of drugs that alter DA neurotransmission on NT transmission in the striatum, as these have been the most extensively studied. It is possible, however, that DA-induced changes in NT neurotransmission in striatal output areas may be functionally more relevant than changes in NT neurotransmission in striatal regions themselves.

1. Patterns of Dopamine Effects on Striatal Neurotensin. Changes in NT release are the most relevant parameter for interpreting the effects of DA-ergic transmission on the NT system. The number of microdialysis studies examining the effects of DA-ergic drugs on NT release is limited (Wagstaff et al., 1996a,b; Huang and Hanson, 1997; Radke et al., 1998). From over a decade's worth of accumulated data, it is apparent that changes in NT release are associated with a discrete time course of changes in NT peptide concentrations and NT/NN mRNA expression. These specific patterns of regulation make it possible to infer changes in NT release from NT tissue concentration and NT/NN mRNA expression data.

In general, DA-ergic drug-induced increase in NT release occurs within 30 min to 1 h of drug administration and normalizes within 2 to 3 h postinjection (Wagstaff et al., 1996b; Huang and Hanson, 1997). This is usually

paralleled by a decrease in the measurable NT tissue concentrations, reflecting a decrease in stored NT (Wagstaff et al., 1996b; Huang and Hanson, 1997). The increase in NT release appears to induce a compensatory increase in NT/NN mRNA expression that peaks between 3 and 7 h after drug administration. Using haloperidol, it was demonstrated that the increases in NT/NN mRNA expression can be preceded by an increase in *c-fos* mRNA expression and Fos peptide (Merchant et al., 1992a; Senger et al., 1993). Additionally, there is some evidence that increased NT release is involved in haloperidol induction of *c-fos* mRNA expression (Fadel et al., 2001). Pretreatment with SR48692 (an NT_1 antagonist) partially blocked haloperidol induction of *c-fos* mRNA expression in the dorsolateral and central striatum, indicating a role of haloperidol-induced NT release. Haloperidol-induced increases in NT/NN mRNA can by prevented by pretreatment with antisense oligonucleotides against *c-fos* mRNA (Merchant, 1994; Robertson et al., 1995). Fos probably regulates NT/NN mRNA expression via the AP-1 site present in the promoter region of the NT/NN gene (Kislauskis and Dobner, 1990). More recently, a protein kinase A pathway has also been implicated. In protein kinase $AII\beta$ subunit-deficient mice, haloperidol does not increase *c-fos* mRNA or NT/NN mRNA expression (Adams et al., 1997). The protein kinase A/Fos pathway does not, however, appear to be involved in the induction of NT/NN mRNA expression in all cases. In fact, methamphetamine (a compound that induces NT release and NT/NN mRNA expression in the striatum) increases *c-fos* mRNA expression in striatal areas that do not overlap regions in which NT/NN mRNA expression is increased (Merchant et al., 1994b). In both cases, however, the increase in NT gene transcription seen 3 to 7 h after drug administration is then followed by an increase in NT/NN mRNA translation and NT peptide concentrations, which are maximally elevated 18 to 24 h after drug injection (Govoni et al., 1980; Kinkead et al., 2000). It is not clear, however, whether this late increase in peptide concentration actually reflects an increase in the releasable NT pool.

If NT release is decreased in response to DA-ergic drugs, there is a parallel increase in NT tissue concentration due to intracellular build-up of NT (Zahm, 1992; Wagstaff et al., 1996a; Huang and Hanson, 1997). NT peptide concentrations usually normalize within 24 h of drug administration. In regions exhibiting this response pattern a late onset (20–24 h postinjection) increase in NT/NN mRNA expression has been observed (Zahm et al., 1996). It is not clear, however, whether this increase in NT/NN mRNA is followed by an increase in NT peptide concentrations. These delayed increases in NT/NN mRNA expression do not appear to be preceded by an increase in *c-fos* mRNA or Fos peptide expression (Zahm et al., 1996).

2. Effects of Dopaminergic Drugs on the Striatal Neurotensin System. Figure 8 illustrates the various effects of DA-ergic manipulations on NT neurotransmission in the striatum. It is important to note that a specific DA-ergic drug can have opposite effects on NT transmission among subregions of the CPu and NAcc (Fig. 8A) as well as along a rostrocaudal gradient (Fig. 8B). In addition, activation of subtypes of D_2-type DA receptors (D_2 versus D_3) appears to have opposite effects on NT transmission within the NAcc shell (Diaz et al., 1994; Tremblay et al., 1997, 1998).

