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Distribution of monoamines in human brain: evidence for neurochemical heterogeneity in subcortical as well as in cortical areas

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Norepinephrine, epinephrine, dopamine, serotonin and their major metabolites were measured by high-performance liquid chromatography with electrochemical detection in 49 regions of the human brain. The regional distribution of the different monoamines in the subcortical areas was similar to previous reports. We report here the distribution pattern of the 4 monoamines observed in the cerebral cortex. Regional differences in concentration were observed for norepinephrine, epinephrine and serotonin, with high concentrations in the frontal and parietal regions. However, no regional difference in dopamine concentrations was detected. The possible role of norepinephrine and serotonin as conventional transmitters, and of dopamine and epinephrine as neurotransmission modulators is discussed.

INTRODUCTION

Postmortem distribution studies remain of particular relevance in terms of understanding clinical manifestations and the underlying pathological process of both psychiatric[39] and neurological disorders[12,40,46]. Regional distribution of biogenic amines and of their major metabolites has been widely studied in laboratory animals[5,31,43–45] and in man[2,22,23,26,30]. Especially in postmortem studies on human brain, only a limited number of monoamines and their metabolites are analyzed, making interpretations of the interrelationship between catecholamines, serotonin and their respective metabolites difficult. Therefore we have undertaken a detailed neurochemical analysis of various nuclei on postmortem human brain. The aim of this study was to quantify the catecholamines norepinephrine (NE), epinephrine (E), dopamine (DA), serotonin (5-HT) and their respective metabolites 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) in 49 areas of the human brain, including cortex, cerebellum, basal ganglia and brainstem areas. The interrelationship between the different monoamines and their metabolites and their possible function in the cortex is discussed.

MATERIALS AND METHODS

Brain dissection

Six human brains were obtained within 6 h after death. Right-handed patients (mean age 68.4 ± 8.6 years) without neuropsychiatric antecedents and who had not been treated with drugs possibly interfering with the catabolism of the biogenic amines, were selected.

The total central nervous system (CNS), including the hemispheres, the cerebellum, the brainstem and the upper part of the cervical medulla was removed from the skull and immediately stored at −24 °C in a sealed box. Four hours prior to dissection the frozen brains were transferred to 4 °C to allow section. In a first step small fragments, weighing 150–200 mg, were dissected from the cerebral cortex. The dissection was based on the topographical landmarks according to a neuroanatomical handbook[36]. Secondly the subcortical areas were identified on coronal sections of 5 mm thickness and tissue samples weighing 10–50 mg were isolated. All samples were collected in separate plastic tubes and stored again at −24 °C till quantitative analysis. Selection of the areas (see Table I) was made on basis of their neurological functional interest. 'Broca area' or motor speech area is defined as the pars triangularis of the gyrus frontalis superior; 'Wernicke area' or sensory speech area relates to the gyrus supramarginalis and posterior part of the gyrus temporalis superior and 'visual cortex' is located around the sulcus calcarina at the inner part of the occipital lobe. The formatio reticularis mesencephali was defined as the area located medioventrally to the aquaduct on transverse section 5 mm below the level of the colliculus inferior, and included the raphe nuclei (nucleus centralis superior, the posterior part of the nucleus raphe dorsalis and the nucleus tegmentalis dorsalis). The nucleus raphe magnus was dissected on transverse section at the level of the nervus glossopharyngeus, medially to the superior part of the oliva inferior.

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TABLE I

Cortical levels of 5-HT and 5-HIAA

Mean values ± S.D. in 6 human brains (pmol/g wet tissue).

Cortical areas	*5-HT*		*5-HIAA*	
	Left	*Right*	*Left*	*Right*
G. precentralis	1683.9 ± 127.7	1636.1 ± 119.0	1006.9 ± 117.1	1286.5 ± 164.9
G. postcentralis	1695.1 ± 133.7	1635.6 ± 111.9	1030.9 ± 142.3	1255.4 ± 112.0
G. front. sup.	1791.6 ± 117.6	1858.8 ± 121.6	1025.0 ± 167.5	1126.8 ± 184.4
G. temp. sup.	1320.3 ± 163.5	1208.8 ± 133.4	1120.1 ± 158.9	1160.9 ± 134.4
Visual cortex	1407.6 ± 91.5	1423.1 ± 103.6	1126.2 ± 194.6	1183.4 ± 229.5
G. cinguli	1567.9 ± 82.0	1372.1 ± 162.3	1033.4 ± 176.5	1305.2 ± 204.3
G. parahippocampi	1475.8 ± 125.7	1402.1 ± 132.9	1135.7 ± 218.6	1421.8 ± 148.9
G. dentatus	1347.2 ± 102.3	1268.6 ± 95.3	1239.4 ± 203.4	1291.5 ± 192.3
Broca area	1721.9 ± 145.9	1813.1 ± 159.3	1076.7 ± 150.3	1417.5 ± 190.6
Wernicke area	1275.7 ± 135.8	1346.4 ± 120.3	1142.6 ± 189.4	1292.8 ± 135.0
G. long. insulae	1351.3 ± 186.9	1038.7 ± 164.6	1331.4 ± 183.8	1328.9 ± 140.6

