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Dopamine Receptor Alternative Splicing

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1. INTRODUCTION

The five dopamine receptor subtypes (D1–D5) are members of the superfamily of G protein-coupled receptors (*see also* Chapter 1). Dopamine receptors. have been known since 1978 to be divided between two families differing in biochemical and pharmacological properties *(1)*. Although the G protein and second messenger systems affected by dopamine receptors in vivo have not been clearly established, in vitro D1-family receptors (D1 and D5) couple to Gs stimulatory proteins, activating adenylyl cyclase, whereas D2-family receptors (D2, D3, D4) couple to Gi inhibitory proteins, inhibiting adenylyl cyclase. Dopamine receptors couple effectively to a wide range of signaling cascades in vitro, including calcium channels, phospholipase C, potassium channels, arachidonic acid release, Na^+/H^+ exchangers, Na+-H+-ATPase, and cell growth and differentiation pathways (reviewed in ref. *2*), suggesting that dopamine may mediate a complex array of neural signaling pathways in vivo. Dopamine systems are believed to exert functional effects through these second-messenger signaling pathways via modulation of the activity of more rapidly acting ionotropic glutamatergic, GABAergic, and nicotinic cholinergic neuronal systems *(3)*.

D1-family receptors are encoded by intronless genes, resulting in expression of a single D1 and a single D5 receptor protein in each tissue expressing these receptors. In contrast, D2-family receptors are encoded by intron-containing genes, as illustrated in Figs. 1 and 2, providing the opportunity for the production of different transcripts, and therefore different proteins, via alternative splicing. The genes for the D2-family receptors are transcribed in the cell nucleus into heteronuclear-RNA (hn RNA or pre-mRNA). This primary pre-mRNA transcript contains sequences for both the exons, or expressed protein sequences, and introns, or non-protein-coding intervening sequences. Alternative splicing in the cell nucleus by spliceosome complexes is the process through which the intronic, non-protein-coding mRNA sequences are removed, leading to the formation of mature, functional mRNA. During this splicing process, individual exon sequences can be included or excluded; the initiation site for protein coding may be altered; exons may be spliced together so that a portion of the protein-coding sequence is excised; exons may be spliced together in a manner in which a new open reading frame is generated, leading to formation of a different protein sequence; or, rarely, intron sequences may be retained in the mature functional mRNA *(4,5)*. In this manner, because of the large number

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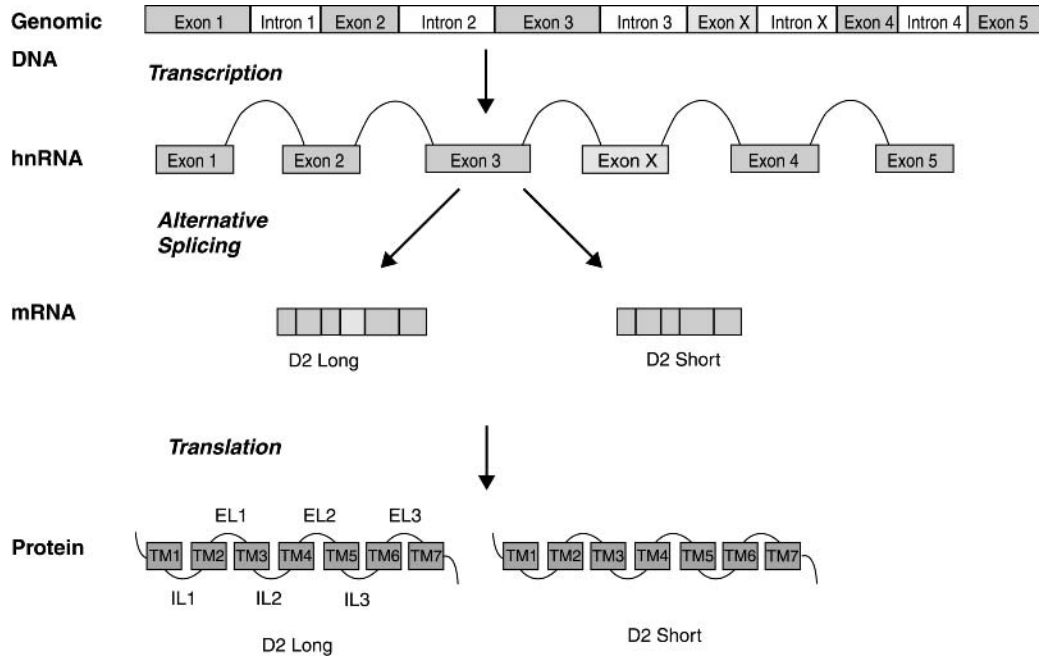