In addition to the illustrated subregion differences (see Fig. 8 for details), D_1 and D_2 receptor-selective drugs differentially effect striatonigral and striatopallidal subpopulations within the same striatal areas. Methamphetamine-induced increases in NT/NN mRNA expression and NT concentrations are blocked by coadministration of D_1 receptor antagonists, suggesting that these effects are mediated via activation of the D_1 receptor. In contrast, combined administration of methamphetamine and D_2 antagonists synergistically increases NT concentrations in striatal areas (Letter et al., 1987b; Merchant et al., 1988; Castel et al., 1993a). Several studies have demonstrated that striatopallidal NT neurons respond to D_2 antagonism, whereas striatonigral NT neurons respond to D_1 agonism, a finding consistent with the segregation of D_1 and D_2 receptors to these two striatal projections (Gerfen et al., 1990, 1995; Harrison et al., 1992; Le Moine and Bloch, 1995). After administration of D_2 receptor antagonists, NT peptide concentrations and NT/NN mRNA expression are increased in neurons colocalizing enkephalin or its mRNA (found exclusively in striatopallidal neurons) (Fuxe et al., 1992; Augood et al., 1997), and there is an increase in NT-positive fibers in the ventral pallidum and the globus pallidus (Eggerman and Zahm, 1988; Zahm, 1992; Brog and Zahm, 1995). Retrograde tracing confirms that D_2 responsive NT neurons project almost exclusively to pallidal areas (Brog and Zahm, 1995). In contrast, methamphetamine administration increases NT-positive terminals in the SNr (an effect that is completely blocked by D_1 but not D_2 antagonists) in regions overlapping dynorphin-positive fibers (a marker for striatonigral efferents) (Letter et al., 1987b; Wachi et al., 1987; Merchant et al., 1990; Castel et al., 1993b, 1994c). It should be noted that in addition to the distinct effects of D_1 receptor agonists and D_2 receptor antagonists on striatonigral and striatopallidal projections, respectively, synergistic effects of D_1 and D_2 receptors on the same cell population have been reported. Combined administration of selective D_1 and D_2 receptor antagonists (Deutch and Zahm, 1992; Zahm, 1992) increases NT-positive neurons in striatal patch areas, an effect not seen after administration of either D_2 or D_1 receptor antagonists alone (Frey et al., 1986; Merchant et al., 1988; Taylor et al., 1991; Zahm, 1992). These findings suggest the existence of an additional subset of NT neu-
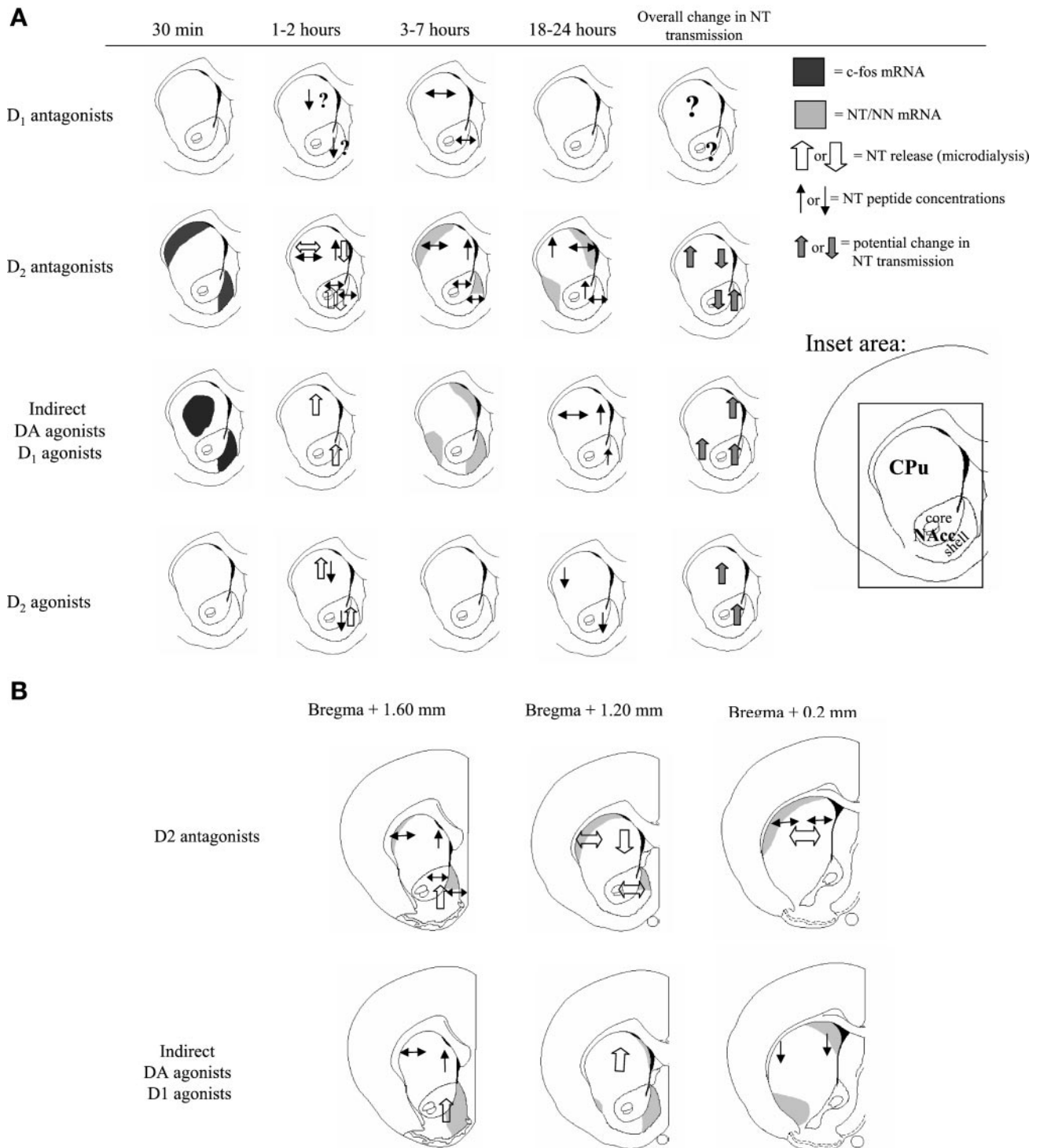
FIG. 8. Panels A and B illustrate a time course of the various effects of DA-ergic manipulations on the NT system, with panel A focusing on regional differences occurring within one coronal plane and panel B on rostrocaudal differences. The information used is derived from studies using single acute drug administrations. In studies using repeated administrations it is more difficult to distinguish between the different phases of NT neuron responses, e.g., changes in NT release or NT synthesis and information from these studies are thus not represented in the figures. The last column represents how NT neurotransmission might potentially be changed following stimulation or antagonism of D_1 or D_2 receptors. It has to be kept in mind, however, that cell-type specific (striatonigral versus striatopallidal) and subregional details on changes in NT neurotransmission are not yet available and these representations are crude approximations. Panel A, D_1 antagonism does not induce any changes in NT/NN mRNA expression (Augood et al., 1991) and reports on the effects of D_1 antagonism on NT tissue levels are inconsistent (Zahm, 1992; Taylor et al., 1995). The effects of D_1 antagonism on extracellular NT concentration have not yet been investigated. D_2 antagonists have been reported to either decrease NT release in the medial CPu and NAcc (eticlopride) (Wagstaff et al., 1996a) or increase release in the anterior NAcc (haloperidol) (Huang and Hanson, 1997) or to not affect NT release or in the posterior NAcc and CPu (haloperidol) (Radke et al., 1998). NT/NN mRNA expression increases in the dorsolateral rim of the CPu and the dorsomedial NAcc shell within 3 to 7 h of D_2 antagonist administration while a delayed (20–24 h postinjection) increase in NT/NN mRNA expression is observed in the dorsomedial and ventrolateral CPu (Merchant et al., 1992a; Zahm et al., 1996). The first increase in NT/NN gene transcription is followed by an increase in NT peptide, this has not yet been documented for the delayed mRNA response (Govoni et al., 1980; Frey et al., 1986; Kilts et al., 1988). The increase in NT/NN mRNA seen in the dorsolateral CPu and NAcc 3 to 7 h after D_2 receptor antagonist

rons that respond only to combined D_1 and D_2 antagonism.