Neurochemical analysis

The monoamines DA, NE, E, 5-HT and their major metabolites DOPAC, HVA, MHPG and 5-HIAA were determined by a combined extraction procedure and high-performance liquid chromatography with electrochemical detection (HPLC-ECD)[18]. The frozen brain tissue was weighed and homogenized in a Braun Potter grinder with a Teflon pestle in 1 ml 1 M HCl containing 1 mM $Na_2S_2O_5$ and 0.1 mM Na_2EDTA and 0.2 ml of a 0.5 M acetic acid solution containing 1.5 10^{-9} M of the internal standards isohomovanillic acid, dihydroxybenzylamine and 5-hydroxy-*N*-methyltryptamine. After centrifugation the supernatant was extracted in ethylacetate at pH 4.0 to isolate the neutral and acidic metabolites MHPG, DOPAC, HVA, 5-HIAA, followed by extraction into heptane in the presence of diphenylborate of the catecholamines DA, NE and E with tetraoctylammonium bromide as counter-ion. The residual supernatant was subsequently injected into the HPLC system for quantitation of 5-HT.

The HPLC system consisted of a Gilson 302 pump (Gilson Med. Electr., France) equipped with a 100 µl Rheodyne injection loop (Rheodyne, CA, U.S.A.). The Gilson 141 amperometric detector was equipped with a 4 µl electrochemical cell fitted with a glass-carbon electrode and an Ag/AgCl reference electrode. Separation of the monoamines and metabolites was performed on a Ultrasphere ODS-column (Altex, Beckman, U.S.A.; 250 × 4.6 mm, particle size 5 µm). The mobile phase consisted of an acetate-citrate buffer containing 1 mM 1-octanesulphonic acid. The flow rate was set at 1 ml/min, and the detector potential was +0.75 V vs the Ag/AgCl reference electrode, sensitivity 20 nA full scale. The limit of quantification of the assay of each amine and metabolite was approximately 10 pmol/g brain tissue.

RESULTS

Influence of age and postmortem stability

Monoamine content in brain tissue has been reported to be age-dependent[2,17]. However, no significant influence of age on monoamine concentrations and their metabolites was demonstrated for the 6 brains we analyzed (multiple regression analysis).

Amine and metabolite concentrations

The concentrations of DA, NE, E, DOPAC, HVA and MHPG in the cortical areas of the same human brains have already been published previously[19] and are not extensively reported here. The data of 5-HT and 5-HIAA in the same cortical areas (Table I) and of DA, NE, E, 5-HT, DOPAC, HVA, MHPG and 5-HIAA in several subcortical regions are now presented (see Table II). The concentrations obtained for all the compounds under study in the cortical and subcortical regions were comparable to those previously published for postmortem human brain[2,12,23,26]. E was up to 50% higher in the nucleus anterior of the thalamus and in the striatum than the concentrations reported in the few papers dealing with this topic[29,30].

Regional distribution in the cortex. Striking and consistent differences were observed in the regional 5-HT concentrations in the neocortical and archicortical areas. Performing two-way analysis of variance (ANOVA) at the 0.05 level of significance, no interindividual differences could be demonstrated, but a significant locoregional difference was found for 5-HT. Using ANOVA, followed by the Student–Newman–Keuls test (SNK)[37] (Table III) it was possible to detect homogeneous subsets at a constant level of significance ($\alpha = 0.05$). Analysis of the 5-HT distribution within the cortex revealed that the gyrus frontalis superior, the pre- and postcentral gyrus and the motor speech area displayed significant higher concentrations than the other cortical areas examined. No significant regional differences were observed for 5-HIAA in the cortical areas we studied. In addition, there were no significant differences in 5-HT and 5-HIAA concentrations between the two hemispheres (Wilcoxon matched-paired test).

