

Striatal Glutamatergic Mechanisms and Extrapyrmidal Movement Disorders

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The nonphysiologic stimulation of striatal dopaminergic receptors, as a result of disease- or drug-related denervation or intermittent excitation, triggers adaptive responses in the basal ganglia which contribute to the appearance of parkinsonian symptoms and later to the dyskinesias and other alterations in motor response associated with dopaminergic therapy. Current evidence suggests that these altered responses involve activation of signal transduction cascades in striatal medium spiny neurons linking dopaminergic to coexpressed ionotropic glutamatergic receptors of the *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) classes. These intraneuronal signaling pathways appear capable of modifying the phosphorylation state of NMDA and AMPA receptor subunits; resultant sensitization enhances cortical glutamatergic input which in turn modifies striatal output in ways that compromise motor behavior. The regulation of these spiny neuron glutamate receptors can also be affected by the activation state of coexpressed nondopaminergic receptors as well as by changes associated with Huntington's disease. These observations lend new insight into molecular mechanisms contributing to the integration of synaptic inputs to spiny neurons. They also suggest novel approaches to the pharmacotherapy of extrapyramidal motor dysfunction.

Keywords: AMPA; Huntington disease; Ionotropic receptor; LTP; Medium spiny neuron; NMDA

INTRODUCTION

The striatum plays a central role in the regulation of human motor function. Within this structure, the vast preponderance of nerve cells are medium-sized spiny neurons. These GABAergic cells receive glutamatergic input from all areas of cerebral cortex and project, both directly and indirectly, to the two major output nuclei of

basal ganglia, the internal segment of globus pallidus and pars reticulata of substantia nigra (Kotter, 1994; Parent and Cicchetti, 1998; Graybiel, 2000). Medium spiny neurons are also host to dopaminergic terminals arising from pars compacta of substantia nigra as well as those of numerous other transmitter systems both intrinsic and extrinsic to the striatum. In view of their strategic location, it is hardly surprising that medium spiny neuron injury or loss substantially affects motor behavior.

MOTOR EFFECTS OF NONPHYSIOLOGIC DOPAMINERGIC STIMULATION

Either hyperkinetic and hypokinetic disorders can result from medium spiny neuron dysfunction. Clinically, the most common basis for either state is the nonphysiologic stimulation of their dopamine (DA) receptors (Chase and Oh, 2000a). The nigrostriatal dopaminergic system generally operates tonically, firing off at a rate of about 4 - 5 Hz, except when occasionally interrupted by phasic bursts related to sensory rather than motor events (Schultz, 1994). The characteristic hypokinetic features of parkinsonism arise when these receptors become denervated either as a consequence of a progressive neurodegenerative disorder such as Parkinson's disease (PD) or acute pharmacologic blockade due to the administration of a DA receptor antagonist (Hornykiewicz, 1998; Wirshing 2001). In contrast, hyperkinetic disorders can result from the intermittent high intensity stimulation associated either with dopaminomimetic PD therapy or from chronic DA antagonist blockade such as occurs in neuroleptic-induced tardive dyskinesia (Sachdev 2000; Chase and Oh 2000b; Ahlskog and Muentner, 2001). In either case, choreiform movements commonly result. Essentially identical abnormal involuntary movements also characterize the degeneration of medium spiny neurons in Huntington's disease (HD).

ANIMAL MODELS OF STRIATAL DYSFUNCTION

Recent research has begun to elucidate pathogenic mechanisms contributing to the appearance of these disorders. Much of this evolving insight derives from studies conducted in rodent and primate models of PD. For instance, rats develop parkinsonian features following injection of 6-hydroxydopamine and then elements of the motor response alterations occurring in parkinsonian patients when the rodents are subsequently treated with levodopa or a DA agonist (Papa *et al.*, 1994). Similarly, monkeys lesioned with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) develop parkinsonism and after a few weeks of dopaminomimetic therapy begin to manifest choreiform dyskinesias (Clarke *et al.*, 1987; Papa *et al.*, 1996; Blanchet *et al.*, 1998). In both cases, motor phenomenology closely resembles that manifested by parkinsonian patients. Observations in these models indicate that changes in the operational state of medium spiny neurons may serve as a critical determinant of the pathogenesis of these hypo- and hyperkinetic disorders (Chase and Oh, 2000a).

STRIATAL MEDIUM SPINY NEURONS

Evidence of striatal medium spiny neuron dysfunction in these disorders arises from biochemical, histochemical and pharmacologic observations. In rats, denervation as well as subsequent dopaminergic treatment produces characteristic changes in spiny neuron peptide cotransmitters such as enkephalin, dynorphin and neurotensin (Gerfen *et al.*, 1990; Engber *et al.*, 1991; 1992; Parent *et al.*, 1996). Histochemical observations of receptor (Anglade *et al.*, 1996; Meshul and Allen, 2000) and signaling molecule changes (Oh *et al.*, 1997; 1998; 1999) as well as pharmacologic studies involving the direct intrastriatal injection of drugs affecting motor function in parkinsonian rats (Papa *et al.*, 1995) provide additional support for striatal involvement. Medium spiny neurons express DA receptors along the necks and shafts of their dendritic spines and ionotropic glutamateric receptors within the post synaptic density at the distal tips (Freund *et al.*, 1984; Smith *et al.*, 1994). Nonphysiologic dopaminergic stimulation leads to characteristic changes in the phosphorylation pattern of both *N*-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subunits (Oh *et al.*, 1997; 1998; 1999). Conceivably, these receptors undergo a resultant increase in synaptic efficacy that enhances cortical glutamatergic input in ways that favor chronic motor dysfunction. In some ways this process appears to

resemble a form of long term potentiation (Calabresi *et al.*, 2000; Chase and Oh 2000a; Centonze *et al.*, 2001).