In view of the close interaction of NT and DA systems with other neurotransmitter systems, some evidence indicates that DA-ergic effects on the NT system could be mediated indirectly via other neurotransmitter systems. First, increased striatal and nigral NT tissue concentration and striatal NT release after D_1 agonism are completely blocked by pretreatment with the NMDA receptor antagonist MK801 (Singh et al., 1990). This suggests that D_1 receptor activation regulates NT systems indirectly via enhanced NMDA transmission, a theory supported by the fact that NMDA itself increases NT concentrations in these brain regions (Singh et al., 1990; Hanson et al., 1995). Second, coadministration of haloperidol and the GABA$_A$ receptor agonist muscimol results in a blunted increase in NT/NN mRNA expression in the dorsolateral CPu, but not the NAcc (Decker et al., 1995). Thus, secondary activation of other neurotransmitter systems appears to be involved in the regulation of NT by DA transmission and regional differences in the intermediary neurotransmitters seem possible.

3. Data Interpretation. From the pattern of NT response to DA drugs presented above, several limitations of previous studies become apparent. Although NT microdialysis studies have yielded important findings, the anatomical resolution of the microdialysis technique may not be precise enough to allow accurate estimations of NT release in subregions of the striatum. In view of the complicated striatal subregion and neuronal subpopulation-dependent responses of NT neurons to DA-ergic stimuli, it is not surprising that NT microdialysis studies are often not in agreement with reported changes in NT peptide content or NT/NN mRNA expression. Below are a few examples of these discrepancies.

In the dorsolateral rim of the CPu, NT/NN mRNA expression increases rapidly after D_2 receptor antagonism (Merchant et al., 1992a). In these neurons, NT immunostaining is relatively weak and does not extend into proximal dendrites, a pattern that is thought to be associated with an increase in NT release (Zahm, 1992). Nonetheless, Wagstaff et al. (1996) did not find increases in extracellular NT release in the lateral CPu after acute administration of the D_2 receptor antagonist eticlopride. Although it is possible that D_2 antagonism

does not induce NT release in the dorsolateral CPu, this negative finding may also be the result of microdialysis sampling from an area much larger than the area in which increases in synthesis are seen, i.e., the dorsolateral rim of the CPu only. In microdialysis studies assessing NT release in the NAcc, the microdialysis probe is placed so that the shell and the core subregions are sampled simultaneously. In light of the evidence indicating that NT release changes in opposite directions in these two areas, results obtained by sampling both regions simultaneously are difficult to interpret. Rostrocaudal differences in the response of the NT system to DA-ergic drugs could explain the conflicting results from Huang and Hanson (1997) versus Radke et al. (1998) in which the effects of acute haloperidol administration on extracellular NT release in the NAcc and CPu were examined. Whereas Huang et al. (sampling from more anterior aspects of both the NAcc and CPu) saw increases in NT release in the NAcc and decreases in the medial CPu, Radke et al. (sampling more caudally) reported no acute effects of haloperidol on extracellular NT release.

It is important to keep in mind that clear interpretation of the effect of specific DA receptors can only be made with highly selective receptor agonists and antagonists. The use of drugs that target several DA receptors simultaneously and/or additional neurotransmitter receptors may complicate data interpretation. For example, NT release in the NAcc is decreased after eticlopride but increased after haloperidol, even though both drugs are considered D_2-type receptor antagonists. The opposite effects of these two receptor antagonists on NT release could be due to their different affinities at D_2 and D_3 receptors and the fact that haloperidol binds to neurotransmitter receptors other than DA receptors (Levant, 1997).

Evaluation of the effects of DA-ergic drugs on NT release is not only complicated by subregion-specific effects and the use of nonreceptor-selective drugs, but also by dose-related differences. For example, NT release in the NAcc and CPu is increased after administration of low doses (0.5–5.0 mg/kg) of methamphetamine, whereas higher doses (15 mg/kg) are ineffective (Wagstaff et al., 1996b). In contrast, high doses (greater than 10 mg/kg and up to 50 mg/kg) (Wachi et al., 1987) or

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administration are preceded by an increase in *c-fos* mRNA expression and Fos peptide. This is not true for NT/NN mRNA expression increases seen 20 to 24 h after D_2 receptor antagonist administration (Merchant et al., 1992a; Senger et al., 1993; Zahm et al., 1996). The effects of selective D_1 receptor agonism and indirect DA agonists (amphetamine/methamphetamine) on the NT system are very similar and are therefore grouped together for illustrative purposes in the figure. D_1 receptor agonism increases NT release in the medial CPu and the NAcc (Wagstaff et al., 1997). Rapid increases in NT/NN mRNA expression are seen in posterior but not anterior aspects of the dorsomedial and ventrolateral CPu and the NAcc shell (Castel et al., 1993a, 1994b) and are followed 18 h later by increases in NT peptide (Letter et al., 1987a; Merchant et al., 1994b). Interestingly, methamphetamine increases *c-fos* mRNA expression in striatal areas in which NT/NN mRNA expression is not increased (Merchant et al., 1994b). D_2 agonism has been shown to increase NT release in the CPu and in the NAcc with a parallel decrease in NT peptide (Wagstaff et al., 1996b). Peptide levels have been reported to stay low even 18 to 20 h post. Data on NT/NN mRNA expression are not available. Panel B, anteroposterior differences in the response of the striatal NT system to D_1 receptor agonists and D_2 receptor antagonists. Values for NT/NN mRNA, peptide, and release are taken in a period of 1 to 4 h postinjection, and changes in all parameters are likely to occur simultaneously. Changes in NT release are indicated at the reported level of microdialysis probe placement. Data on NT peptide concentration and NT release have been combined with NT/NN mRNA changes following methamphetamine since it has been reported that methamphetamine-induced increases in NT/NN mRNA can be completely blocked by D_1 antagonists (Castel et al., 1994b).

repeated administrations (Merchant et al., 1988) of methamphetamine are necessary to achieve detectable increases in NT peptide concentration or NT/NN mRNA expression. This indicates that the type of NT response after methamphetamine varies with the dose and that increasing doses may be followed not only by quantitative, but also by qualitative, changes in the NT response.

All of these issues have to be taken into account when trying to correlate the results of neurochemical and behavioral studies. For many DA-ergic drugs, doses used in behavioral studies are far below those necessary to obtain detectable changes in NT peptide or NT/NN mRNA expression, e.g., 0.5 to 2 mg/kg versus 10 to 50 mg/kg methamphetamine or 0.1 to 0.5 mg/kg versus 1 to 2 mg/kg haloperidol for behavioral versus neurochemical studies, respectively (Wachi et al., 1987; Swerdlow and Geyer, 1993; Wagstaff et al., 1996b; Kinkead et al., 2000). Microdialysis studies have also used high doses, likely not behaviorally relevant, to examine DA drug-induced changes in extracellular NT concentrations (Wagstaff et al., 1996b; Huang and Hanson, 1997). In view of the previously discussed dose-related difference in elicited NT release, the effects on NT release elicited by a high dose cannot necessarily be generalized to lower, behaviorally relevant doses.