Fig. 1. D2 receptor alternative splicing.

of possible recombinations, alternative splicing provides the potential for significantly increased functional diversity in a given protein.

2. STRUCTURAL DOMAINS INVOLVED IN RECEPTOR FUNCTION

Dopamine receptors mediate ligand-induced modulation of second-messenger signaling through interactions of distinct functional domains. Ligand binding is achieved through interaction of ligand with a cleft formed by seven highly conserved primarily hydrophobic membrane-spanning domains *(6–8)*. The third intracytosolic loop, which extends between transmembrane domains five and six, is more variable, allowing greater functional diversity among receptor subtypes. Interactions between receptor and G protein occur through interaction with this third intracytosolic loop and also the region of the second transmembrane domain *(9–11)*. Dopamine receptors are believed to exist in vivo as higher ordered multimeric structures *(12–18)*. Receptor dimerization is believed to be achieved through specific intermolecular noncovalent interactions requiring at least one full transmembrane domain, in addition to intermolecular disulfide bonds *(13,18,19)*.

Alterations in primary protein sequence structure resulting from alternative splicing may lead to both predictable alterations in receptor function, based on the information described above, and may also lead to alterations in secondary and tertiary protein structure, and receptor function, which would be difficult to predict from the change in primary protein sequence. Functional consequences of receptor alternative splicing would include alterations in ligand-binding properties, signaling pathways, coupling efficiency to G proteins, receptor localization, and temporal expression of receptors. One of the major areas in which receptor function might be expanded through alternative splicing would be receptor desensitization, trafficking, and internalization, which represents an important mode of regulation of G protein-coupled receptor function.