STRIATAL NMDA RECEPTOR REGULATION

Observations from studies in parkinsonian rats seem consistent with this possibility, since NMDA receptor antagonists, such as MK801 and CPP, have been found to act both palliatively and prophylactically to decrease response alterations (Engber *et al.*, 1994; Papa *et al.*, 1995; Marin *et al.*, 1996; 2000; Cepeda and Levine, 1998). Later findings in parkinsonian primates provide additional support for this hypothesis. Co-administration of various NMDA antagonists to monkeys substantially reduce the dyskinesigenic effects of levodopa (Gomez-Mancilla and Bedard, 1993; Papa *et al.*, 1995; Papa and Chase, 1996; Blanchet *et al.*, 1997; 1998). Similarly, studies in parkinsonian patients given noncompetitive NMDA receptor antagonists, including dextrorphan and amantadine, indicate that certain drugs of this type can alleviate parkinsonism as well as dyskinesias and other response modifications produced by dopaminergic therapy (Blanchet *et al.*, 1996; Danysz *et al.*, 1997; Mitchell and Carroll, 1997; Karcz-Kubicha *et al.*, 1998; Metman *et al.*, 1998a,b,c; Merello *et al.*, 1999; Del Dotto *et al.*, 2001).

STRIATAL AMPA RECEPTOR REGULATION

Functional alterations in glutamate receptors of the AMPA subtype also appear to contribute to levodopa-induced motor dysfunction. For example, administration of the competitive AMPA receptor antagonist, NBQX, to parkinsonian rats or monkeys reportedly has little or no effect on motor function, but can potentiate the antiparkinsonian action of levodopa (Klockgether *et al.*, 1991; Luquin *et al.*, 1993). In rats, NBQX also acts to reverse levodopa-associated motor response alterations (Marin *et al.*, 2000). In primates, a selective, noncompetitive antagonist at the AMPA allosteric modulation site (LY 300164) alone did not modify the severity of parkinsonian signs, but did attenuate levodopa-induced dyskinesias. Conversely, a selective AMPA agonist (CX516) by itself had no antiparkinsonian activity, but potentiated levodopa-associated dyskinesias (Konitsiotis *et al.*, 2000). Taken together, these data suggest that upregulation of ionotropic glutamatergic receptors participates in the pathogenesis of the motor disorder.

Ionotropic glutamate receptors are ligand-gated ion channels that function as the primary mediators of fast excitatory transmission within the mammalian CNS. NMDA and AMPA class receptors have been differenti-

ated on the basis of their physiological and pharmacological characteristics: NMDA receptors are highly permeability to calcium and other divalent cations and act as coincidence detectors, since activation only occurs in the presence of concurrent membrane depolarization (Mayer and Westbrook, 1987). AMPA receptors, on the other hand, activate and desensitize quickly in response to glutamate and are permeable mainly to sodium and other monovalent cations (Westbrook, 1994). Both receptors are composed of oligomeric complexes, most likely tetramers or pentamers of homologous subunits (Hollmann and Heinemann, 1994). NMDA receptors are assembled from one or two NR1 subunits, expressed in eight currently recognized splice variants (a–h), and two or three NR2 subunits composed of four homologous isoforms (A–D) (Wollmuth *et al.*, 1996; Ozawa *et al.*, 1998). In rat striatum, medium spiny neurons express NR1 variants along with NR2B and, to a lesser extent, NR2A subunits (Chen and Reiner, 1996). AMPA receptors are combinations of four subunits, GluR1–4(A–D) that can exist as either a flip or a flop splice variant (Sommer *et al.*, 1990). Membrane topology models currently suggest two agonist binding domains (one within the extracellular M3–M4 loop, the other just *N* terminal to M1) as well as a large intracellular *C*-terminus that contains consensus sites for a variety of protein kinases (Swope *et al.*, 1999).

GLUTAMATE RECEPTOR PHOSPHORYLATION

Protein phosphorylation serves as a major regulatory mechanism for NMDA and AMPA receptors (Gurd *et al.*, 1997; Yu *et al.*, 1997; Suen *et al.*, 1998; Swope *et al.*, 1999). By this mechanism, receptor expression, mobility and localization as well as channel function are tightly controlled (Ulas and Cotman, 1996; Dunah and Standaert, 2001). For example, the phosphorylation of tyrosine residues reportedly modulates channel opening probability (Yu *et al.*, 1997) and receptor trafficking to the postsynaptic membrane (Dunah and Standaert, 2001), while serine / threonine phosphorylation by calcium / phospholipid-stimulated or cAMP-stimulated protein kinases appears to affect their subcellular distribution, plasma membranes anchoring (Tingley *et al.*, 1997) and synaptic clustering (Crump *et al.*, 2001). Recently, PKC has also been shown to influence NMDA currents by direct serine phosphorylation of the NR2B subunits *C*-terminus at residues S1303 and S1323 (Liao *et al.*, 2001) or by direct tyrosine phosphorylation of the NR2A and NR2B subunits (Groschans *et al.*, 2001). AMPA receptor GluR1 subunits can be phosphorylated by PKA at S 845 and by PKA or CaMKII at S 831 (Snyder *et al.*, 2000), while GluR2 subunits are phosphorylated by PKC