One factor complicating attempts to correlate neurochemical changes with behavior is the detection limits of the methods used to analyze extracellular NT release, NT peptide, and NT/NN mRNA expression. For example, pretreatment with the NTR antagonist SR48692 enhances methamphetamine-induced DA release as well as hyperlocomotion within 30 min of methamphetamine administration (Wagstaff et al., 1994). Nonetheless, measurable increases in extracellular NT release in the NAcc and CPu after the same dose of methamphetamine are delayed by 75 to 100 min (Wagstaff et al., 1996b). The sensitivity of the microdialysis technique is compromised by the inherent "stickiness" of neuropeptides, especially NT, to the dialysis membrane, leading to only a 2 to 15% effective recovery of peptide. Detection methods with increased sensitivity for extracellular NT (e.g., electrospray mass spectroscopy and matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy) have already shown promising results (Javerfalk-Hoyes et al., 1999; Gobom et al., 2000). Thus, it is difficult to make definitive statements on the importance of NT transmission in certain behaviors based on the anatomical resolution and detection limits of the currently available methods.

IV. Behavioral Interactions between Neurotensin and Dopamine

This section approaches the discussion of behavioral interactions between the NT and DA systems from the viewpoint of potential clinical relevance. Where possible, the significance of these behaviors in specific disorders

and the potential for novel treatment strategies afforded by the unique interactions between the NT and DA systems will be emphasized. Primary focus is given to the role of NT in the pathophysiology of schizophrenia, and the mechanism of action of antipsychotic drugs. Other behaviors that are covered on a more superficial level include the role of NT/DA interactions in the effects of drugs of abuse and the reward system, stress response, analgesia, and hypothermia.

A. Neurotensin and Dopamine in Schizophrenia and the Mechanism of Action of Antipsychotic Drugs

Schizophrenia is a devastating psychiatric disease with a worldwide prevalence of approximately 1%. Antipsychotic drugs have repeatedly been shown to be effective in reducing some of the cardinal symptoms of schizophrenia and yet none of the available antipsychotic drugs are curative at least not in the vast majority of cases, all have less than ideal side effect profiles and the underlying neurochemical actions responsible for clinical efficacy remain poorly understood. Antipsychotic drug development has focused primarily on targeting specific neurotransmitter systems such as the DA system; a functional hyperactivity of the mesolimbic DA system is considered as one of the critical pathophysiologic abnormalities in schizophrenia (Carlsson, 1988; Goldstein and Deutch, 1992). It has become increasingly clear, however, that schizophrenia does not result from the dysfunction of a single neurotransmitter system, but rather an imbalance between several interacting systems, including dopaminergic, serotonergic, glutamatergic, cholinergic, and GABA-ergic systems (Joyce, 1993). Targeting of neuropeptide neuromodulator systems, capable of concomitantly regulating all affected transmitter systems, may therefore be a promising approach for the development of increasingly effective and side effect free antipsychotic drugs.

Decades of cumulative evidence strongly implicate the NT system in the pathophysiology of schizophrenia and the mechanism of action of antipsychotic drugs. It has been repeatedly demonstrated that subgroups of drug-free schizophrenic patients have low NT cerebrospinal fluid (CSF) concentrations compared with nonschizophrenic controls (Widerlöv et al., 1982; Lindström et al., 1988; Nemeroff et al., 1989; Garver et al., 1991; Breslin et al., 1994; Sharma et al., 1997). Low NT in the CSF has been associated with increased severity of psychopathology in schizophrenia including thought disorder, delusions, and hallucinations (Breslin et al., 1994; Sharma et al., 1997). One of the most robust findings in these reports is that NT concentrations in schizophrenic patients with decreased CSF NT increase to control values after antipsychotic drug treatment and clinical improvement (Garver et al., 1991; Sharma et al., 1997).

Similarities between the effects of peripherally administered antipsychotic drugs and centrally administered NT led to the hypothesis that NT may be an

endogenous antipsychotic (Nemeroff, 1980). Although to date, there has not been consistent demonstration of abnormalities in either the DA or NT systems in human postmortem tissue, NT and NTRs are prevalent in the human mesolimbic DA system, a circuit believed to play an important role in the positive symptoms of schizophrenia (e.g., delusions and hallucinations), and in the limbic cortical areas implicated in the genesis of negative symptoms of schizophrenia (e.g., amotivation, anhedonia, flat affect, cognitive dysfunction, and social withdrawal). By its association with the nigroneostriatal DA system and the 5-HT system, NT may well play a role in the extrapyramidal side effect (e.g., Parkinsonian motor disturbances, acute dystonias, and tardive dyskinesia) liability of antipsychotic drugs. Anatomically, NT is therefore in a key position for involvement in the pathophysiology of schizophrenia and for mediation of antipsychotic drug actions.

The following section will provide support for a role of increased NT transmission in the mechanism of action of antipsychotic drugs, detail the behavioral similarities between the effects of NT and antipsychotic drugs and evaluate the evidence for disrupted NT transmission contributing to behavioral abnormalities associated with schizophrenia.

1. Effects of Antipsychotic Drugs on the Neurotensin System. In the same year that NT was hypothesized to be an endogenous neuroleptic (Nemeroff, 1980), the first report concerning the effects of antipsychotic drug administration on NT-like immunoreactivity was published (Govoni et al., 1980). To date, all clinically effective antipsychotic drugs examined have specific effects on the NT system of the rat brain (for review, see Kinkead and Nemeroff, 1994). Additionally, the effects of antipsychotic drugs on the NT system are selective for drugs with antipsychotic efficacy; compounds from other classes of psychoactive drugs (e.g., anxiolytics, antidepressants, and antihistamines) as well as clinically ineffective phenothiazines, do not alter the NT system (Govoni et al., 1980; Myers et al., 1992). Perhaps of greatest interest, is the finding that typical and atypical antipsychotic drugs differentially regulate the NT system. Clinically efficacious antipsychotic drugs are classified as either "typical" or "atypical" based on their effectiveness in the treatment of positive and negative symptoms and their propensity for inducing extrapyramidal side effects such as Parkinsonian motor disturbances, acute dystonias, and tardive dyskinesia. Typical antipsychotic drugs have actions on both the mesolimbic (VTA to NAcc) and nigroneostriatal (SN to CPu) NT systems, whereas atypical antipsychotic drugs act preferentially on the mesolimbic NT system (Kilts et al., 1988; Merchant et al., 1994a). This last finding has generated the hypothesis that the nigroneostriatal NT system may play a role in the side effect profile of typical antipsychotic drugs, whereas the mesolimbic NT system

may be involved in the clinical efficacy of all antipsychotic drugs.