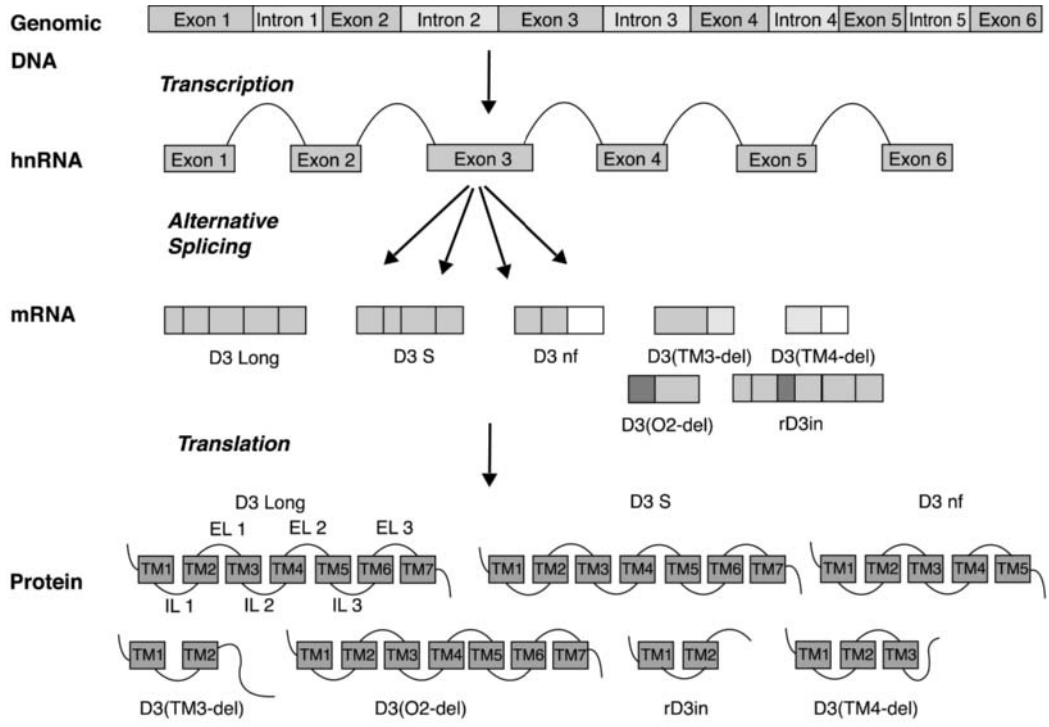

Fig. 2. D3 receptor alternative splicing.

3. REGULATION OF DOPAMINE RECEPTOR FUNCTION

G protein-coupled receptor function is regulated via receptor desensitization, a process involving receptor phosphorylation resulting in alterations in receptor internalization and receptor trafficking. Receptor desensitization, the tendency of a receptor-mediated response to diminish in the face of continued agonist stimulation, may be either homologous (agonist-specific) or heterologous (agonist-nonspecific) desensitization. G protein receptor desensitization has been most thoroughly characterized in β-adrenergic receptors, in which desensitization has been shown to involve receptor phosphorylation by a G protein-coupled receptor kinase (GRK). This results in binding of an arrestin-like protein to the receptor, uncoupling the receptor and G protein and decreasing receptor function. Arrestin binding promotes receptor internalization. Following internalization β-adrenergic receptors may be either proteolyzed in lysosomes, or recycled to the plasma membrane through a process involving dephosphorylation by a G protein-coupled receptor phosphatase *(20,21)*. Whether an analogous machinery exists for any of the dopamine receptor subtypes has not been clearly established. Of the dopamine receptors, D1 receptor desensitization has been most thoroughly characterized. D1 receptor is phosphorylated by both GRK and PKA (protein kinase A), however the relative importance of these kinases in desensitization in vivo has not been established *(22)*. The receptor is internalized into endosomal compartments following agonist activation *(23)*; however, dephosphorylation may precede internalization mediated by a phosphatase distinct from G protein-coupled receptor phosphatase *(24)*. The D2 receptor, in contrast, has been shown in a variety of settings to be resistant to agonist-induced desensitization, and in some cases

agonist treatment results in increased receptor expression *(25,26)*. D3 receptor desensitization has been far less well characterized, in part because of the difficulty in identifying second-messenger systems tightly coupled to D3 receptor stimulation. D3 receptors coupled to G protein-coupled inward rectifier potassium channels in Chinese hamster ovary cells exhibit desensitization following agonist activation *(27)*, however a more detailed understanding of an analogous desensitization process that might occur in vivo awaits further study.

4. D2 DOPAMINE RECEPTOR ALTERNATIVE SPLICING

4.1. Overview

D2 receptor mRNA and protein are expressed in most projection regions of dopamine neurons, consistent with a postsynaptic function, and are also expressed in presynaptic brain regions, suggesting the D2 receptor also functions as an autoreceptor. D2 receptor mRNA and protein are expressed in nucleus accumbens, caudate-putamen, piriform cortex, and olfactory tubercle, with lower expression detected in amygdala, hippocampus, lateral septum, hypothalamus, and other regions of limbic cortex. Abundant D2 receptor mRNA and protein expression is also observed presynaptically in dopamine cell body regions including substantia nigra, zona incerta, and ventral tegmentum *(28–42)*.

