process separately from granular storage is to use synaptosomes from reserpinized preparations, an approach not altogether feasible in the present experimental model.

The changes in the binding of [^{3}H]desipramine to presynaptic norepinephrine uptake sites are in a direction opposite to changes in binding to postsynaptic adrenergic receptors. However, both alterations appear to reflect homeostatic attempts of these synaptic systems to normalize norepinephrine synaptic transmission after perturbation by drugs. Thus, depletion of norepinephrine by reserpine gives rise to an increased number of postsynaptic adrenergic receptors, providing a supersensitivity to the smaller amount of synaptic transmitter.

In contrast to the substantial changes in desipramine binding sites, treatment with reserpine and iproniazid has little effect on [^{3}H]imipramine binding to serotonin uptake sites. The only change detected was a 20 percent reduction 9 days after a high dose of reserpine (5 mg/kg). Conceivably, this finding reflects a less stringent regulation of synaptic serotonin than of norepinephrine. Thus, injections of tryptophan produce considerable increases in the brain levels and possibly the synaptic concentrations of serotonin, whereas treatment with tyrosine produces much smaller changes in norepinephrine (*17*).

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Narcolepsy: Biogenic Amine Deficits in an Animal Model

Abstract. *Concentrations of biogenic amine metabolites in discrete brain areas differed significantly between dogs with genetically transmitted narcolepsy and age- and breed-matched controls. Dopamine and 3,4-dihydroxyphenylacetic acid were consistently elevated in the brains of narcoleptic animals, while homovanillic acid was not. Narcoleptic animals consistently exhibited lower utilization of dopamine and higher intraneuronal degradation of dopamine but no uniform decrease in serotonin utilization. Hence neuropathology appears to be associated with genetically transmitted canine narcolepsy. The data indicate a nonglobal depression of dopamine utilization or turnover or both.*

Narcolepsy, an incurable human sleep disorder, has been recognized for nearly a century, but its etiology is still undefined (*1*). The disease is characterized in its complete form by a severe and permanent daytime somnolence and by attacks of flaccid paralysis called cataplexy. These attacks can strike spontaneously or be elicited by laughter, excitement, anger, or fear. Two other frequent symptoms are sleep paralysis and hypnagogic hallucinations. Finally, polysomnographic testing of narcoleptic patients consistently shows pathognomonic periods of rapid eye movement (REM) at the onset of sleep. Thus, human narcolepsy is well defined pathophysiologically and can be accurately diagnosed. Many studies have indicated that human narcolepsy has genetic determinants (*2*).

In the past decade narcolepsy has been described in the dog and the horse (*3*). At Stanford University two breeds of dogs, Labrador retrievers and Doberman pinschers, have been isolated that transmit narcolepsy to their offspring through an autosomal recessive mechanism (*4*). A breeding colony now supplies a homogeneous population of affected animals.

Our early neurochemical studies were limited to sampling cerebrospinal fluid in narcoleptic and normal miniature poodles, a breed that apparently does not transmit the illness. The most consistent finding was a decreased turnover of serotonin in narcoleptic poodles and a trend toward decreased turnover of catecholamines (*5*). We attempted to replicate this result in normal and genetically narcoleptic Doberman pinschers. No significant differences in monoamine metabolites were found between control and affected animals (*6*). This suggested either that biogenic amines play no role in narcolepsy in this breed or that any deficits in the central nervous system were too subtle or localized to be reflected in cisternal cerebrospinal fluid.

We now report the results of a direct neurochemical analysis of brain tissues from genetically narcoleptic Doberman pinschers and age- and breed-matched controls. We measured the concentrations of norepinephrine, epinephrine, dopamine, serotonin, 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3,4-dihydroxyphenylacetic acid (DOPAC) in specific brain areas selected for study because of their suspected role in regulation of sleep and waking states.