2. Behavioral Similarities between the Effects of Antipsychotic Drugs and Centrally Administered Neurotensin. Despite the fact that typical antipsychotic drugs (e.g., haloperidol and chlorpromazine) are very effective at reducing positive symptoms, they induce extrapyramidal side effects and are believed by many to be relatively ineffective in the treatment of negative symptoms. In contrast, atypical antipsychotic drugs (e.g., clozapine, quetiapine, risperidone, ziprasidone, and olanzapine) improve both positive and negative symptoms and are relatively lacking in extrapyramidal side effect liability (Barnes and McPhillips, 1998; Blin, 1999; Campbell et al., 1999). To account for the salutary effects of antipsychotic drugs on both negative and positive symptoms, as well as the difference in the extrapyramidal side effect potential of typical versus atypical antipsychotic drugs, pathophysiologic approaches to schizophrenia have evolved from a simple over-activity of the mesolimbic DA system to more complex models. This trend is reflected in part by the animal models used to screen for antipsychotic drug effects. Behavioral screening of prospective antipsychotic drugs employs animal models designed to evaluate three properties: 1) induction of behaviors related to the motor side effects of antipsychotic drug administration in humans (e.g., catalepsy and vacuous chewing movements); 2) reduction of the effects of stimulation of the DA system (e.g., hyperlocomotion, yawning, rearing, stereotyped sniffing, licking, and biting); and 3) activity in behaviors thought to model the psychophysiologic disturbances underlying schizophrenic symptoms (e.g., sensorimotor gating and selective attention). Where possible, the behavioral effects of NT will be compared with those of typical versus atypical antipsychotic drugs.

a. Behaviors Related to the Side Effect Potential of Antipsychotic Drugs. In conjunction with the clinically efficacious effects of antipsychotic drugs, typical antipsychotic drugs also induce several potentially severe side effects. Parkinsonian-type movement disorders and acute dystonias are seen after acute administration of antipsychotic drugs whereas tardive dyskinesia (characterized by involuntary movements primarily of the head and neck) result from long term use of antipsychotic drugs. Catalepsy is viewed as an animal model of the acute side effects of antipsychotic drug administration, whereas the induction of vacuous chewing movements (VCMs) in animals after chronic administration of antipsychotic drugs is posited to represent an animal model of tardive dyskinesia. Several studies have examined the involvement of the NT system in both these behaviors.

i. Catalepsy. Immobility, increased muscle tone, and abnormal postures characterize catalepsy. Both typical antipsychotic drugs and i.c.v. NT induce cataleptic symptoms in rats (Adams et al., 1997; Shibata et al.,

1987). This behavioral effect is believed to be due to activation of the dorsolateral striatum as compounds that induce catalepsy in the absence of any beneficial antipsychotic effects, increase *c-fos* mRNA expression only in the dorsolateral striatum and not in the NAcc (Deutch et al., 1992). As previously discussed, the typical antipsychotic drug haloperidol rapidly induces *c-fos* mRNA expression (possibly in response to a rapid release of NT) followed by an increase in NT/NN mRNA expression and finally increased NT tissue concentrations within the dorsolateral CPu (Merchant and Miller, 1994; Kinkead et al., 2000). In contrast, the atypical antipsychotic drug clozapine has no effect on *c-fos* mRNA or NT/NN mRNA expression in this brain region (Merchant et al., 1992b). In a genetically mutated mouse lacking the RII 36 regulatory subunit of protein kinase A, administration of haloperidol does not induce *c-fos* mRNA expression or NT/NN mRNA expression in the dorsolateral CPu or catalepsy (Adams et al., 1997). Intracerebroventricular administration of NT induces catalepsy in both the mutant and wild-type mice, indicating that protein kinase A activity is somehow necessary for the enhanced release of NT in this brain region. In addition, both a specific adenosine A2a receptor antagonist and the general adenosine receptor antagonist theophylline reduced haloperidol-dependent induction of striatal NT and *c-fos* mRNA (Ward and Dorsa, 1999). Administration of these agents also greatly reduced the degree of catalepsy induced by haloperidol. These results indicate that antipsychotic drug-induced NT release within the dorsolateral CPu may play a role in the acute extrapyramidal side effects of typical antipsychotic drugs. On the other hand, studies examining the effects of peripherally administered NTR agonists (modified NT peptide fragments) report that these agonists do not induce catalepsy (Sarhan et al., 1997; Cusack et al., 2000). In fact, in a manner similar to clozapine (Ward and Dorsa, 1999), peripheral administration of NTR agonists blocks haloperidol-induced catalepsy in rats (Cusack et al., 2000).

ii. Vacuous Chewing Movements. Chronic administration of typical antipsychotic drugs induces VCMs in rats. VCMs are typified by a delayed onset, relatively slow offset with neuroleptic cessation, and low prevalence with clozapine. This symptom is believed to be due to an imbalance between the activity of striatonigral and striatopallidal pathways. The striatonigral pathway is activated by D_1 receptors whereas the striatopallidal pathway is inhibited by D_2 receptor activation. Anatomically, NT projections are found in both the striatonigral and striatopallidal pathways. Typical antipsychotic drugs selectively increase NT concentrations in striatopallidal projections (Senger et al., 1993; Castel et al., 1994c).