4.2. Splice Variants

The first known example of alternative splicing identified for a G protein-coupled receptor was that of D2 receptor alternative splicing *(43–46)*. The splice event results in retention or omission of a 29 amino acid sequence within the third cytoplasmic loop, resulting in formation of D2 receptors referred to as D2 (short) (lacking the 29 amino acid sequence) and D2 (long) (retaining the 29 amino acid sequence) (Fig. 1). More recently, a third alternatively spliced human receptor has also been identified, called D2 (longer), containing an additional two amino acids within the third cytoplasmic loop *(47)*. The location of the alternative splice site within the third cytoplasmic loop, the protein region believed to be integrally involved in coupling with G protein, would suggest a critical role in functional diversity between receptor isoforms, though unambiguously elucidating functional differences between D2 (short) and D2 (long) has proven difficult. The D2 (short) and D2 (long) receptor isoforms are differentially glycosylated, suggesting that differences in posttranslational modification may result in different intracellular trafficking pathways for the receptor isoforms *(48)*. Following dopamine-depleting lesions, however, expression of both D2 (short) and D2 (long) increases significantly and in the same ratio as prior to lesion in the denervated neostriatum, suggesting that splicing is regulated by tissue-specific factors *(49)*. Consistent with these observations, recent studies suggest that the D2 (short) isoform serves primarily in an autoreceptor role, whereas the D2 (long) receptor is expressed primarily at postsynaptic sites *(50)*. The two receptor isoforms also assume different subcellular localizations when transfected into NG 108-15 cells, with D2 (short) receptors localized at the plasma membrane, whereas D2 (long) receptors were localized, in this cell culture system, in the perinuclear region around the Golgi apparatus, associated with heart-type fatty-acid binding protein *(51)*. Also in keeping with a presynaptic role for the D2 (short) isoform, this isoform was found to be relatively more abundant in substantia nigra, as well as in hypothalamus *(52)*. In the same study, manipulation of sex steroid hormone levels by castration or sex steroid hormone

substitution altered the relative ratio of D2 (long)/D2 (short) expression, suggesting that sex hormones, through their hormone receptors, may play a regulatory role in D2 receptor alternative splicing *(52)*.

Of interest, D2 (long) receptors were found to be resistant to agonist-induced desensitization when expressed in culture in Sf9 cells *(25)*. Whether D2 receptor alternative splicing impacts receptor desensitization remains an area for future study.

4.3. Role in Disease

Alternative splicing of the D2 receptor has not been implicated, to date, in the pathophysiology of neuropsychiatric disease. There has been significant interest in reported associations between a *Taq*I-A1 polymorphism, which maps to a noncoding region 3′ to the *D2* receptor gene *(53)*, and several psychiatric conditions, including alcohol dependence *(54)*, pathological gambling *(55)*, obesity *(56)*, and schizoid and avoidant personality traits *(57)*. Several studies *(58,59)*, including a large, family-based sample *(60)*, have failed to confirm the reported association between this polymorphism and alcohol dependence. Further studies will be needed to elucidate the functional importance of D2 dopamine receptor splicing in these and other neuropsychiatric conditions (Table 1).

5. D3 DOPAMINE RECEPTOR ALTERNATIVE SPLICING

5.1. Overview

D3 dopamine receptor mRNA and protein are expressed primarily in olfactory tubercle, nucleus accumbens, islands of Calleja (located ventral to the ventral pallidum and nucleus accumbens), substantia nigra, ventral tegmentum, and prefrontal cortex *(41,42,61–66)*, phylogenetically ancient limbic brain regions linked to motivated and emotional behaviors. The earliest reports describing the highly restricted expression pattern of the D3 receptor suggested a role for this receptor in psychosis *(67,68)*. The cellular pattern of D3 protein expression does not overlap with expression of synaptic proteins such as synaptophysin, suggesting that receptor localization is primarily extrasynaptic *(66)*. Protein and mRNA expression are highly colocalized, suggesting receptor expression occurs primarily on perikarya, proximal dendrites, and short axons as opposed to long axon terminals from other brain regions *(61)*. D3 receptor protein has been described in tyrosine hydroxylase-positive neurons in substantia nigra and ventral tegmentum, indicative of presynaptic D3 receptors *(66)*, although the functional role of these D3 autoreceptors has not yet been elucidated *(69,70)*.