Brains from five narcoleptic and seven

Table 1. Distribution of biogenic amines and metabolites in brain regions of genetically narcoleptic (N) and control (C) dogs. Values other than ratios are nanograms per gram of tissue (wet weight). Values are means ± standard errors. N.D., not determined.

Group	Norepi-nephrine	Epi-nephrine	Dopamine	DOPAC	HVA	Serotonin	5-HIAA	5-HIAA/5-HT	HVA/DA	DOPAC/DA
					Nucleus caudatus, rostral					
C	N.D.	N.D.	7,171 ± 330	1,173 ± 85	14,102 ± 627	252.2 ± 61.1	248.2 ± 20.5	1.103 ± 0.173	1.99 ± 0.14	0.165 ± 0.014
N	N.D.	N.D.	7,769 ± 530	1,882 ± 112*	14,418 ± 793	215.0 ± 11.0	237.0 ± 13.0	1.230 ± 0.133	1.87 ± 0.10	0.245 ± 0.014*
					Nucleus caudatus, medial					
C	N.D.	N.D.	7,138 ± 1,021	1,081 ± 205	14,410 ± 1,923	328.2 ± 37.7	295.8 ± 35.4	0.913 ± 0.078	2.04 ± 0.059	0.145 ± 0.016
N	N.D.	N.D.	8,126 ± 741	1,546 ± 193	14,278 ± 1,284	379.2 ± 39.1	308.4 ± 34.6	0.818 ± 0.073	1.77 ± 0.085†	0.188 ± 0.011†
					Nucleus caudatus, caudal					
C	118.8 ± 17.7	6.9 ± 2.3	5,381 ± 620	675.8 ± 94.1	8,742 ± 1,041	192.3 ± 27.4	168.5 ± 25.0	0.888 ± 0.061	1.63 ± 0.046	0.124 ± 0.007
N	140.0 ± 35.4	11.2 ± 4.7	5,589 ± 494	855.4 ± 115.3	8,208 ± 881	202.0 ± 32.6	175.8 ± 18.9	0.924 ± 0.101	1.46 ± 0.062†	0.152 ± 0.011†
					Nucleus accumbens septi					
C	1,240 ± 146	117.0 ± 22.8	2,379 ± 783	276.0 ± 76.6	6,324 ± 919	1,575 ± 164	1,232 ± 104	0.818 ± 0.096	4.09 ± 1.14	0.121 ± 0.019
N	1,267 ± 201	138.4 ± 31.2	3,155 ± 436	513.4 ± 104.2	6,044 ± 247	1,829 ± 215	1,132 ± 109	0.628 ± 0.031	2.01 ± 0.18	0.158 ± 0.014
					Preoptic hypothalamus					
C	1,394 ± 121	263.5 ± 32.6	816.3 ± 260.6	136.5 ± 4.42	3,126 ± 299	986.5 ± 106.3	672.5 ± 22.1	0.712 ± 0.067	5.99 ± 1.61	0.162 ± 0.015
N	1,088 ± 60†	203.4 ± 27.0	892.2 ± 314.9	184.4 ± 78.0	3,179 ± 223	1,183.6 ± 149.1	757.0 ± 73.4	0.678 ± 0.121	5.43 ± 1.40	0.198 ± 0.021
					Medial hypothalamus					
C	1,846 ± 137	342.3 ± 41.1	207.2 ± 16.7	40.1 ± 5.9	1,297 ± 72.6	698.3 ± 32.5	615.3 ± 48.8	0.873 ± 0.043	6.53 ± 0.76	0.198 ± 0.03
N	1,597 ± 290	355.0 ± 96.2	254.8 ± 23.1	56.1 ± 11.2	1,340 ± 79.4	725.8 ± 81.8	600.6 ± 36.5	0.852 ± 0.076	5.36 ± 0.33	0.218 ± 0.033
					Posterior hypothalamus					
C	689.0 ± 69.2	41.1 ± 5.7	621.3 ± 72.6	137.0 ± 22.3	2,370 ± 513	1,259 ± 108	1,018 ± 103	0.808 ± 0.060	3.77 ± 0.56	0.213 ± 0.013