NT injected into the ventrolateral CPu induces VCMs in rats (Stoessl, 1995). In addition, i.c.v. NT potentiates the induction of VCMs after chronic administration of low dose fluphenazine (a dose that had no effect on its own) (Stoessl and Szczutkowski, 1991). Peripheral administration of the NTR antagonist SR48692 blocked VCMs induced by either chronic administration of antipsychotic drugs or NT injected into the ventrolateral caudate (Stoessl, 1995). VCMs are also induced by acute administration of D_1 receptor agonists. These VCMs, however, are not blocked by SR48692 indicating that VCMs induced by D_1 receptor agonists are not dependent on release of endogenous NT (Stoessl et al., 1997). These results indicate that after chronic antipsychotic drug administration, increases in NT release in the ventrolateral CPu may contribute to the development of tardive dyskinesia.

b. Antidopaminergic Effects. Several lines of evidence lead to the hypothesis of a functional hyperactivity of the DA system in schizophrenia. First, the clinical efficacy of typical antipsychotic drugs is closely correlated to their binding affinity at the DA D_2 receptor. Second, the behavioral effects of DA receptor agonists (including the indirect DA receptor agonists amphetamine and cocaine) resemble the positive symptoms of schizophrenia (Reynolds, 1994). Classically, the primary DA-related behaviors used to screen for antidopaminergic properties (and hence antipsychotic potential) were a blockade of hyperlocomotion and stereotyped behaviors following administration of DA receptor agonists. With the identification of a group of atypical antipsychotic drugs whose clinical efficacy appears not to be associated with antidopaminergic activity, these tests have lost face validity.

i. Locomotion. One of the first experiments associating the NT system with the action of antipsychotic drugs demonstrated that both i.c.v. NT and peripherally administered antipsychotic drugs block stimulant-induced increases in locomotor activity. Intracerebroventricular NT attenuates amphetamine, apomorphine, methylphenidate, PCP, and cocaine-induced hyperlocomotion (Kalivas et al., 1986; Skoog et al., 1986; Sarhan et al., 1997) and decreases spontaneous locomotor activity (Nemeroff et al., 1977; Jolicoeur et al., 1983; Meisenberg and Simmons, 1985). The inhibitory effects of NT on locomotor activity are believed to be due to effects of NT at the level of the NAcc, because local injections of NT into the NAcc block DA- and stimulant-induced hyperlocomotion (Ervin et al., 1981; Kalivas et al., 1981, 1982, 1983; Jolicoeur et al., 1983; Nemeroff et al., 1983; Ford and Marsden, 1990). In contrast, bilateral intra-VTA injections of NT increase locomotion similar to that seen after administration of CNS stimulants (Kalivas et al., 1982, 1983; Cador et al., 1985; Elliott and Nemeroff, 1986). These behavioral data are supported by anatomical and biochemical data demonstrating that NT injected into the VTA increases dopaminergic cell firing and increases DA turnover in the posterior NAcc (Sotty et al., 1998). Simultaneous injection of NT into the NAcc and VTA leads to increases in DA turnover in the NAcc

without increasing locomotion, indicating that the effects of NT in the NAcc are on postsynaptic cells (Kalivas et al., 1986).

It is unclear which NTR is responsible for the locomotor effects of NT. In the midbrain, NN is more effective than NT at increasing locomotion, but has a lesser effect on DA turnover in the NAcc. In contrast, NN injected into the NAcc is markedly less potent than NT at blocking stimulant-induced hyperlocomotion (Kalivas et al., 1986). The potential existence of subtypes of the high affinity NT_1 receptor in the mesolimbic system is supported by the fact that peripheral administration of SR48692 does not block the DA releasing effects of intra-VTA NT, but does block the turning behavior and increases in DA release seen after unilateral intra-accumbens NT injections.

ii. Stereotypy. High doses of DA receptor agonists induce stereotyped behaviors, characterized by repetitive sniffing, biting, grooming, and head movements. Peripheral as well as local injections of haloperidol into the NAcc or CPu block both increased locomotion and stereotypy induced by direct or indirect acting DA receptor agonists (Ford and Marsden, 1990). In contrast to haloperidol, local injections of NT into the striatum or peripheral administration of stable NT analogs or atypical antipsychotic drugs do not block apomorphine-, NPA- or *d*-amphetamine-induced stereotypy (Ervin et al., 1981; Ford and Marsden, 1990; Cusack et al., 2000). The inability of atypical antipsychotic drugs to block DA receptor agonist-induced stereotypy has decreased the face validity of this test for screening potential antipsychotic drugs. The similar lack of effect of NT in this paradigm indicates that NT may have a behavioral profile more similar to that of atypical antipsychotic drugs. Supporting the lack of involvement of endogenous NT in the pathways mediating stereotyped behaviors, peripheral administration of the NTR antagonist SR48692 has no effect on apomorphine- or cocaine-induced stereotypy (Poncelet et al., 1994; Betancur et al., 1998)

c. Animal Models of Sensorimotor Gating and Selective Attention. There is increasing evidence that a deficit in sensorimotor gating is a cardinal feature of the underlying pathophysiology of schizophrenia. This hypothesized deficit in gating or internal screening of sensory input in schizophrenic patients is viewed as leading to an involuntary flooding of indifferent sensory data, likely contributing to the cognitive fragmentation and thought disorder characteristic of this disease. Classically, the ability to inhibit avoidance, but not escape behavior, in a conditioned-avoidance paradigm was used to test for antipsychotic activity. NT injected i.c.v. has effects similar to antipsychotic drugs in this behavioral paradigm (Luttinger et al., 1982). Two additional tests commonly used to assess deficits in sensorimotor gating are the latent inhibition (LI) paradigm and prepulse inhibition (PPI) of the acoustic startle reflex. In humans, LI and PPI have repeatedly and consistently been shown

to be disrupted in schizophrenic patients and patients with high schizotypal scores (McGhie and Chapman, 1961; Baruch et al., 1988; Freedman et al., 1991; Grillon et al., 1992; Lubow and Gewirtz, 1995; Perry et al., 1999; Kumari et al., 2000). Although somewhat controversial, antipsychotic drug treatment has been reported to normalize LI and PPI in schizophrenic patients (Venables, 1966; Gray et al., 1995b; Braff et al., 1999; Kumari et al., 1999). Because schizophrenia is a uniquely human disorder, it is essential to choose the correct animal models to assess antipsychotic drug activity. Both LI and PPI have been shown to have face, predictive, and construct validity as animal models of deficient sensorimotor gating in schizophrenic patients and to detect antipsychotic drug activity (Gray et al., 1995b; Swerdlow and Geyer, 1998). Administration of amphetamine, an indirect DA receptor agonist, or hippocampal lesions, disrupt performance in both paradigms. These disruptions are restored by typical as well as atypical antipsychotic drugs, but not by other clinically effective drugs such as antidepressants or anxiolytics (Weiner and Feldon, 1997; Swerdlow and Geyer, 1998). Increased DA release in the NAcc has been shown to reduce LI and PPI, implicating the mesostriatal system in the regulation of LI as well as PPI (Swerdlow et al., 1994; Gray et al., 1995a).

i. Prepulse Inhibition of the Acoustic Startle Reflex. PPI of the acoustic startle reflex measures preattentive sensorimotor gating (for review, see Swerdlow et al., 1994). PPI refers to the inhibition of a startle reflex by the presentation of a weak intensity prepulse immediately prior to the startle stimulus. Feifel et al. (1997) presented the first evidence of NT effects on PPI. In two consecutive reports, this group observed that similar to antipsychotic drugs, low doses (0.25 and 1.0 µg) of NT administered into the NAcc blocked amphetamine-mediated disruption, whereas a higher dose (5.0 µg) enhanced amphetamine effects (Feifel et al., 1997a,b). These contradicting findings most likely reflect the action of NT on NTRs located on striatal output cells versus DA terminals, respectively. Evidence that endogenous NT may be important in the regulation of PPI is supported by recent data from our laboratory. The NTR antagonist SR142948A (Gully et al., 1997) enhanced PPI disruption induced by the direct DA receptor agonist apomorphine, but attenuated disruptions induced by the indirect DA receptor agonist amphetamine. These dual effects are illustrative of the complexity of NT interactions with the mesostriatal DA system.