Colocalization studies of D1, D2, and D3 receptors indicate that the majority of D3 expressing neurons in islands of Calleja and nucleus accumbens shell also express D1 receptor mRNA *(71)*. In human brain, most D3-mRNA-expressing cells also express D2 mRNA *(64)*, whereas in rodent brain, in contrast, D2 and D3 receptors appear to have predominantly complementary rather than overlapping patterns of expression *(62)*.

D3 receptor function is of particular interest because evidence suggests its effects are primarily inhibitory *(72–77)*, and that loss of this inhibitory function might contribute pathologically to neuropsychiatric disease *(77–79)*.

5.2. D3 Receptor Splice Variants

The single gene coding for the D3 receptor is organized to allow for the production of different transcripts via two distinct types of alternative splicing of D3 receptor

Table 1
Functional and Physiological Correlates of Dopamine Receptor Alternative Splicing

Receptor	Isoform	Splice site location	Functional effect	Physiological effect	Reference
D2	D2S	Third cytoplasmic loop	Altered glycosylation and membrane trafficking	Autoreceptor	*43–46,50*
	D2L	Third cytoplasmic loop	Altered glycosylation and membrane trafficking	Postsynaptic signaling; resistant to agonist-induced desensitization	*25,50*
D3	D3 (short)	Third cytoplasmic loop	High-affinity dopamine binding intact	Unknown	*84*
	D3 (TM3-del)	Third transmembrane domain	No dopamine binding	Unknown	*82,86*
	D3 (TM4-del)	Fourth transmembrane domain	No dopamine binding	Unknown	*88*
	D3 (O2-del)	Second extracellular loop and fifth transmembrane domain	No dopamine binding	Unknown	*82*
	rD3in	First extracellular loop	No dopamine binding	Unknown	*89*
	D3nf	Third cytoplasmic loop	No dopamine binding; altered membrane trafficking of D3	Potential involvement in development of behavioral sensitization and psychosis	*85,90*

heteronuclear RNA (hn RNA or pre-mRNA) in the cell nucleus *(80–83)*. At least seven distinct alternative splicing variants of the D3 receptor are produced through these splicing events.

Similar to D2 splicing, a splicing event with classical donor and acceptor splice sites within the third cytoplasmic loop results in formation of either the full-length D3 receptor (called "D3"), or a shorter receptor isoform, D3S, lacking 21 amino acids *(84)* (Fig. 2). Both D3 and D3S exhibit high-affinity dopamine binding.

A distinct set of splicing events lead to formation of deletion receptor variants. These splicing events involve cleavage at an unusual, nonconsensus sequence 3′ acceptor splice site *(85)*. Five additional alternatively spliced variants have been described that do not bind dopamine, and are believed to function instead through regulation of receptor dimerization *(86)* and receptor localization *(87)*. These include D3 (TM3-del) *(82,86)*, D3 (TM4-del) *(88)*, D3 (O2-del) *(82)*, rD3in *(89)*, and D3nf *(85,90)*.

5.2.1. D3nf

D3nf is the best characterized of the non-dopamine-binding splice variants. D3nf is formed through a deletion of 98 base pairs in the third cytoplasmic loop, causing a coding frame shift resulting in creation of a novel 55 amino acid peptide and appearance of a new premature stop codon. The prematurely truncated protein thus lacks transmembrane domains 6 and 7 *(85,90)*, and does not bind dopamine *(91)*. D3nf mRNA and protein are expressed in rat, monkey, and human brain *(15,85)*. Importantly, the highly conserved nature of D3nf splicing and protein expression, from rat to human, suggests D3nf likely plays an important, although currently unknown, biological function. Evidence from at least three labs demonstrates that D3nf binds to the full-length D3 receptor subunit *(15,87,91)*. D3nf expression inhibits dopamine binding to full-length D3 receptor *(91)*, and also redirects full-length D3 receptor localization away from the plasma membrane, and instead into an intracellular compartment *(87)*. Importantly, D3 mRNA expression is decreased in cortex of schizophrenia patients *(90)*, whereas increased D3nf splicing efficiency was observed in cortex of postmortem tissue from schizophrenia patients *(92)*. These findings suggest that increased D3nf expression may contribute to functional states of altered dopaminergic activity. Collectively, these studies suggest that, in a manner analogous to dimerization playing an important role in modulation of cell signaling for the homologous insulin and gonadotropin-releasing hormone receptors *(93,94)*, dimerization of D3nf with full-length D3 receptor (or perhaps D1 or D2 receptor) could regulate dopamine signaling. A major gap in our current understanding of D3 dopamine receptor function lies in a lack of information regarding the occurrence of alterations in D3 receptor isoform expression in altered functional states.