Regional distribution in the subcortical areas. The concentration of NE was clearly highest in the hypothalamus (periventricular area), followed by the mesencephalic periaqueductal gray (in which the formatio reticularis mesencephali is located), the nucleus raphe

TABLE II

Brain levels of (A) DA, DOPAC and HVA, (B) NE, E and MHPG and (C) 5-HT and 5-HIAA in the subcortical areas

Mean values ± S.D. in 6 human brains. All data are expressed in pmol/g wet tissue.

(A)	*DA*		*DOPAC*		*HVA*	
	Left	*Right*	*Left*	*Right*	*Left*	*Right*
Thalamus (nu. ant.)	257.5 ± 47.6	308.2 ± 56.0	212.6 ± 49.5	225.4 ± 65.2	4022.8 ± 1121.9	3615.0 ± 992.7
Basal ganglia						
Nu. accumbens	6129.1 ± 2844.9	6809.4 ± 1801.4	3585.2 ± 1234.7	4039.2 ± 1837.0	27416.1 ± 11073.6	27424.3 ± 14557.3
Nu. caudatus	6799.3 ± 3455.4	7066.6 ± 4435.4	5876.6 ± 3450.6	5999.3 ± 2314.7	39046.5 ± 16933.4	29703.9 ± 13066.0
Putamen	7604.0 ± 2943.0	7160.9 ± 4435.4	5977.6 ± 4283.5	5953.5 ± 4250.4	50740.5 ± 21807.6	53167.3 ± 28377.0
Globus pallidum (lat.)	1024.7 ± 226.9	932.7 ± 187.8	1513.9 ± 352.6	1475.2 ± 364.3	28924.2 ± 6075.0	28433.2 ± 7452.2
Globus pallidum (med.)	1310.1 ± 322.6	866.4 ± 195.2	1583.3 ± 383.8	1277.1 ± 1051.5	28949.5 ± 6389.6	24503.7 ± 6388.9
Cerebellum						
Cortex-hemisphere	65.2 ± 39.0		60.3 ± 21.6		967.3 ± 300.4	
Vermis	45.4 ± 12.1		79.1 ± 24.9		1096.6 ± 51.6	
Hippocampus	71.8 ± 11.0		304.7 ± 80.6		5472.7 ± 1009.6	
Nu. amygdalis	132.2 ± 49.9		256.3 ± 32.6		2246.5 ± 664.5	
Corp. genic. lat.	258.3 ± 170.3		184.9 ± 157.3		2187.9 ± 308.0	
Hypothalamus (periventric.)	1190.9 ± 878.7		1595.6 ± 585.0		10474.5 ± 6270.4	
Corp. mammilare	167.6 ± 74.6		1033.7 ± 139.8		5891.0 ± 392.2	
Collic. sup.	177.0 ± 118.8		275.5 ± 128.7		5568.1 ± 440.4	
Collic. inf.	215.9 ± 134.5		482.2 ± 100.5		4830.9 ± 613.7	
Subst. nigra (p. comp.)	2501.8 ± 428.8		2757.5 ± 856.6		28079.0 ± 9013.6	
Nu. ruber	410.8 ± 79.1		673.5 ± 131.8		14957.4 ± 2721.8	
Oliva inferior	183.8 ± 128.5		165.0 ± 53.7		3005.9 ± 1204.5	
Locus coeruleus	369.7 ± 137.5		1660.7 ± 933.9		12314.0 ± 1566.5	
Form. retic. mesenceph.	892.4 ± 206.0		1924.7 ± 2249.6		23359.4 ± 1728.2	
Nu. raphe magnus	223.4 ± 29.5		777.6 ± 297.7		11577.2 ± 3879.3	