To examine the role of endogenous NT in the behavioral effects of antipsychotic drugs in the PPI paradigm, the effects of pretreatment with the NTR antagonist SR142948A on antipsychotic drug-induced restoration of isolation rearing-induced deficits in PPI were examined (Binder et al., 2001). Isolation rearing is a nonpharmacologic means of disrupting PPI (Geyer et al., 1993). Typical and atypical antipsychotic drugs restore isolation rearing-induced deficits in PPI (Geyer et al., 1993;

Varty and Higgins, 1995; Bakshi et al., 1998). Because it is independent of primary pharmacologic manipulations, isolation rearing-induced disruption of PPI may therefore represent a superior animal model for investigating the neural circuits involved in antipsychotic activity. To date, all tested antipsychotic drugs have been shown to restore isolation rearing-induced disruptions in PPI (Swerdlow and Geyer, 1998). The NTR antagonist alone had no effect on PPI, but blocked the effects of haloperidol, a typical antipsychotic drug and quetiapine, an atypical antipsychotic drug, suggesting that increased NT neurotransmission may be a common component involved in the behavioral effects of all clinically effective antipsychotic drugs. In this same study, isolation reared animals were shown to have decreased NT/NN mRNA expression and increased NTR binding in the shell subdivision of the nucleus accumbens, indicating the decreased NT neurotransmission in these animals. These results suggest that intact NT neurotransmission is necessary for the effects of antipsychotic drugs in this paradigm, and deficits in NT neurotransmission may be related to a deficit in sensorimotor gating.

ii. The Latent Inhibition Paradigm. The LI paradigm, first presented by Lubow and Moore (1959) is a measure of attentive sensory gating. LI consists of a reduction in associative learning if the subject has first been preexposed to the "to be conditioned stimulus" without consequences because the stimulus has now been categorized as nonrelevant.

Lambert et al. (1995) reported that the NTR antagonist SR48692 dose dependently blocked LI in rats. This is opposite to the effect of antipsychotic drugs that have been shown to enhance baseline LI (Dunn et al., 1993). This finding was replicated using the new NTR antagonist SR142948A (Binder et al., 1998). Endogenous NT therefore seems to be essential for the expression of LI. Compelling preliminary data also indicate that the NTR antagonist is able to block the LI-enhancing effects of the typical antipsychotic drug haloperidol (Binder et al., 2001). These results not only indicate that NT may be involved in regulation of PPI and LI, but also provide strong evidence for a preeminent role of NT circuits in the behavioral effects of antipsychotic drugs.

Although there are no data available from clinical trials with either NTR antagonists or agonists, the cumulative results of the last two decades provide an extremely strong rationale for the use of NT-ergic agonists in the treatment of schizophrenia.

B. Neurotensin, Dopamine, and Drugs of Abuse

Drug addiction is one of the major health issues in today's society, with an enormous human and financial cost. Although advances in the treatment of drug addiction have been made, most available treatments are still relatively ineffective, especially in preventing relapse. Drugs of abuse span a wide range of psychoactive

agents, including opiates, psychomotor stimulants, cannabinoids, alcohol, nicotine, and hallucinogens, all of which have very different neurochemical targets. Nonetheless, all drugs abused by humans are considered to have reinforcing and rewarding properties, and the rewarding properties of a drug are believed to be at the core of its addictiveness. In animal models, drugs of abuse are self-administered, facilitate intracranial self-stimulation (ICSS) and are positive reinforcers in a conditioned place preference paradigm. From animal studies, it is clear that the mesolimbic DA system, in particular projections from the VTA to the NAcc, is critical for the rewarding properties of drugs and thus their abuse potential (Koob and Nestler, 1997). Specific lesions of DA projections to the NAcc block self-administration of opiates and stimulants, and opiates, stimulants, ethanol, nicotine and cannabinoids all increase DA release in the NAcc. Furthermore, chronic administration of stimulants and opiates causes specific molecular changes in the mesolimbic DA system (Nestler, 1992, 1997). The close anatomical and functional associations of NT with the mesolimbic DA systems have prompted researchers to investigate the role of the NT system in the effects of drugs of abuse. Although clinical or postmortem studies examining the NT system in drug addicts have not yet been published, a large database of preclinical studies suggests an involvement of NT in drug addiction. For the purposes of this review, our discussion will focus on psychomotor stimulants because of the extensive literature available on the involvement of NT in the effects of these drugs of abuse.

All psychomotor stimulants are indirect DA receptor agonists that increase DA transmission by binding to the DA transporter and blocking DA reuptake (cocaine) and/or increasing DA release (amphetamine and its derivatives including methamphetamine). NT may be involved in the locomotor and rewarding effects, as well as the abuse potential of these drugs.

Psychomotor stimulant-induced increases in DA release in the NAcc are a critical component of the locomotor and rewarding effects of stimulants (Koob and Nestler, 1997). Intra-NAcc administration of NT antiserum or peripheral administration of an NTR antagonist both enhance methamphetamine-stimulated DA release in the NAcc (Wagstaff et al., 1994). In addition, methamphetamine itself increases NT release in the NAcc. Endogenous NT, most likely acting in the NAcc, therefore appears to antagonize stimulant-induced DA release in the NAcc.

