

Appendix A14.8

Dopaminergic System

Once thought to function solely as a precursor to noradrenaline (NA) and adrenaline synthesis, it was later discovered that dopamine (DA) is more than just an intermediate for monoamine anabolism. Indeed, this neurochemical is present in the brain, as well as in peripheral tissues, but the fact that it is distributed differently than NA in brain tissues was the first clue that it functions as a neurotransmitter. DA synthesis requires adequate transport of the amino acid tyrosine across the blood brain barrier and into the cell. Once tyrosine enters the neuron, the rate-limiting step is conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase. Then, the conversion of DOPA to dopamine requires L-aromatic amino acid decarboxylase. This rate-limiting enzyme can be controlled by many factors, including neuronal activity, for which the production of transmitter may be regulated. Furthermore, catecholamines function as an end-product inhibitor of tyrosine hydroxylase by competing with a tetrahydrobiopterin cofactor.

Upon calcium-dependent release of DA, it is converted to DOPAC by intraneuronal monoamine oxidase (MAO) after reuptake of the molecule. However, if DA is not allowed to be taken up, as is the case in the presence of a reuptake inhibitor, it can be converted into homovanillic acid (HVA). The latter conversion probably occurs at an extraneural site through the sequential action of catechol-O-methyltransferase (COMPT) and MAO. The major metabolites of DA in rodent and human brain are DOPAC and HVA, respectively, and these metabolites have been used as indices of neuronal activity. A considerable amount of work has been directed at correlating these levels with psychiatric disorders.

Dopamine can be located in nearly all regions of the brain and plays an important role in the control of central nervous system function. There are four major DA projections in the brain: nigrostriatal, mesolimbic, tuberoinfundibular, and incertohypothalamic. The first two circuits have been implicated in psychiatric/neurological disorders and will be the focus herein. The nigrostriatal circuit is composed of DA neurons from mesencephalic reticular formation (region A8) and par compacta region of the substantia nigra (region A9) of the mesencephalon. These DA neurons, which make up the nigrostriatal circuit, are critical for maintaining normal body movement; destruction of these neurons is associated with Parkinson's disease. These neurons give rise to axons that travel via the medial forebrain bundle to innervate the caudate nucleus and putamen (Anden et al., 1964; Ungerstedt, 1971). This is also consistent with a decrease in DA transporter density in these brain regions in bipolar disordered patients with Parkinson's disease (Cooper et al., 1996).

The mesolimbic DA circuit consists of DA neurons located in the midbrain just medial to the A9 cells in an area termed the ventral tegmental area (VTA). This circuit shares aspects similar to that of the nigrostriatal in that it is a parallel circuit consisting of axons which make

up the medial forebrain bundle. Unlike the nigrastriatal circuit, these axons ascend through the lateral hypothalamus and project to the nucleus accumbens, olfactory tubercle, bed nucleus of the stria terminalis, lateral septum, and frontal, cingulate, and entorhinal regions of the cerebral cortex (Lindvall, 1975; Lindvall et al., 1974; Moore, 1978; Nauta et al., 1978; Ungerstedt, 1971). This circuit innervates many limbic structures deemed to be important in imparting effects on mood, and it is linked to the rewarding effects of drugs of abuse.

Table A14.8a: Controlled Baseline Studies of CSF HVA in Depression and Mania

Study	Control	Patients N		Control Mean %		
		Depressed	Manic	50	100	150
Med-free ≥ 10 days						
Papeschi & McClure, 1971	18	17		◆ ^b		
					50.0	
Brodie et al., 1973	6	7		◆ ^b		
					51.0	
Goodwin et al., 1973	28	53	16	◆		○
					22.4	
Koslow et al., 1983	30 M	49 M	9 M	◆ ^b		○
					40.1	
	32 F	43 F	5 F	◆		○ ^a
					43.7	
Roy et al., 1985b	41	27		◆		
					28.2	
Widerlov et al., 1988a	10	22		◆		
					37.0	
Potter et al., unpublished	49	101		◆		
					32.8	
Widerlov et al., 1988 c	10(166.4±20.1)	22(151.2±14.1)			ns	
De Bellis et al 1993	46(219.5±109.9)	9(182.9±49.7)				ns
Med-free < 10 days						
Van Praeg & Korf, 1971	12	20			◆	
					42.0	

Wilk et al.,1972	19	5	6	◆	○	18.0	
Van Praag et al.,1973	12	28					◆
Takahashietal.,1974	30	30 UP				35.8	◆
						37.5	
Subrahmanyam, 1975	12	24				40.2	◆
Ashcroff et al.,1976	31	11 UP 9 BP	11	◆ ^a	○	41.0	◆
Banki,1977	32F	71F	10F	◆ ^b		33.4	ob
Vestergaard et al.,1978	23	29	4			45.0	oa
Oreland et al.,1981	28 M	6 M				39.1	(256%)
	14 F	14 F				47.8	◆
Traskman et al., 1981	45	8		◆ ^b		44.5	
Kasa et al.,1982	16	13		◆		41.8	
Gemer et al. 1984	37	38	13			28.6	◆
Asberg et al.,1984	66	43 UP 4 BP I 11 BP II				44.7	◆ ^b

The mean metabolite level (ng/ml) for the control group in each study appears in the 100% column. The shaded bar indicates standard error (expressed in percentage points) around the control mean expressed as 100%. (Data not available in Wilk study.) ;