(B)	*NE*		*E*		*MHPG*	
	Left	*Right*	*Left*	*Right*	*Left*	*Right*
Thalamus (nu. ant.)	1424.7 ± 316.3	1511.8 ± 360.0	41.9 ± 7.2	46.9 ± 11.5	340.1 ± 111.2	330.4 ± 96.0
Basal ganglia						
Nu. accumbens	86.8 ± 29.2	68.4 ± 36.8	53.6 ± 12.4	54.4 ± 16.9	306.3 ± 68.8	274.5 ± 32.7
Nu. caudatus	99.5 ± 29.7	92.1 ± 26.0	55.5 ± 10.2	54.7 ± 12.8	272.9 ± 49.8	327.3 ± 99.7
Putamen	106.6 ± 20.9	127.5 ± 39.6	54.1 ± 13.4	45.3 ± 12.6	301.9 ± 59.5	284.2 ± 45.3
Globus pallidum (lat.)	251.7 ± 55.7	228.6 ± 41.0	124.6 ± 36.1	120.7 ± 25.2	287.2 ± 30.9	293.8 ± 103.3
Globus pallidum (med.)	260.3 ± 86.1	189.8 ± 52.6	123.4 ± 38.7	135.3 ± 26.8	277.0 ± 68.0	252.9 ± 67.2
Cerebellum						
Cortex-hemisphere	110.6 ± 36.7		27.1 ± 6.2		298.1 ± 61.1	
Vermis	254.3 ± 114.0		40.9 ± 16.2		291.3 ± 78.6	
Hippocampus	693.7 ± 65.6		72.2 ± 18.1		328.5 ± 59.6	
Nu. amygdalis	120.6 ± 22.0		225.1 ± 8.8		220.6 ± 47.9	
Corp. genic. lat.	101.9 ± 13.6		59.5 ± 13.8		302.0 ± 73.5	
Hypothalamus (periventric.)	5554.2 ± 1639.9		1531.7 ± 828.3		842.0 ± 158.0	
Corp. mammilare	1846.8 ± 412.1		126.3 ± 78.4		255.2 ± 43.9	
Collic. sup.	1186.9 ± 174.0		103.7 ± 27.3		454.6 ± 63.1	
Collic. inf.	1562.9 ± 146.3		130.1 ± 68.3		597.6 ± 72.0	
Subst. nigra (p. comp.)	649.7 ± 150.0		172.5 ± 38.9		278.6 ± 50.4	
Nu. ruber	1030.0 ± 283.8		63.5 ± 29.7		239.1 ± 35.5	
Oliva inferior	512.0 ± 162.4		54.0 ± 14.5		600.6 ± 43.3	
Locus coeruleus	2901.8 ± 807.9		1443.7 ± 577.4		2332.3 ± 114.3	
Form. retic. mesenceph.	4950.9 ± 528.8		78.2 ± 31.0		1568.1 ± 774.6	
Nu. raphe magnus	1224.3 ± 236.8		105.1 ± 51.1		914.0 ± 368.3	

(*continued*)

TABLE II (*continued*)

(C)	5-HT		5-HIAA	
	Left	*Right*	*Left*	*Right*
Thalamus (nu. ant.)	2073.5 ± 197.0	1895.2 ± 154.7	1767.8 ± 219.1	2099.0 ± 293.1
Basal ganglia				
Nu. accumbens	1117.4 ± 175.6	1226.1 ± 122.2	1287.6 ± 433.2	1997.9 ± 453.4
Nu. caudatus	3292.5 ± 655.2	3792.9 ± 784.0	1598.7 ± 471.6	1337.2 ± 241.2
Putamen	1966.5 ± 287.1	2142.5 ± 393.8	2049.9 ± 216.4	1777.5 ± 386.8
Globus pallidum (lat.)	3068.8 ± 710.8	2956.9 ± 787.4	2015.9 ± 262.1	1596.3 ± 299.6
Globus pallidum (med.)	2564.6 ± 815.1	3271.4 ± 641.4	1965.7 ± 386.6	1956.8 ± 308.4
Cerebellum				
Cortex-hemisphere	1527.2 ± 106.6		827.4 ± 286.7	
Vermis	1663.3 ± 95.9		1325.6 ± 264.8	
Hippocampus	2511.7 ± 481.6		1539.2 ± 231.1	
Nu. amygdalis	3796.7 ± 293.3		1819.1 ± 165.2	
Corp. genic. lat.	1035.3 ± 72.1		820.2 ± 220.4	
Hypothalamus (periventric.)	3946.8 ± 222.7		4329.1 ± 365.7	
Corp. mammilare	1611.4 ± 129.8		2324.4 ± 259.8	
Collic. sup.	1101.5 ± 120.4		3654.9 ± 592.1	
Collic. inf.	1632.2 ± 111.1		2790.8 ± 485.7	
Subst. nigra (p. comp.)	4535.7 ± 387.6		6512.6 ± 1166.6	
Nu. ruber	3183.3 ± 193.9		9954.5 ± 1993.9	
Oliva inferior	5319.4 ± 443.1		12077.7 ± 2659.9	
Locus coeruleus	7793.0 ± 549.1		71423.0 ± 7377.1	
Form. retic. mesenceph.	6791.1 ± 679.1		84600.3 ± 9215.3	
Nu. raphe magnus	3181.3 ± 331.1		75630.1 ± 6321.7	