at S 863 and S 880 (McDonald *et al.*, 2001). It now appears that alterations in the phosphorylation state of striatal ionotropic glutamate receptors may reflect the aberrant activation of signaling cascades linking coexpressed DA and glutamate receptors (Chase *et al.*, 2000). More specifically, nonphysiological dopaminergic stimulation of medium spiny neurons can alter the balance between specific kinase and phosphatase activity, thus affecting the degree and pattern of glutamate receptor subunit phosphorylation (Oh *et al.*, 1997; 1998).

SIGNAL TRANSDUCTION IN SPINY NEURONS

With respect to NMDA receptors, increasing evidence suggests that the chronic nonphysiological stimulation of rat DA receptors activates various kinases responsible for direct subunit phosphorylation (Oh *et al.*, 1997; 1998; 1999; Dunah and Standaert, 2001). These include serine kinases, such as cyclic AMP-protein kinase A (PKA), calcium/ calmodulin-dependent protein kinase II (CaMKII), and calcium-activated protein kinase (PKC), as well as src family tyrosine kinases (Menegoz *et al.*, 1995; Oh *et al.*, 1997; 1998; 1999; Suen *et al.*, 1998; Greengard *et al.*, 1999; Bayer *et al.*, 2001; Lan *et al.*, 2001; Liao *et al.*, 2001). The intrastriatal administration of inhibitors of certain of these serine and tyrosine kinases can mitigate parkinsonian dysfunction as well as the response alterations produced by dopaminomimetic therapy (Oh *et al.*, 1997; 1998; 1999).

In the case of striatal AMPA receptor subunits, changes in the phosphorylation state of serine residues by a PKC signaling cascade may also affect motor function. Preliminary results indicate that an abundance of constitutively active PKC as a consequence of striatal pCMVpkc Δ gene transfer may be sufficient to promote the initial appearance of levodopa-induced motor response alterations, in part, by the phosphorylation of AMPA receptor subunits and consequent modification of the strength of corticostriatal glutamatergic input (Snyder *et al.*, 2001; Oh, unpublished observations). Taken together, differential activation of signal transduction pathways within striatal spiny neurons lead to characteristic changes in the phosphorylation state of NMDA and AMPA glutamate receptors and thus in their sensitivity to corticostriatal synaptic input. As a result of these molecular events, striatal output changes in ways that contribute to the motor complications associated with levodopa therapy.

STRIATAL MOTOR MEMORY

In animal models of learning and memory (Oh *et al.*, 1998), a rise in the sensitivity of glutamatergic receptors, especially those of the NMDA class, appears to contribute to the persisting, activity-dependent changes in neuronal responses (Nicoll and Malenka, 1995; Cain, 1997). Similarly, mechanisms underlying the development, expression, and maintenance of long-lasting motor response alterations induced by dopaminomimetic therapy may also involve changes in the balance between striatal kinase and phosphatase activity that affect receptor phosphorylation (Oh *et al.*, 1997; Khan *et al.*, 1999). Onset of levodopa-induced response changes can take only a few weeks in parkinsonian animals and PD patients (Mouradian *et al.*, 1990). Offset time also is similar in animal models and in patients with motor complications: in either case, the altered responses to dopaminergic challenge persist for weeks following withdrawal of intermittent dopaminomimetic treatment or conversion to more physiologic continuous administration (Mouradian *et al.*, 1990). Levodopa-induced motor response complications thus possess features characteristic of long term memory, ie, longevity and reversibility.

A striatal transcriptional factor, cAMP response element-binding protein (CREB), has been linked to DA receptor mediated mechanisms and implicated in the long-term maintenance of synaptic plasticity elsewhere in the CNS (Cervo *et al.*, 1996; Gurd, 1997; Bartsch *et al.*, 1998; Cenci *et al.*, 1998; 1999; Graybiel *et al.*, 1998; Huang and Stevens, 1998; Impey *et al.*, 1998; Silva *et al.*, 1998; Ahn *et al.*, 1999; Khan *et al.*, 1999). Since the late phase of memory appears to depend on new transcription and translation (Pittenger and Kandel, 1998), CREB might act by regulating the synthesis of proteins involved in these consolidation processes. CREB is a member of a large family of structurally related transcription factors that binds to cAMP-response-element (CRE) promoter sites on target genes (Ginty, 1997). CREB protein, which can exist in multiple alternatively spliced isoforms in rat CNS, has been implicated in the transcriptional regulation of a number of genes, especially those which are rapidly expressed in response to elevations in cytoplasmic cAMP and Ca²⁺ (Quinn, 1993; Hu *et al.*, 1999; Pietruck *et al.*, 1999). Similar to such other inducible transcription factors as Jun and Fos, CREB protein has several functional domains — a leucine zipper domain which mediates dimerization, a DNA binding domain, and a transcriptional activation domain which contains crucial phosphorylation sites (Pietruck *et al.*, 1999). The transcriptional activation of CREB depends on its phosphorylation at Ser-133 either directly or indirectly by such kinases as PKA and CaMK (Gonzalez *et al.*, 1991; Sheng