N	707.6 ± 13.5	61.6 ± 7.4†	676.4 ± 112.6	156.6 ± 37.8	2,414 ± 364	1,276 ± 116	1,127 ± 172	0.880 ± 0.102	3.64 ± 0.23	0.22 ± 0.031
					Amygdala					
C	186.5 ± 17.9	4.8 ± 0.82	494.5 ± 136.2	36.3 ± 10.2	1,943 ± 929	987.1 ± 82.2	538.2 ± 57.1	0.557 ± 0.070	3.23 ± 0.55	0.079 ± 0.016
N	218.6 ± 21.8	10.1 ± 2.1†	990.2 ± 70.9*	100.0 ± 4.5*	4,281 ± 966	925.0 ± 114.6	643.2 ± 52.8	0.726 ± 0.079	4.41 ± 1.09	0.102 ± 0.005
					Substantia nigra					
C	372.8 ± 50.8	23.5 ± 3.7	1,147 ± 84.1	282.5 ± 22.9	5,534 ± 285	1,596 ± 262	1,647 ± 172	1.195 ± 0.260	4.89 ± 0.26	0.247 ± 0.13
N	463.0 ± 52.1	35.0 ± 7.1	1,059 ± 250	314.6 ± 76.0	4,699 ± 665	1,479 ± 324	1,643 ± 158	1.698 ± 0.790	5.35 ± 1.07	0.307 ± 0.040
					Nucleus interpenduncularis					
C	688.3 ± 30.7	N.D.	180.2 ± 87.9	N.D.	2,067 ± 447	1,751 ± 592	4,180 ± 539	3.872 ± 1.04	20.60 ± 4.96	
N	770.0 ± 42.9	N.D.	370.4 ± 149.9	N.D.	2,944 ± 687	2,587 ± 605	5,399 ± 361	2.544 ± 0.554	11.84 ± 2.73	
					Hippocampus					
C	79.2 ± 12.3	N.D.	22.4 ± 5.2	N.D.	183.0 ± 23.4	230.7 ± 32.8	243.2 ± 30.1	1.067 ± 0.024	9.70 ± 1.96	
N	89.2 ± 10.1	N.D.	33.4 ± 7.2	N.D.	245.2 ± 40.5	220.4 ± 40.1	205.6 ± 22.2	0.988 ± 0.081	8.34 ± 1.83	
					Substantia grisea centralis					
C	813.2 ± 71.0	74.8 ± 5.9	112.2 ± 30.3	34.5 ± 10.8	1,139 ± 48.5	1,745 ± 165	3,037 ± 349	1.728 ± 0.057	12.30 ± 1.64	0.298 ± 0.044
N	846.6 ± 31.1	89.0 ± 4.2	114.2 ± 6.9	22.0 ± 2.6	1,150 ± 17.6	2,099 ± 126	2,833 ± 101	1.374 ± 0.117*	10.20 ± 0.64	0.191 ± 0.025†
					Dorsal raphe					
C	1,139 ± 45.8	93.7 ± 25.9	183.3 ± 42.8	107.2 ± 48.9	1,968 ± 424	5,151 ± 179	8,759 ± 598	1.70 ± 0.12	12.0 ± 1.7	0.604 ± 0.260
N	1,212 ± 128	95.5 ± 15.5	173.2 ± 30.0	108.5 ± 27.7	1,709 ± 113	4,668 ± 1,142	7,993 ± 783	1.92 ± 0.30	10.6 ± 1.5	0.684 ± 0.217
					Locus coeruleus					
C	2,494 ± 223	129.8 ± 12.8	195.7 ± 10.2	175.0 ± 25.0	1,725 ± 225	1,133 ± 50.3	2,481 ± 131	2.20 ± 0.09	8.75 ± 0.90	0.877 ± 0.102
N	2,381 ± 460	135.8 ± 18.8	330.0 ± 47.2	244.2 ± 32.3	1,959 ± 368	1,427 ± 175	2,914 ± 467	2.03 ± 0.19	7.05 ± 2.70	0.748 ± 0.050
					Formatio reticularis tegmenti					
C	778.7 ± 89.2	86.0 ± 7.7	N.D.	31.0 ± 8.4	2,374 ± 222	936 ± 122	2,227 ± 290	2.42 ± 0.18		
N	1,291 ± 509	101.0 ± 22.0	N.D.	69.5 ± 16.8†	2,461 ± 536	1,057 ± 114	2,259 ± 340	2.13 ± 0.20		