5.2.1.1. Proposed Model of D3nf Role in Behavioral Sensitization and Psychiatric Disease

The information described above suggests a model of a mechanism underlying behavioral sensitization, an altered functional state characterized by the progressive and enduring enhancement of certain stimulant-induced behaviors that develops following repetitive stimulant drug administration (*see* ref. *95* and Chapters 15 and 16). Behavioral sensitization serves as a well-studied model of behavioral plasticity with some features in common with the development of psychosis in man *(95–98)*. Following repeated, intermittent treatment with stimulant drugs such as amphetamine (AMPH) or cocaine, behavioral responses may occur more intensely, with shorter latency, and at lower stimulant doses *(99)*. Sensitization is an enduring behavioral change, persisting for at least 1 yr in rats *(100)*. In humans, sensitized behaviors following extended repetitive stimulant drug administration may include psychotic symptoms of paranoia, ideas of reference, and auditory and visual hallucinations in otherwise healthy individuals *(101,102)*. Because pretreatment with amphetamine also facilitates the later acquisition of drug self-administration *(103)*, it has been theorized that sensitization may also underlie the development of drug craving, and thus initiate addictive behaviors seen in drug dependence *(104)*. Additionally, it has been postulated that aspects of behavioral sensitization may play a role in the development of recurrent affective disorders *(105)* and posttraumatic stress disorder *(106)*.

Behavioral sensitization could be accounted for by the increase in D3nf expression that one would predict accompanies repetitive stimulant drug administration, as illustrated