et al., 1991; Das *et al.*, 1997; Hu *et al.*, 1999). Preliminary results suggest that striatal DA receptor-activated PKA/ CREB-mediated mechanisms contribute to the development and maintenance of the motor response changes associated with levodopa treatment of parkinsonian rats (Oh, unpublished observation).

The effects of the nonphysiologic stimulation of striatal dopaminergic receptors on motor function may also involve compensatory neural and behavioural adaptations similar to those occurring with psychoactive drug addiction. Delta FosB is a transcription factor that has been implicated in compensatory neural and behavioral adaptations associated with repeated drug treatment. Its elevated expression in the striatum has been linked to chronic cocaine-induced alterations (Hope *et al.*, 1994; Kelz *et al.*, 1999; Bibb *et al.*, 2001) as well as to chronic levodopa-induced striatal dysregulation (Andersson *et al.*, 1999). A recent study identified Cdk5 as a downstream target gene of Δ FosB; upon activation, Cdk5 influences the efficacy of dopaminergic PKA signaling via positive feedback mechanisms in a mutually antagonistic manner (Lew *et al.*, 1994; Nishi *et al.*, 2000). Preliminary observations indicate that chronic nonphysiological stimulation of striatal DA receptors in parkinsonian rats augments striatal Cdk5/ p35 immune complex formation, Cdk5 activation, and DARPP-32-Thr-75 phosphorylation (Oh, unpublished observation). These results support the possibility that striatal DA receptor-activated Cdk5 may be involved in adaptive mechanisms occurring when repeated nonphysiological DA receptor stimulation leads to dyskinesias and other motor response complications.

NMDA RECEPTOR UPREGULATION IN HUNTINGTON'S DISEASE (HD)

The choreatic movements associated with HD can be essentially indistinguishable from those occurring in parkinsonian patients with dopaminomimetic induced dyskinesia or schizophrenic patients with neuroleptic-induced tardive dyskinesia. Striatal medium-sized spiny neurons are the primary target of the selective neurodegenerative process in HD and presumably the source of choreatic movements (Vonsattel and DiFiglia, 1998). Recently amantadine has been found to reduce the severity of these dyskinesias (Verhagen *et al.*, 2001). While it is not known whether antagonistic effects at striatal NMDA receptors account for this clinical response, our results seem consistent with the hypothesis that NMDA receptor sensitization can contribute to the production of choreiform dyskinesias in HD just as appears to be the case in PD (Chase, 2000b). In HD, the same

spiny neurons are preferentially targeted for degeneration (Reiner, 1988; Goto, 1989). Conceivably, NMDA receptor upregulation may also occur in residual spiny neurons due to the presence of mutant huntingtin protein. Indeed, recent *in vitro* evidence suggests that a polyglutamine expansion blocks the ability of wild type huntingtin to bind to a scaffolding protein that normally prevents NMDA receptor upregulation (Sun *et al.*, 2001). Thus it is tempting to speculate that medium spiny neurons expressing hypersensitive NMDA-receptors may indeed relate to the pathogenesis of huntingtin-induced chorea in HD as well as of levodopa-induced chorea in PD.