				Nucleus centralis superior						
C	602.0 ± 28.1	23.0 ± 3.7	407.3 ± 94.5	65.2 ± 19.2	1,710 ± 356	1,932 ± 534	5,859 ± 897	3.49 ± 0.39	4.58 ± 0.85	0.142 ± 0.009
N	660.2 ± 69.8	33.5 ± 7.8	348.5 ± 57.6	40.5 ± 18.3	1,829 ± 439	2,132 ± 749	6,210 ± 1,202	2.58 ± 0.78	5.28 ± 0.84	0.113 ± 0.043
				Nucleus reticularis pontis oralis						
C	852.8 ± 65.2	80.5 ± 12.6	80.8 ± 15.0	25.3 ± 4.4	2,017 ± 190	702.8 ± 71.8	2,911 ± 119	4.34 ± 0.42	28.3 ± 3.9	0.3188 ± 0.014
N	1,416 ± 178*	159.2 ± 15.3*	187.5 ± 19.8*	54.0 ± 5.6*	2,784 ± 500	980.7 ± 134.5	3,894 ± 877	3.94 ± 0.60	15.5 ± 3.4†	0.308 ± 0.069
				Nucleus reticularis pontis caudalis						
C	659.7 ± 60.4	52.2 ± 9.1	113.8 ± 11.0	9.0 ± 0.95	959 ± 175	384.5 ± 46.7	1,922 ± 253	5.14 ± 0.44	9.44 ± 2.30	0.085 ± 0.014
N	882.8 ± 117.7	77.0 ± 8.9	217.5 ± 77.6	22.2 ± 5.3†	1,165 ± 257	440.5 ± 30.1	1,869 ± 199	4.28 ± 0.47	8.89 ± 3.62	0.138 ± 0.038
				Nucleus reticularis gigantocellularis						
C	480.8 ± 52.5	32.8 ± 3.1	93.8 ± 13.6	5.3 ± 0.34	293.3 ± 32.3	586.7 ± 115.4	2,363 ± 320	4.32 ± 0.37	3.46 ± 0.65	0.060 ± 0.005
N	586.8 ± 69.2	46.8 ± 1.4*	130.8 ± 15.4	9.2 ± 2.8	325.5 ± 48.6	478.0 ± 71.6	2,183 ± 231	4.80 ± 0.80	2.55 ± 0.44	0.073 ± 0.025
				Nucleus reticularis parvicellularis						
C	805.5 ± 19.2	61.2 ± 4.5	53.7 ± 4.9	29.7 ± 4.1	340.8 ± 43.1	782.8 ± 71.0	1,474 ± 76	1.95 ± 0.17	6.43 ± 0.81	0.562 ± 0.086
N	912.0 ± 141.8	66.0 ± 13.8	78.2 ± 16.5	60.8 ± 15.0†	497.0 ± 146	707.2 ± 118.0	1,553 ± 360	2.15 ± 0.29	6.17 ± 0.81	0.777 ± 0.073

*Significanty different from corresponding control value at $P < .01$. †$P < .05$.