magnus, the locus coeruleus, the corpora mammilare, the nucleus anterior of the thalamus and the colliculus superior and inferior. The striatum contained low NE levels, as well as the globus pallidum and the cerebellum. In the hippocampus, the substantia nigra and the oliva inferior intermediary concentrations of NE were measured. E levels were highest in the hypothalamus, followed by the locus coeruleus. In all the other subcortical areas studied E was more equally distributed. The concentrations of MHPG were very elevated in the hypothalamus (periventricular area), less high in successively the mesencephalic periaqueductal gray, the nucleus raphe magnus area, the corpora mammilare, the nucleus anterior of the thalamus, the colliculus superior and inferior, and the locus coeruleus. In the other subcortical areas studied, MHPG was more homogeneously distributed. DA, DOPAC and HVA concentrations were highest in the basal ganglia, especially in the striatum (putamen and nucleus caudatus-accumbens), followed by the hypothalamus, substantia nigra and mesencephalic reticular formation. Low DA and metabolite concentrations were found in the cerebellum, the thalamus (nucleus anterior), hippocampus, nucleus amygdalis, colliculi, oliva inferior and the nucleus raphe magnus. The highest 5-HT concentrations were detected in the hypothalamus, nucleus amygdalis, substantia nigra, oliva inferior, locus coeruleus and in the raphe areas (formatio reticularis mesencephali and nucleus raphe dorsalis). The hippocampus, the nucleus anterior of the thalamus and the colliculi contained low amounts of 5-HT. The 5-HIAA measured in the different subcortical areas correlated well with the 5-HT concentrations.

TABLE III

Student–Newman–Keuls procedure performed for 5-HT and 5-HIAA content in different neocortical areas

It was possible to detect homogeneous subsets with high and low levels in both compounds studied at a constant level of significance ($\alpha = 0.05$).

	Subset 1 (high levels)	*Subset 2 (low levels)*
5-HT	G. frontalis sup.	G. temporalis sup.
	G. precentralis	Visual cortex
	G. postcentralis	G. cinguli
	Motor speech area	G. parahippocampi
		G. dentatus
		Sensory speech area
		G. longus insulae
5-HIAA	homogeneous distribution	

DISCUSSION

No detailed investigation of postmortem stability was carried out prior to this work, since such information has

been reported elsewhere[26]. Based on this review paper we are confident that, provided thawing did not occur between initial freezing at –24 °C and homogenization, there was no significant loss of amines nor metabolites. No further correlations between the concentrations of any compound measured and time elapsed between death, necropsy and freezing was calculated since all these factors are comparable in all cases examined.

The subcortical distribution of catecholamines, serotonin and their major metabolites found in our study was very similar to previous reports dealing with man[23,27] and other species: rat[42,45], dog[31], monkey[5,6]. As expected, high concentrations of DA and its metabolites DOPAC and HVA were found in the striatum, globus pallidum, hypothalamus (periventricular area) and substantia nigra. Areas rich in serotonin were the hypothalamus, the amygdala, the substantia nigra, nucleus ruber, oliva inferior, locus coeruleus and raphe nuclei. In the subcortical areas NE and E exhibited a different pattern. High NE and E levels were observed in the hypothalamus (pars ventricularis) and locus coeruleus. In all the other subcortical localizations examined E concentrations were low and homogeneously distributed. This was, however, not the case for NE which was present in high amounts in the hippocampus, the colliculi, the substantia nigra, nucleus ruber and reticular formations. This different regional NE and E ratio points towards the existence of a distinct functional adrenergic neurotransmission in human brain, distinct from the well-known noradrenergic system.