References

- Ahlskog JE and MD Muentner (2001) Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov. Disord.* **16**, 448-458.
- Ahn S, DD Ginty and DJ Linden (1999) A late phase of cerebellar long-term depression requires activation of CaMKIV and CREB. *Neuron* **23**, 559-568.
- Andersson M, A Hilbertson and MA Cenci (1999) Striatal fosB expression is causally linked with L-DOPA-induced abnormal involuntary movements and the associated upregulation of striatal prodynorphin mRNA in a rat model of Parkinson's disease. *Neurobiol. Dis.* **6**, 461-474.
- Anglade P, A Mouatt-Prigent, Y Agid and E Hirsch (1996) Synaptic plasticity in the caudate nucleus of patients with Parkinson's disease. *Neurodegeneration* **5**, 121-128.
- Bartsch D, A Casadio, KA Karl, P Serodio and ER Kandel (1998) CREB1 encodes a nuclear activator, a repressor, and a cytoplasmic modulator that form a regulatory unit critical for long-term facilitation. *Cell* **95**, 211-223.
- Bayer KU, P De Koninck, AS Leonard, JW Hell and H Schulman (2001) Interaction with the NMDA receptor locks CaMKII in an active conformation. *Nature* **411**, 801-805.
- Bibb JA, JS Chen, JR Taylor, P Svenningsson, A Nishi, GL Snyder, Z Yan, ZK Sagawa, CC Ouimet, AC Nairn, EJ Nestler and P Greengard (2001) Effects of chronic exposure to cocaine are regulated by the neuronal protein Cdk5. *Nature* **410**, 376-380.
- Blanchet PJ, LV Metman, MM Mouradian and TN Chase (1996) Acute pharmacologic blockade of dyskinesias in Parkinson's disease. *Mov. Disord.* **11**, 580-581.
- Blanchet PJ, SM Papa, LV Metman, MM Mouradian and TN Chase (1997) Modulation of levodopa-induced motor response complications by NMDA antagonists in Parkinson's disease. *Neurosci. Biobehav. Rev.* **21**, 447-453.
- Blanchet PJ, S Konitsiotis and TN Chase (1998) Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys. *Mov. Disord.* **13**, 798-802.
- Blanchet PJ, S Konitsiotis, N Whitmore, R Woodward and TN Chase (1999) Different effects of subunit specific NMDA antagonists in parkinsonian monkeys. *J. Pharmacol. Exp. Ther.* **290**, 1034-1040.
- Cain DP (1997) LTP, NMDA, genes and learning. *Curr. Opin. Neurobiol.* **7**, 235-242.
- Calabresi P, P Giacomini, D Centonze and G Bernardi (2000) Levodopa-induced dyskinesia: a pathological form of striatal synaptic plasticity? *Ann Neurol.* **47** (4 Suppl 1), S60-S8.
- Cenci MA, CS Lee and A Björklund (1998) L-Dopa-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin and glutamic acid decarboxylase mRNA. *Eur. J. Neurosci.* **10**, 2694-2706.
- Cenci MA, A Tranberg, M Andersson and A Hilbertson (1999) Changes in the regional and compartmental distribution of FosB- and JunB-like immunoreactivity induced in the dopamine-denervated rat striatum by acute or chronic L-dopa treatment. *Neuroscience* **94**, 515-527.
- Centonze D, B Picconi, P Gubellini, G Bernardi and P Calabresi (2001) Dopaminergic control of synaptic plasticity in the dorsal striatum. *Eur. J. Neurosci.* **6**, 1071-1077.
- Cepeda C and MS Levine (1998) Dopamine and *N*-methyl-D-aspartate receptor interactions in the neostriatum. *Dev. Neurosci.* **20**, 1-18.
- Cervo L and R Samanin (1996) Effects of dopaminergic and glutamatergic receptor antagonists on the establishment and expression of conditioned locomotion to cocaine in rats. *Brain Res.* **731**, 31-38.
- Chase TN and JD Oh (2000a) Striatal dopamine- and glutamate-mediated dysregulation in experimental parkinsonism. *Trends Neurosci.* **23**, S86-S91.
- Chase TN and JD Oh (2000b) Striatal mechanisms and pathogenesis of parkinsonian signs and motor complications. *Ann. Neurol.* **4**(Suppl 1), S122-S129.
- Chase TN, JD Oh and S Konitsiotis (2000) Antiparkinsonian and antidyskinetic activity of drugs targeting central glutamatergic mechanisms. *J. Neurol.* **247** (Suppl 2), 36-42.
- Chen Q and A Reiner (1996) Cellular distribution of the NMDA receptor NR2A / 2B subunits in the rat striatum. *Brain Res.* **743**, 346-352.
- Clarke CE, MA Sarnbrook, IJ Mitchell and ARH Crossman (1987) Levodopa-induced dyskinesia and response fluctuations in primates rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *J. Neurol. Sci.* **78**, 273-280.
- Crump FT, KS Dillman and AM Craig (2001) cAMP-dependent protein kinase mediates activity-regulated synaptic targeting of NMDA receptors. *J. Neurosci.* **21**, 5079-5088.
- Danysz W, CG Parsons, J Kornhuber, WJ Schmidt and G Quack (1997) Amino-adamantanes as NMDA receptor antagonists and antiparkinsonian agents-preclinical studies. *Neurosci. Biobehav. Rev.* **21**, 455-468.
- Das S, M Grunert, L Williams and SR Vincent (1997) NMDA and D₁ receptors regulate the phosphorylation of CREB and the induction of *c-fos* in striatal neurons in primary culture. *Synapse* **25**, 227-233.
- Del Dotto P, N Pavese, G Gambaccini, S Bernardini, LV Metman, TN Chase and U Bonuccelli (2001) Intravenous amantadine improves levodopa-induced dyskinesias: an acute double-blind placebo-controlled study. *Mov. Disord.* **16**, 515-520.
- Dunah AW and DG Standaert (2001) Dopamine D₁ receptor-dependent trafficking of striatal NMDA glutamate receptors to the postsynaptic membrane. *J. Neurosci.* **21**, 5546-5558.
- Engber TM, Z Susel, S Kuo, CR Gerfen and TN Chase (1991) Levodopa replacement therapy alters enzyme activities in striatum and neuropeptide content in striatal output regions of 6-hydroxydopamine lesioned rats. *Brain Res.* **552**, 113-118.
- Engber TM, RC Boldry, S Kuo and TN Chase (1992) Dopaminergic modulation of striatal neuropeptides, differential effects of D₁ and D₂ receptor stimulation on somatostatin, neuropeptide Y, neurotensin, dynorphin and enkephalin. *Brain Res.* **581**, 261-268.
- Engber TM, SM Papa, RC Boldry and TN Chase (1994) NMDA receptor blockade reverses motor response alterations induced by levodopa. *Neuroreport* **5**, 2586-2588.