control Doberman pinschers were used. No pharmacological agents were administered before the study. The first signs of cataplexy appeared spontaneously in every F_1 offspring between 6 and 10 weeks of age. At 90 to 100 days of age the dogs were killed with sodium thiopental between 10 a.m. and 11 a.m. The brains were removed by rapid dissection, immediately frozen by submersion in liquid nitrogen for 1.5 minutes, placed on dry ice, and stored at −80°C until being analyzed. Micropunches of specific brain regions were taken from partially thawed slices (*7*). Norepinephrine, epinephrine, dopamine, serotonin, 5-HIAA, HVA, and DOPAC were assayed in each sample by high-performance liquid chromatography with electrochemical detection (*8*). Data for individual brain areas were subjected to multivariate analysis and Hotelling's *t*-test (Table 1) (*9*). Statistical treatment of trends was accomplished with the binomial test for proportionality (*9*).

Narcoleptic dogs had significantly higher concentrations of dopamine and its metabolite DOPAC than control animals in some of the brain regions studied ($P = .02$ and $P < .001$, respectively, binomial test). Homovanillic acid was elevated in most of the same regions, although not significantly. Norepinephrine and epinephrine were also elevated, although frequently not significantly. Serotonin was elevated in several areas as well. Table 1 summarizes the absolute concentrations measured in 20 brain areas.

The finding of elevated concentrations of DOPAC, dopamine, and HVA in narcoleptic dogs confirms our earlier observation in adult narcoleptic dogs that were not age-matched with the control animals (*10*). The elevated DOPAC is probably a result of the higher concentration of dopamine. Slower impulse flow could lead to an accumulation of dopamine in nerve endings and result in greater degradation of dopamine by mitochondrial monoamine oxidase. Increased dopamine and DOPAC could also result from enhanced re-uptake of released dopamine, in which case one would anticipate increased HVA as well as increased DOPAC. Either interpretation might account for the differences seen between the two groups.

The *O*-methylated metabolites of dopamine, HVA, and 3-methoxytyramine, have been considered to reflect extracellular metabolism or inactivation of dopamine (*11*), thus presenting a barrier to circulating dopamine in extracellular space. DOPAC, on the other hand, is formed by intraneuronal degradation (*11*). We therefore used the ratio of HVA to dopamine as an index of dopamine turnover or utilization and the ratio of DOPAC to dopamine as an index of intracellular degradation of dopamine. Similarly, the ratio of 5-HIAA to serotonin can be used as an index of serotonin utilization (*12*). The ratio of DOPAC to dopamine was consistently higher in the narcoleptic animals ($P = .007$, binomial test) and the ratio of HVA to dopamine was consistently lower ($P = .03$), suggesting that the relative turnover of dopamine was lower in the narcoleptic animals (Table 1).

We did not measure metabolites of norepinephrine and epinephrine. As a result, it was not possible to accurately assess their utilization. However, the increased concentrations of these amines suggests that their utilization is depressed in narcoleptic animals. Unlike the catecholamines, there is no consistent picture of serotonin utilization; however, there does appear to be a tendency toward lower utilization of serotonin in some regions.

The current consensus is that cataplexy, sleep paralysis, and hypnagogic hallucinations are dissociated manifestations of REM sleep (*1*). It is probable that the muscle atony of cataplexy is produced by the same central mechanisms and descending pathways as the generalized atony observed during REM sleep. Our neurochemical findings are consistent with pharmacological evidence that suggests involvement of catecholamine systems in canine and human narcolepsy and of serotonergic and cholinergic mechanisms as well. Tricyclic antidepressants such as imipramine, amitriptyline, and chlorimipramine significantly reduce the amount of cataplexy in canine (*13*) and human (*14*) narcolepsy, are effective in suppressing REM sleep (*15*), block the uptake of serotonin, norepinephrine, epinephrine, and dopamine, and have anticholinergic properties. Nisoxetine, a specific blocker of norepinephrine uptake, completely suppresses cataplexy in dogs (*13*) and has been found to suppress REM sleep (*16*).