◆ = Mean for depressed group expressed as % of control mean

○ = Mean for mank group expressed as % of control mean

^a $p < .05$ vs. controls ^b $p < .01$ vs. controls

c Positive correlation between CRF and HVA

Dopaminergic Receptors

The first two types of DA receptors, D1 and D2, were initially classified by using behavioral and pharmacological techniques in the 1980s (Clark and White, 1987; Stoof and Kebabian, 1984). Indeed, each of these receptors have distinct anatomical locations, as visualized with immunohistochemistry (Bouthenet et al., 1987; Boyson et al., 1986; Charuchinda et al., 1987; Dawson et al., 1988; Mansour et al., 1990; Wamsley et al., 1989). It was later observed via molecular biology techniques that these receptors also have distinct molecular entities and are equipped with divergent transducing units. It is currently accepted that there are five types of DA receptors in the mammalian brain (D1-D5). Although these receptors are classified as subtypes of either D1 or D2 receptors, their particular function and the evaluation of their effects in the CNS has been limited by the scarcity of selective ligands directed at these subtypes.

D1-receptors

The D1 receptor in humans and in rats has been cloned, expressed in cells, and characterized by several laboratories (Cooper et al., 1996). D1 receptors also comprise the D5 receptors. Stimulation of D1 or D5 receptors with the agonist SKF39383 is able to pharmacologically differentiate D2 receptor effects from those of the former. Furthermore, the affinity of the D1 receptor family for the antagonist SCH23390 does not bind D2 receptors, and is yet another agent used for discrimination between the two. D1 receptors are coupled to Gs proteins and stimulate adenylate cyclase activity when an agonist or endogenous ligand binds to the receptor complex. Of note, other second messenger pathways are also activated by D1 receptors and it is interesting that the function of D1 receptors can be influenced by D2 receptor effects (Clark and White, 1987). Many antipsychotic agents possess affinity for DA receptors; however, the DA hypothesis of this disorder does not support a D1 pathophysiology, as the density of these receptors are normal in these patients.

D2-receptors

Four types of D2 receptors have been identified. The two subtypes of D2 receptors (short and long form, D2s and D2L, respectively) are derived from alternative splicing of the D2 gene. Although a seemingly identical pharmacological profile for these receptors exists, what is not known is the physiological relevance between these two subtypes. D2 receptors mediate their cellular effects via the Gi/Go proteins to impart an inhibitory influence on adenylate cyclase activity. It is also worthwhile to mention that stimulation of D2 receptors is linked to a decrease in phospholipase C, changes in K⁺ and Ca²⁺ currents, and increases in achiidonic acid. D2 receptors are located on DA neurons and function as autoreceptors. Activation of D2 receptors, which are an agonist, or DA itself imparts an inhibitory action on the firing activity DA neurons. D2 receptors have consistently been shown to be attenuated in caudate and putamen of postmortem brains from neuroleptic-free schizophrenic patients. The D2 receptor hypothesis of schizophrenia is largely based on the observation that drugs which have a high affinity for this receptor are effective antipsychotic agents (Seeman 2005).

D3- and D4-receptors

The D3 receptor, which makes up the D2 receptor family, was isolated by screening cDNA libraries from rat brains (Cooper et al., 1996). This receptor possesses a different anatomical distribution than the D2 receptor. D3 receptors are primarily located in limbic regions and have a distinct pharmacological profile in comparison to the D1 receptor family. For instance, there is roughly a 100-fold increase in the affinity of this receptor for the DA receptor agonist quinpirol (Cooper et al., 1996). D4 receptors were discovered in 1991 and lumped into the D2 receptor family due to their similarity to that of the D2 and D3 subtypes. There are selective ligands for this receptor, and these receptors are able to produce effects different from that of other DA receptors. Much attention has focused on the D4 receptor as being important to the treatment or pathophysiology of numerous psychiatric disorders, most notably that of attention deficit hyperactivity disorder (ADHD) and various substance abuse disorders.

D5-receptors

This receptor subtype has properties similar to that of the D1 receptor in that it stimulates adenylate cyclase activity when activated. This is not surprising, as the D5 receptor (477 amino acid protein) has very similar homology to the cloned D1 receptor. Interestingly, a 10-fold higher affinity for that of DA is witnessed for this receptor as its D1 cohort (Sunahara et al., 1991). The D5 receptor is a neuron-specific receptor that is primarily located in limbic areas of the brain. The mRNA for the D5 receptor is found in hypothalamus, hippocampus, and the parafascicular nucleus of the thalamus. As for the function of these receptors in the brain, they probably do not function as autoreceptors, as do receptors of the D2 family, because mRNA for these receptors is absent in the VTA and substantia nigra. For a summary of the distribution of DA receptor mRNAs in the brain please refer to the Table A15.8a.

DA Transporters

The dopamine transporter is a 12-membrane-spanning domain protein. It is located somatodendritically as well as on axon terminals and is important in the termination of synaptic transmission. DAT, as do all monoamine transporters, functions as a Na/K⁺ pump to take up DA from the synaptic cleft upon its release. Thus, depending on the concentration gradient, DA can either be taken up into the neuron or released. Many drugs of abuse are capable of altering the function of these transporters. The amphetamines are thought to mediate their effects by reversing the direction of the transporter so that it releases DA. Cocaine and antidepressant agents are capable of blocking the reuptake of DAT, and lead to an increase in DA within the synaptic cleft. It should be mentioned that the affinity of most antidepressants for the DAT is much less than that for the other monoamines and is not currently thought to be of significance to the mechanism of action of the currently available antidepressants. Of

interest, DA in the medial frontal context is taken up predominantly by NAT. The functional significance of this is not currently known, however it goes against the dogma of a transporter being able to selectively take-up only its respective neurotransmitter (Madras et al., 2002).

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