- Freund TF, JF Powell and AD Smith (1984) Tyrosine hydroxylase-immunoreactive boutons in synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. *Neuroscience* **4**, 1189-1215.
- Gerfen CR (1992) The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. *Ann. Rev. Neurosci.* **15**, 285-320.
- Gerfen CR, TM Engber, LC Mahan, Z Susel, TN Chase, FJ Monsma Jr and DR Sibley (1990) D₁ and D₂ dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* **250**, 1429-1432.
- Ginty DD (1997) Calcium regulation of gene expression: isn't that spatial? *Neuron* **2**, 183-186.
- Gomez-Mancilla B and PJ Bedard (1993) Effect of nondopaminergic drugs on L dopa-induced dyskinesias in MPTP-treated monkeys. *Clin. Neuropharmacol.* **16**, 418-427.
- Gonzalez GA, P Menzel, J Leonard, WH Fischer and MR Montminy (1991) Characterization of motifs which are critical for activity of the cyclic AMP-responsive transcription factor CREB. *Mol. Cell. Biol.* **11**, 1306-1312.
- Goto S, A Hirano A and RR Rojas-Corona (1989) Immunohistochemical visualization of afferent nerve terminals in human globus pallidus and its alteration in neostriatal neurodegenerative disorders. *Acta Neuropathol. (Berl.)* **78**, 543-550.
- Graybiel AM (1998) The basal ganglia and chunking of action repertoires. *Neurobiol. Learn. Mem.* **1**, 119-136.
- Graybiel AM (2000) The basal ganglia. *Curr. Biol.* **14**, R509-R511.
- Greengard P, PB Allen and AC Nairn (1999) Beyond the dopamine receptor: the DARPP-32/protein phosphatase-1 cascade. *Neuron* **23**, 435-447.
- Grosshans DR and MD Browning (2001) Protein kinase C activation induces tyrosine phosphorylation of the NR2A and NR2B subunits of the NMDA receptor. *J. Neurochem.* **76**, 737-744.
- Gurd JW (1997) Protein tyrosine phosphorylation: Implications for synaptic function. *Neurochem. Int.* **31**, 635-649.
- Hollmann M and S Heinemann (1994) Cloned glutamate receptors. *Ann. Rev. Neurosci.* **17**, 31-108.
- Hope BT, HE Nye, MB Kelz, DW Self, MJ Ladarola, Y Nakabeppu, RS Duman and EJ Nestler (1994) Induction of a long-lasting AP-1 complex composed of altered Fos-like proteins in brain by chronic cocaine and other chronic treatments. *Neuron* **13**, 1235-1244.
- Hornykiewicz O (1998) Biochemical aspects of Parkinson's disease. *Neurology* **51**, S2-S9.
- Hu SC, J Chrivia and A Ghosh (1999) Regulation of CBP-mediated transcription by neuronal calcium signaling. *Neuron* **22**, 799-808.
- Huang EP and CF Stevens (1998) The matter of mind: molecular control of memory. *Essays Biochem.* **33**, 165-178.
- Impey S, DM Smith, K Obrietan, R Donahue, C Wade and DR Storm (1998) Stimulation of cAMP response element (CRE)-mediated transcription during contextual learning. *Nature Neurosci.* **1**, 595-601.
- Karcz-Kubicha M, G Quack and W Danysz (1998) Amantadine attenuates response alterations resulting from repetitive L-DOPA treatment in rats. *J. Neural Transm.* **105**, 1229-1236.
- Kelz MB, JS Chen, WA Carlezon, K Whisler, L Gilden, AM Beckmann, C Steffen, YJ Zhang, L Marotti, DW Self, T Tkatch, G Baranaukas, DJ Surmeier, RL Neve, RS Duman, MR Picciotto and EJ Nestler (1999) Expression of the transcriptional factor Δ FosB in the brain controls sensitivity to cocaine. *Nature* **401**, 272-276.