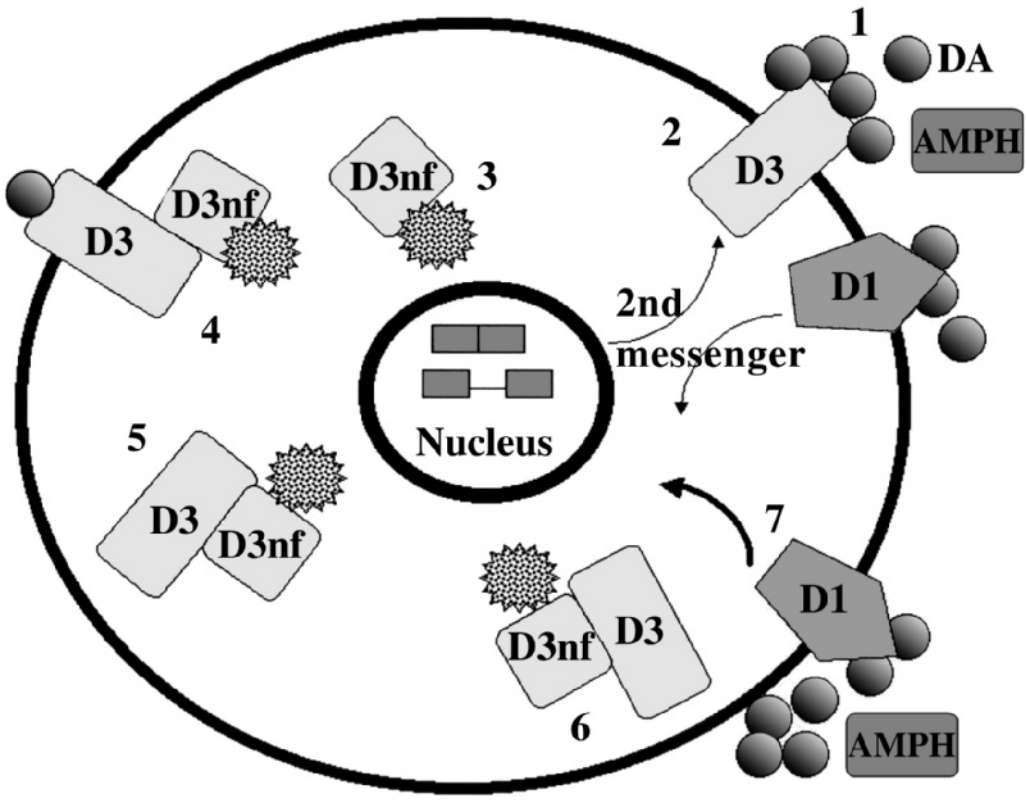

Fig. 3. D3/D3nf mechanism of behavioral sensitization to amphetamine. **(1)** Amphetamine increases extracellular dopamine, activating second-messenger systems downstream of dopamine receptor stimulation. **(2)** D3 receptor has highest dopamine affinity. D3 stimulation results in homeostatic mechanisms opposing receptor stimulation, including **(3)** increased D3nf expression. **(4)** D3nf and D3 dimerize, directing the D3/D3nf dimer **(5)** toward intracytoplasmic trafficking pools and removing D3 receptor from the synaptic membrane. **(6)** At the next amphetamine exposure D3 receptor is not available to bind dopamine. **(7)** The result is release of D3 receptor–mediated opposition to D1 receptor stimulation of adenylate cyclase activity. (Details are described in text.)

in Fig. 3. **(1)** AMPH increases extracellular dopamine, activating second-messenger systems downstream of dopamine receptor stimulation. D3 and D1 receptor stimulation interact at the second-messenger level *(71,107)*, for example through opposing effects on adenylate cyclase activity. Because D3 and D1 receptors are frequently coexpressed *(71)* this interaction is depicted in the diagram as occurring within the same cell; however, the interaction could also occur at the systems level *(108–110)*. **(2)** The D3 receptor has highest dopamine affinity, and excessive D3 stimulation results in homeostatic mechanisms opposing receptor stimulation. This homeostatic response would include **(3)** increased D3nf expression resulting from a change in D3 hnRNA alternative splicing in the cell nucleus. D3nf is a receptor splice variant whose function is thought to oppose D3 receptor stimulation. D3nf shares an NH3-terminus "dimerization domain" with the D3 receptor, resulting in **(4)** dimerization between D3nf and D3. D3nf also contains a unique protein sequence at the COOH-tail, which

may direct the D3/D3nf dimer **(5)** toward intracytoplasmic trafficking pools, thereby removing the D3 receptor from a functional position at the synaptic membrane. In this manner at the next AMPH exposure **(6)** the D3 receptor is localized in an intracytoplasmic pool, and is not available to bind dopamine at the synapse. The resulting loss of D3 receptor "brake," at both the cellular and systems level, includes for example **(7)** the loss of D3 receptor-mediated opposition to D1 receptor stimulation of adenylate cyclase activity.

5.3. Role in Disease

The model described above suggests D3 receptor alternative splicing may play a critical role in sensitization phenomenon. As sensitization may underlie the development of drug craving, and thus initiate addictive behaviors of drug dependence *(104)*, D3 receptor alternative splicing could play an important role in drug dependence, consistent with a large body of data implicating the D3 receptor in various aspects of drug-dependent behavior *(111–115)*. Through a similar mechanism, sensitization and D3 receptor alternative splicing could also play a role in psychosis *(79)*. An amino acid substitution polymorphism in the amino terminus of the D3 receptor has been reported to modulate vulnerability to schizophrenia (*see* refs. *116,117*; reviewed in ref. *118*), suggesting an interaction between D3 receptor function and other genetic and environmental factors in mediating development of a chronic psychotic illness. The D3 receptor has also been implicated in vulnerability to other neuropsychiatric disorders, including tardive dyskinesia (reviewed in ref. *119*).