The possible role of E as a neurotransmitter in human brain has only recently been questioned[41]. Neuroimmunocytochemical studies concerning specific adrenergic nerve terminals remain scarce. Different authors have demonstrated a phenylethanolamine-*N*-methyltransferase (PNMT) activity in human neocortex, in quantities comparable to that in the hypothalamus[24,34]. Most data are based on histochemical studies with PNMT-immunoreactivity in the rat[20]. PNMT-positive cells, termed C1 and C2, are located at the rostral end of the A1 and A2 noradrenergic cell groups. E nerve endings had a considerably more restricted distribution than those of the other monoamines. They extended from the forebrain to the spinal cord, and were mostly concentrated along the ventricular system. To our knowledge no PNMT-positive terminals have been described in the cerebral cortex yet.

At the level of the cerebral cortex a different locoregional distribution was observed for NE, E[19] and 5-HT (this report). DA was homogeneously distributed over the areas of the cerebral cortex we examined[19]. NE and 5-HT concentrations were high in the frontal and parietal areas and decreased along a fronto-occipital axis. These data are in agreement with observations made in the rat[28]. 5-HT fibers projecting to the cortex in man arise almost exclusively in the cells of the nucleus centralis superior and nucleus raphe dorsalis[4]. Most of the fibers reach all layers of the cortex via the medial forebrain bundle. Serotonergic synapses in the cortex are morphologically comparable to noradrenergic fibers[33]. Noradrenergic fibers from the locus coeruleus ascend to all layers of the cortex, but considerable differences in brain areas and among species were found regarding the layers in which they are most concentrated[33]. NE was found in the cortex in conventional synapses, predominantly with dendritic spines. Their morphology suggests an excitatory effect. DA-containing afferents reaching the cerebral cortex arose mainly from cells of the ventral tegmental area of the midbrain in the rat[16] and in the human[21]. The axons reached the neocortex at the frontal pole and along the medial surface of the hemisphere by following a route similar to that of the major group of cortical noradrenergic afferent fibers. In the cortex DA fibers were till recently only described in the prefrontal cortex, the cingulate area, the entorhinal cortex and adjacent areas. A more recent publication describes an expansion of the DA innervation to the whole cortex with a peak of highest density in the motor areas[15].

Our neurochemical findings are in agreement with morphological data since we found a widespread distribution in DA concentrations in all the cortical areas examined. DA neurons apparently terminated primarily in deep cortical layers. Interestingly dopaminergic synapses were till now not yet described in any area of the cerebral cortex[32]. Our observation might point to a non-conventional synaptic morphology of DA terminals in the cortex. An alternative explanation is that DA may be released into the general extracellular space of deep cortical areas, resulting in a different, more diffuse effect on neurotransmission. Dopaminergic receptor studies in human cerebral cortex failed to demonstrate the presence of the D_2-receptor with ligand binding in membrane preparations[9,25], autoradiography[7] and PET[11]. In contrast to the absence of D_2 receptors, moderate levels of D_1 receptors were measured in all parts of the cerebral cortex using [^{3}H]SCH 23390 binding[8,10]. These data correlate well with our findings suggesting that the human cerebral cortex receives a much more widespread DA input than was previously thought. The functional role of the D_1-receptor in the cerebral cortex is till now not completely understood. D_1-agonists administered to rodents stimulate behavioral arousal and induce desynchronization of the electroencephalogram[38]. The D_1 antagonist SCH 23390, on the other hand, may exhibit antipsychotic activity and a general reduction in locomotor activity and rearing in the rat[35]. High levels of levodopa administered to parkinsonian patients in whom

there is an up-regulation of DA receptors due to a deficiency of DA, can induce impairment of cognitive functioning and psychosis. All these data support the hypothesis that DA has a neurochemical action in the human cerebral cortex.

Less data are available about the exact significance of the presence and locoregional difference of E in the CNS, especially within the cerebral cortex. Since adrenergic fibers are limited to the periventricular area, attention has been focused mainly on their influence on neuroendocrine regulation, blood pressure regulation and stress. Although a fair number of experimental studies have been published[1,13,14], it has till today not been possible to reach a consensus concerning the exact role of E as a neurotransmitter. Partial overlap between E and NE neurons and their similarity for adrenergic receptor binding, lack of pharmacological specificity for receptor binding studies and PNMT inhibition, makes a further interpretation difficult[3]. Since E and NE neurons have the same embryological origin, and since immunohistochemically E and NE neurons are coupled, it is not surprising that those neurons act synergically or exhibit similar functions. In the cerebral cortex E neurons possibly influence the state of activity of NE neurons. E may act, in analogy with DA, as a modulator of neurotransmission. The reason why the geographical localization as well as the concentration of NE and E in the cerebral cortex is different remains unclear.

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