- Khan SM, TS Smith and JP Bennett (1999) Effects of single and multiple treatments with L-dihydroxyphenylalanine (L-DOPA) on dopamine receptor-G Protein interactions and supersensitive immediate early gene responses in striata of rats after reserpine treatment or with unilateral nigrostriatal lesions. *J. Neurosci. Res.* **55**, 55-71.
- Klockgether T, L Turski, T Honore, Z Zhang, DM Gash, R Kurlan and JT Greenamyre (1991) The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys. *Ann. Neurol.* **30**, 717-723.
- Konitsiotis S, PJ Blanchet, L Verhagen, E Lamers and TN Chase (2000) AMPA receptor blockade improves levodopa-induced dyskinesia in MPTP monkeys. *Neurology* **8**, 1589-1595.
- Kotter R (1994) Postsynaptic integration of glutamatergic and dopaminergic signals in the striatum. *Prog. Neurobiol.* **44**, 163-196.
- Lan JY, VA Skeberdis, T Jover, SY Grooms, Y Lin, RC Araneda, X Zheng, MVL Bennett and RS Zukin (2001) Protein kinase C modulates NMDA receptor trafficking and gating. *Nature Neurosci.* **4**, 382-390.
- Lew J, Q Huang, Q Zhong, R Winkfein, R Aebersold, T Hunt and J Wang (1994) A brain-specific activator of cyclin-dependent kinase 5. *Nature* **271**, 423-426.
- Liao GY, DA Wagner, MH Hsu and JP Leonard (2001) Evidence for direct protein kinase-C mediated modulation of *N*-methyl-D-aspartate receptor current. *Mol. Pharmacol.* **59**, 960-964.
- Luquin MR, JA Obeso, J Laguma, J Guillen and JM Martinez-Lage (1993) the AMPA receptor antagonist NBQX does not alter the motor response induced by selective dopamine agonists in MPTP-treated monkeys. *Eur. J. Pharmacol.* **235**, 297-300.
- Marin C, S Papa, TM Engber, M Bonastre, E Tolosa and TN Chase (1996) MK-801 prevents levodopa-induced motor response alterations in parkinsonian rats. *Brain Res.* **736**, 202-205.
- Marin C, A Jimenez, M Bonastre, TN Chase and E Tolosa (2000) Non-NMDA receptor-mediated mechanisms in levodopa-induced motor response alterations in parkinsonian rats. *Synapse* **36**, 267-274.
- Mayer ML and GL Westbrook (1987) The physiology of excitatory amino acids in the vertebrate central nervous system. *Prog. Neurobiol.* **3**, 197-276.
- McDonald BJ, HJ Chung and RL Haganir (2001) Identification of protein kinase C phosphorylation sites within the AMPA. *Neuropharmacology* **6**, 672-679.
- Menegoz M, LF Lau, D Herve, RL Haganir and JA Girault (1995) Tyrosine phosphorylation of NMDA receptor in rat striatum: effects of 6-OH-dopamine lesions. *Neuroreport* **7**, 125-128.
- Merello M, MI Nouzeilles, A Cammarota and R Leiguarda (1999) Effect of memantine (NMDA antagonist) on Parkinson's disease: a double blind crossover randomized study. *Clin. Neuropharmacol.* **22**, 273-276.
- Meshul CK and C Allen (2000) Haloperidol reverses the changes in striatal glutamatergic immunolabeling following a 6-OHDA lesion. *Synapse* **2**, 129-142.
- Metman LV, PJ Blanchet, P van den Munckhof, P Del Dotto, R Natta and TN Chase (1998a) A trial of dextromethorphan in parkinsonian patients with motor response complications. *Mov. Disord.* **13**, 414-417.
- Metman LV, PD Dotto, P van den Munckhof, J Fang, MM Mouradian and TN Chase (1998b) Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology* **50**, 1323-1329.
- Metman LV, PD Dotto, R Natta, P van den Munckhof and TN Chase (1998c) Dextromethorphan improves levodopa-induced dyskinesias in Parkinson's disease. *Neurology* **51**, 203-206.
- Mitchell IJ and CB Carroll (1997) Reversal of parkinsonian symptoms