6. D4 DOPAMINE RECEPTOR ALTERNATIVE SPLICING

6.1. Overview

The pattern of D4 receptor mRNA and protein expression is distinct from that of D2 and D3 receptors, with D4 receptor expressed in highest levels in limbic regions including prefrontal cortex, hippocampus, nucleus accumbens, and amygdala, and relatively lower expression in striatum *(42,120–124)*. Interest in the clinical relevance of D4 receptor function has been heightened by the observation that clozapine, an atypical antipsychotic medication with unique antipsychotic efficacy, exhibits higher affinity binding to D4 than to D2 and D3 receptors *(125)*. Additionally, elevated D4 receptor binding has been reported in the brains of schizophrenia patients *(126,127)*. Although selective D4 receptor antagonists have not demonstrated antipsychotic efficacy *(128)*, interest in the clinical relevance of D4 receptor function remains high.

6.2. D4 Receptor Splice Variants

Alternatively spliced variants analogous to those reported for D2 and D3 receptors have not been reported for the D4 receptor. Although alternative splicing is not known to contribute to variability in receptor structure, D4 sequence variability is conferred by genetic variability of D4 receptor isoforms. Specific D4 receptor isoforms have been linked, in some studies, to neuropsychiatric disease. Within the human D4 receptor third cytoplasmic loop, a 48-base pair sequence is variably repeated between 2- to 8- or 10-fold *(129,130)*. Each human therefore has two copies of the D4 gene, each gene containing 2–8 or 10 repeat units. (The sequences of the rat D4 receptor differs significantly from the human homologue in this third intracytosolic loop domain, and the rat

receptor does not have a corresponding variable repeat region.) Although it would be expected that variability within the third cytoplasmic loop protein domain thought to be integrally involved in G protein coupling would exert an important functional effect, elucidating the functional role of D4 receptor polymorphisms has been challenging. Receptor isoforms differ in sensitivity to the effect of sodium chloride on ligand binding affinity *(129)*, however overall the presence or absence of repeat sequences appears to have only minor effects on ligand binding, G protein interactions, and second-messenger signaling *(131,132)*. Further studies will be needed to clearly elucidate a functional mechanism through which D4 receptor polymorphisms play a role in neuropsychiatric disorders.

6.3. Role in Disease

The role of D4 receptor third cytoplasmic loop polymorphisms in neuropsychiatric conditions has been an area of both interest and controversy. The 7-repeat allele has been associated in some studies with the personality trait of novelty seeking *(133,134)*; however this finding has not been confirmed in other samples *(135,136)*. There has been similar interest and controversy surrounding the potential role of this polymorphism in the risk for Tourette syndrome (*see* e.g., *137,138*). To date, stronger evidence appears to support a contribution of the polymorphism within this region as one of several factors contributing to the heritable vulnerability for attention deficit hyperactivity disorder (reviewed in ref. *139*). Again, further studies will be needed to clarify the potential contribution of variability within this region of the D4 dopamine receptor in these neuropsychiatric conditions.

7. CONCLUSIONS AND FUTURE DIRECTIONS

The greatly expanded functional diversity provided by alternative splicing suggests the likelihood that dopamine receptor alternative splicing could play an important role in both the pathophysiology, as well as treatment response, of a range of neuropsychiatric conditions, including psychotic disorders, substance dependence, Parkinson's disease, Tourette syndrome, and attention deficit hyperactivity disorder. Much remains to be learned, however, regarding the functional neuroanatomy of receptor isoform expression, particularly as it relates to receptor subcellular localization and important mechanisms of receptor regulation such as receptor desensitization, trafficking, and internalization. Further studies are needed evaluating the role of receptor isoforms in neuropsychiatric disease; elucidating the effect of receptor isoform overexpression in mouse models; elaborating the effect of receptor isoform coexpression on subcellular localization and second-messenger signaling in cell culture systems. These studies will identify the cellular function of alternatively spliced isoforms, and may thereby suggest specific, previously untested interventions for neuropsychiatric conditions in which dopamine is known to play an important role, including psychosis and drug abuse.

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