Even though increased DA release in the NAcc is critical for both the locomotor and rewarding effects of stimulants, NT neurotransmission appears to be differentially involved in these two behavioral parameters. Intra-NAcc and i.c.v. administration of NT blocks stimulant-induced hyperlocomotion (Ervin et al., 1981; Kalivas et al., 1984) and peripheral administration of the NTR antagonist SR48692 enhances the locomotor effect

of a low dose of methamphetamine (Wagstaff et al., 1994). These data suggest that enhanced accumbal NT release may attenuate the locomotor stimulant effects of these drugs. Surprisingly, doses of NT injected into the NAcc, which were able to block cocaine-induced hyperlocomotion, did not attenuate self-administration of cocaine even though both behaviors have been linked to an increase in DA release in the NAcc (Robledo et al., 1993). In fact NT may enhance the rewarding properties of these drugs. NT injected into the VTA is an effective positive reinforcer in conditioned place preference models (Glimcher et al., 1984), and rats will self-administer NT into the VTA (Glimcher et al., 1987). Work by Rompré and colleagues was aimed to specifically isolate the reinforcing properties of NT by examining the effects of NT on ICSS with stimulus intensities ranging from sub- to suprathreshold. With this method, this group was able to show that NT, NN, as well as NT_{8-13} injected into the VTA or i.c.v., enhance the rewarding properties of a subthreshold stimulus, similar to psychostimulants, but at the same time decrease maximal stimulation rate, similar to antipsychotic drugs (Rompré et al., 1992; Rompré and Gratton, 1992, 1993; Rompré, 1995). Thus, NT is self-administered and enhances ICSS, all properties shared with systemic stimulant administration.

In conclusion, enhanced NT release in the NAcc appears to antagonize stimulant-induced DA release and hyperlocomotion. The effects of NT transmission on the reinforcing properties of stimulants have not yet been completely elucidated but they are probably not mediated by the same anatomical substrates that are involved in the effects of NT on locomotion. Most of the available data would argue for an enhancing effect of NT on the reinforcing properties of stimulants.

Although the acute administration of psychomotor stimulants are associated with their rewarding and locomotor effects, chronic administration is necessary to develop drug addiction and craving. Chronic exposure to stimulants alters NT neurotransmission differently than acute administration indicating that specific changes in NT transmission may be involved in drug addiction. Acute administration of psychomotor stimulants increases NT release in the NAcc, CPu, and the PFC (During et al., 1992; Hertel et al., 1995; Wagstaff et al., 1996b), NT/NN mRNA expression in the NAcc and CPu (Castel et al., 1994b; Betancur et al., 1997; Feldpausch et al., 1998), and NT peptide concentrations in the NAcc, CPu, and the SNr (Letter et al., 1987b; Wachi et al., 1987; Merchant et al., 1988; Hanson et al., 1989) (see *Section III.B.* for subregional details). Chronic administration of stimulants (cocaine), in contrast, has been shown to increase NT peptide concentrations in the PFC and CPu, whereas levels in the NAcc return to normal (Cain et al., 1993). After subchronic cocaine treatment, NTR binding is decreased in the VTA, hypothalamus and central nucleus of the amygdala, but increased in the medial PFC and unchanged in striatal areas (Pilotte et al., 1991). This suggests that there are important differences in the NT response after acute versus chronic psychomotor stimulant administration that may account for the development of chronic stimulant effects such as drug addiction and craving. Interestingly, a report by Alburges and Hanson (1999) has implicated NT in the mechanism of action of ibogaine, a compound that has been shown to interrupt cocaine and methamphetamine abuse in patients. Even as ibogaine increases NT concentrations in the NAcc, CPu, and SNr when administered alone, it also attenuates cocaine-induced increases in NT peptide in the CPu and SNr.

After chronic cocaine treatment, NT neurotransmission may be increased in the VTA and other limbic areas where NT has been shown to potentiate the rewarding effects of stimulant drugs. NT could therefore be enhancing the reinforcing properties of stimulants and an NTR antagonist might decrease their abuse potential. Further studies in this area are definitely warranted.

C. Neurotensin and Dopamine Interactions in Other Behaviors

Interactions of NT and DA transmission have also been reported in several behaviors other than sensorimotor gating, locomotion, and reward. Stress has been shown to activate NT-ergic as well as DA-ergic pathways (Deutch et al., 1987; Kilts et al., 1992). In addition, stress-induced gastric ulcers are attenuated by i.c.v. NT, and this protective effect is blocked by DA antagonists (Nemeroff et al., 1982; Hernandez et al., 1986; Ray et al., 1987). Data suggest that the gastric protective effects of NT are mediated by increased DA release in the central nucleus of the amygdala (Ray et al., 1987). The analgesic effects of centrally administered NT are also dependent on DA transmission. DA receptor antagonists such as chlorpromazine but not haloperidol enhance, whereas DA receptor agonists such as amphetamine or apomorphine block NT-induced analgesia (Hernandez et al., 1986). The fact that amphetamine has analgesic properties by itself but blocks the analgesic effects of NT, indicates the complex interaction of these two systems in analgesia. The same is true for the hypothermic effects of NT. DA receptor agonists such as amphetamine, cocaine and methylphenidate, but not the direct DA receptor agonist apomorphine block the effects of NT on body temperature regulation (Nemeroff et al., 1979, 1980). One pathway that might mediate NT hypothermia is DA-ergic projection from the VTA to the diagonal band of Broca. The hypothermic effect of intra-VTA NT is blocked by injections of a DA receptor antagonist into the diagonal band of Broca whereas DA antagonism in the lateral septum, NAcc, or preoptic area is ineffective (Kalivas et al., 1985). Direct applications of DA into the diagonal band of Broca also induce hypothermia (Cox et al., 1978).

V. Conclusions

In the last two decades, a vast amount of information on the interactions between the DA and NT system has been collected and the complexities of these interactions are remarkable. Future studies will probably reveal even more complex associations. Additional NTR subtypes, as predicted by pharmacologic and behavioral studies are likely to be cloned. The investigation of selective modulation of the NT system by various DA receptor subtypes will be facilitated once more selective DA receptor agonists are available. The exact functional and behavioral role of NT/DA interactions in the central nucleus of the amygdala, BNST, and lateral septum has not yet been extensively investigated, despite the fact that dense NT innervation and NTR expression indicate an important physiologic role for NT in these areas. Further anatomical correlation of certain behaviors with various NAcc subregions, will lead to a better understanding of the behavioral consequences of subregional differences in accumbal NT/DA interactions.

The clinically most relevant advance will be the investigation of NT/DA interactions in humans which is at least partly dependent on the development of positron emission tomography and single photon emission computer tomography ligands for human NTR subtypes. If preclinical findings of this peptide's involvement in schizophrenia and drug abuse hold true in humans, high potency, peripherally administerable NT-ergic compounds may represent very promising novel therapeutic agents.

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