In a study by Delashaw *et al.* (*17*), physostigmine, a cholinesterase inhibitor, and arecoline, a muscarinic cholinomimetic, significantly increased cataplexy, whereas the muscarinic blockers atropine and scopolamine significantly reduced cataplexy. Related compounds that do not effectively cross the blood-brain barrier did not significantly affect cataplexy, indicating that at least this major symptom of narcolepsy is central in origin. These results are consistent with reports that carbachol introduced

directly into pontine sites elicits cataplexy in cats (*18*) and that physostigmine elicits REM sleep in humans (*19*) and suggest that muscarinic cholinergic mechanisms are also involved in cataplexy. This cholinergic component may be involved in the decreased utilization of catecholamines and serotonin reported here.

Our results support a proposed theory linking the initiation and maintenance of REM sleep to reciprocal interactions and a critical balance between serotonergic, adrenergic, and cholinergic neuronal networks in the pontine area of the brainstem (*20, 21*). A final link in the medullary reticular formation would inhibit the discharge of extensor and flexor motoneurons via reticulospinal pathways (*22*). Our genetic studies of narcolepsy in Dobermans point to an autosomal recessive defect in a single gene (*4*). This gene may be involved in the regulation of biogenic amine metabolism or release—whether through enzymatic activity, receptor sensitivity, or uptake mechanisms.

While the results do not explain the basic defect in genetic narcolepsy, they do reflect an unequivocal deficit that will allow the formulation of testable neurochemical hypotheses. These findings are direct neurochemical evidence of a biogenic amine deficit in a genetic animal model of narcolepsy.

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Path-Guided Apparent Motion

Abstract. *A curved gray path, briefly flashed between two alternately displayed black dots, induced a compelling illusion of a single dot moving back and forth over that path. The minimum interval between dot onsets yielding this apparent motion increased not with the direct distance between the dots but, linearly, with the length of the curved path.*

In the classical phenomenon of apparent motion, two stationary visual stimuli presented in alternation and in different spatial locations (Fig. 1A) yield the illusion of a single object moving back and forth over the shortest path between them (*1, 2*). This phenomenon provides evidence for the internalization of principles of object conservation and least action (*3–5*). The brain evidently prefers the interpretation that a persisting object moved over the most direct path consistent with the available evidence rather than an interpretation that the object moved over some longer path or, worse, that one object went out of existence and a second object simultaneously materialized at another location. Moreover, the preferred interpretation tends to be automatically instantiated in the most concrete perceptual form, as an actual movement over the interpolated path. Indeed, apparent motion can be indistinguishable from real motion if the two locations are sufficiently close together (*6*).

Although apparent motion is also possible over larger spatial separations, it then tends to be less compellingly real. Furthermore, the brain's ability to achieve a concrete instantiation of motion over a longer path seems to be constrained by inherent limitations on its own rate of processing. Thus, in accordance with Korte's third law (*2*), the maintenance of good apparent motion requires, with each increase in the spatial separation between the stimuli, a corresponding increase in the delay between the onset of one stimulus and the onset of the other [called the stimulus onset asynchrony (SOA)]. Indeed, the minimum SOA yielding good apparent motion increases linearly with this distance (*5, 7, 8*). If the SOA is shorter than specified by this law, the appearance of a single stimulus moving back and forth breaks down into the appearance of two stimuli blinking on and off independently.

Discrimination between real and apparent motion is presumably based on whether or not sensory receptors along the retinal path corresponding to the experienced motion are physically stimulated. We conjectured that the brain interprets such intermediate sensory events as the "blurred streak of motion" over the path even when those intermediate events occur so rapidly that their temporal order is not resolved. This conjecture led to our exploration of two specific hypotheses.

The first is that the brief presentation of a faint stationary connecting band between two alternately presented stimuli (Fig. 1B) should stimulate the relevant intermediate receptors and, despite the absence of temporal sequencing along the path, provide a good imitation of the blur of rapid motion. In support of this hypothesis, when we flashed a low-