- in primates by antagonism of excitatory amino acid transmission: potential mechanisms of action. *Neurosci. Biobehav. Rev.* **21**, 469–475.
- Mouradian MM, IJ Heuser, F Baronti and TN Chase (1990) Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. *Ann. Neurol.* **27**, 18–23.
- Nicoll RA and RC Malenka (1995) Contrasting properties of two forms of long-term potentiation in the hippocampus. *Nature* **377**, 115–118.
- Nishi A., JA Bibb, GL Snyder, H Higashi, AC Nairn and P Greengard (2000) Amplification of dopaminergic signaling by a positive feedback loop. *Proc. Natl. Acad. Sci. USA* **97**, 12840–12845.
- Oh JD, PD Dotto and TN Chase (1997) Protein kinase A inhibitor attenuates levodopa-induced motor response alterations in the hemi-parkinsonian rat. *Neurosci. Lett.* **228**, 5–8.
- Oh JD, D Russell CL Vaughan and TN Chase (1998) Enhanced tyrosine phosphorylation of striatal NMDA receptor subunits: Effect of dopaminergic denervation and levodopa administration. *Brain Res.* **813**, 150–159.
- Oh JD, CL Vaughan and TN Chase (1999), Effect of dopamine denervation and dopamine agonist administration on serine phosphorylation of striatal NMDA receptor subunits. *Brain Res.* **821**, 433–442.
- Ozawa S, H Kamiya and K Tsuzuki (1998) Glutamate receptors in the mammalian central nervous system. *Prog. Neurobiol.* **54**, 581–618.
- Papa SM and TN Chase (1996) Levodopa-induced dyskinesias improved by a glutamate antagonist in Parkinsonian monkeys. *Ann. Neurol.* **39**, 574–578.
- Papa SM, TM Engber AM Kask and TN Chase (1994) Motor fluctuations in levodopa treated parkinsonian rats: relation to lesion extent and treatment duration. *Brain Res.* **662**, 69–74.
- Papa SM, RC Boldry, TM Engber, AM Kask and TN Chase (1995) Reversal of levodopa-induced motor fluctuations in experimental parkinsonism by NMDA receptor blockade. *Brain Res.* **701**, 13–18.
- Parent A and F Cicchetti (1998) The current model of basal ganglia organization under scrutiny. *Mov. Disord.* **2**, 199–202.
- Parent A, MC Asselin and PY Cote (1996) Dopaminergic regulation of peptide gene expression in the striatum of normal and parkinsonian monkeys. *Adv. Neurol.* **69**, 73–77.
- Pietruck C, G-X Xie, M Sharma, T Meuser and PP Palmer (1999) Multiple splice patterns of cyclic AMP response element-binding protein mRNA in the central nervous system of the rat. *Mol. Brain Res.* **69**, 286–289.
- Pittenger C and E Kandel (1998) A genetic switch for long-term memory. *Life Sci.* **321**, 91–96.
- Quinn PG (1993) Distinct activation domains within cAMP response element-binding protein (CREB) mediate basal and cAMP-stimulated transcription. *J. Biol. Chem.* **268**, 16999–17009.
- Reiner A, R Albin, KD Anderson, CJ D'Amato, JB Penney and AB Young (1988) Differential loss of striatal projection neurons in Huntington's disease. *Proc. Natl. Acad. Sci. USA* **85**, 5733–5737.
- Sachdev PS (2000) The current status of tardive dyskinesia. *Aust. NZ J. Psychiatry* **3**, 355–369.
- Schultz W (1994) Behavior-related activity of primate dopamine neurons. *Rev. Neurol.* **150**, 634–639.
- Sheng M, MA Thompson and ME Greenberg (1991) CREB, a Ca(2+) regulated transcription factor phosphorylated by calmodulin-dependent kinase. *Science* **252**, 1427–1430.
- Silva AJ, JH Kogan, PW Frankland and S Kida (1998) CREB and memory. *Ann. Rev. Neurosci.* **21**, 127–148.
- Smith Y, BD Bennett, JP Bolam, A Parent and AF Sadikot (1994) Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. *J. Comp. Neurol.* **1**, 1–19.
- Snyder GL, PB Allen, AA Fienberg, CG Valle, RL Haganir, AC Nairn and P Greengard (2000) Regulation of phosphorylation of the GluR1 AMPA receptor in the neostriatum by dopamine and psychostimulants *in vivo*. *J. Neurosci.* **12**, 4480–4488.
- Snyder GL, Z Yan, S Galdi, PB Allen, AA Feinberg, JA Bibb, RL Haganir, AC Nairn and P Greengard (2001) A D₁-receptor/PKA/DARPP-32/PPI pathway regulates AMPA receptor phosphorylation and conductance in the neostriatum. *Brit. J. Pharmacol.* **133**, 268.
- Sommer B, K Keinanen, TA Verdoorn, W Wisden, N Burnashev, A Herb, M Kohler, T Takagi, B Sakmann and PH Seeburg (1990) Flip and flop: a cell-specific functional switch in glutamate-operated channels of the CNS. *Science* **249**, 1580–1585.
- Suen PC, K Wu, JL Xu, SY Lin, ES Levine and IB Black (1998) NMDA receptor subunits in the postsynaptic density of rat brain: expression and phosphorylation by endogenous protein kinases. *Mol. Brain Res.* **59**, 215–228.
- Sun Y, A Savanenin, PH Reddy and YF Liu (2001) Polyglutamine-expanded huntingtin promotes sensitization of *N*-methyl-D-aspartate receptors via post-synaptic density 95. *J. Biol. Chem.* **27**, 24713–24718.
- Swope SL, SI Moss, LA Raymond and RL Haganir (1999) Regulation of ligand-gated ion channels by protein phosphorylation. *Adv. Second Messenger Phosphoprot. Res.* **33**, 49–78.
- Tingley WG, MD Ehlers, K Kameyama, C Doherty, JB Ptak, CT Riley and RL Haganir (1997) Characterization of protein kinase A and protein kinase C phosphorylation of the *N*-methyl-D-aspartate receptor NR1 subunit using phosphorylation site specific antibodies. *J. Biol. Chem.* **272**, 5157–5166.
- Ulas J and C Cotman (1996) Dopaminergic denervation of striatum results in elevated expression of NR2A subunit. *J. Neuroreport* **7**, 1789–1793.
- Verhagen L, M Morris, C Farmer, M Gillespie, J Wu and TN Chase (2001) A double-blind placebo-controlled crossover study of the effect of amantadine on chorea in Huntington's disease. *Neurology* **56** (Suppl 3), A386.
- Vonsattel JP and M DiFiglia (1998) Huntington disease. *J. Neuropathol. Exp. Neurol.* **5**, 369–384.
- Westbrook GL (1994) Glutamate receptor update. *Curr. Opin. Neurobiol.* **3**, 337–346.
- Wirshing WC (2001) Movement disorders associated with neuroleptic treatment. *J. Clin. Psychiatry* **62** (Suppl 21), 15–18.
- Wollmuth LP, T Kuner, PH Seeburg and B Sakmann (1996) Differential contribution of the NR1- and NR2A-subunits to the selectivity filter of recombinant NMDA receptor channels. *J. Physiol. (Lond.)* **491**, 779–797.
- Yu XM, R Askalan, GJ Keil II and MW Salter (1997) NMDA channel regulation by channel-associated protein tyrosine kinase Src. *Science* **275**, 674–678.