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Distribution of 5-Hydroxytryptamine and 5-Hydroxyindoleacetic Acid in Human Brain in Relation to Age, Drug Influence, Agonal Status and Circadian Variation

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With 4 Figures

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Summary

The post-mortem brain concentrations of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were determined in 16 parts of the brain from patients with no history of neurologic, psychiatric or metabolic illness. The causes of death were either ischemic heart disease, infections disease, cancer or accidents. Forty-two men with a mean age of 57 years (range 18—95 years) and 19 women with a mean age of 62 years (range 23—79 years) were included. The influence of several factors were studied: brain weight, time between death and autopsy, storage time before chemical analysis, age, sex, agonal status, cerebral arteriosclerosis, cancer, opiate treatment and time of death during the day.

Most correlations between the 5-HT concentrations in different brain parts were positive, the strongest correlations in the basal ganglia and the limbic system. No consistent pattern of age-related 5-HT changes were found. The females had significantly higher 5-HIAA concentrations in the cortex of the gyrus hippocampus. Final hypoxia seemed to decrease 5-HT concentrations. Opiate treatment reduced 5-HT and increased 5-HIAA concentrations. A marked circadian variation of 5-HT was found, most pronounced in the hypothalamus, the limbic system and some neocortical areas.

Key words: Human brain, 5-hydroxytryptamine, 5-hydroxyindoleacetic acid, normal aging, opiate treatment, circadian variation.

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Introduction

The highest amounts of 5-hydroxytryptamine (5-HT) in ma
are found in the enterochromaffin cells of the intestinal tract a
pineal gland. It is estimated that 90 % of the total 5-HT in the
is contained in the gastrointestinal tract, 8—10 % in the pla
whereas only 1—2 % is found in the central nervous system (
However, there is considerable evidence to suggest that 5-HT ac
neurotransmitter in the CNS. 5-HT is found only within s
tracts in the CNS, that can be visualized by fluorescence m
(*Fuxe* and *Jonsson*, 1974). Ascending pathways start in the
nuclei of the midbrain and pons and terminate in the hypotha
the cortex, especially the frontal and parietal cortical regions, an
diencephalon. Descending pathways start in the medulla oblo
and extend into the spinal cord. The cerebellum is more v
innervated. When 5-HT cell bodies are stimulated the 5-HT
centration in the ventricular fluid and 5-hydroxyindole
acid (5-HIAA) in terminal rich regions both increase (*Ashke*
1973).

Drugs which interact with 5-HT change mood and beha
(*Barchas* and *Usdin*, 1972). Changes in 5-HT metabolism seem
of importance in some psychiatric and neurological disorders.
mortem investigations have established the presence of distu
5-HT metabolism in Parkinson's disease (*Bernheimer*, 1961)
Huntington's chorea (*Mattson et al.*, 1974). In affective diso
changes in 5-HT metabolism have been demonstrated (*Shaw*, 1
Bourne, 1968; *Pare*, 1969; *Birkmayer* and *Riederer*, 1975). In
age, lowered 5-HT concentrations in various brain regions have
found to be associated with dementia (*Adolfsson et al.*, 1979
chronic schizophrenias there also seem to be a disorder in 5
metabolism (*Winblad*, 1979). Synthesis of 5-HT seems to be incr
in metabolic coma of various origin (*Jellinger et al.*, 1977; *L.*
et al., 1978).

Seasonal and circadian variations of 5-HT concentration
been found in the brains of experimental animals (*Montague*, 1
Scapagnini and *Preciosi*, 1972; *Reis et al.*, 1968) and in hum
platelets (*Wirz-Justice* and *Pühringer*, 1978). To our knowledge, th
is only one report of circadian and seasonal variation in 5-HT fr
different brain regions investigated post-mortem in man (*Carls*
et al., 1980 a).

The present study reports on factors that might influence
measured levels of 5-HT and its deaminated metabolite 5-HIAA
the normal human brain.

Material and Methods

ıe brains of 61 patients were collected at autopsy (42 males with a ıge of 57 years, range 18—95 years, and 19 females with a mean age years, range 23—79 years). The causes of death were cardiovascular, ant and infectious diseases or accidents. Patients who had histories rological, psychiatric or metabolic disorders were not included in ıdy.

ıe corpses were brought to the refrigerator room 2—4 hours after and kept at +4 °C until the autopsy was performed. The date and f day when death occurred was noted. The times that elapsed between and autopsy and between autopsy and freezing of the samples to C were recorded as well as the time the samples had been stored an determination of monoamines and monoamine metabolites. The degree)lc eriosclerosis in the basal vessels was estimated on a rating scale with w tages (0—3), according to a coding system adopted by the World [T ation of Neurology (1959). The weight of the brain, the presence of)le r and the degree of hypoxia were recorded. A hypoxia rating scale)k ps; 0—3) was used to describe the degree of hypoxia, judged by the rence of pneumonia, pulmonary embolism, ephysema and pulmonary sis, pulmonary oedema and signs of asphyxia in peripheral organs. tment with opiates and neuroleptic drugs during the last weeks was tered.

5-HT and 5-HIAA concentrations were determined in 16 well-defined ons of the brain. The preparation of brain nuclei or brain parts was ied out macroscopically in the autopsy room (*Adolfsson et al.*, 1979). brain parts were placed in air tight plastic vials and immediately frozen -20 °C. 5-HT was determined according to the method of *Magnusson Andén* (1967) and 5-HIAA according to the method of *Jansson* and *nder* (1970). In part of this material the brain tissue was analyzed for r transmitters as well, and therefore, due to lack of material 5-HT d be determined in only 14—44 brains and 5-HIAA in only 16 to brains, depending on the part of the brain analyzed.

Pearson's r was calculated to study the relationship between concentra- ns in various brain regions. Student's t-test was used for analysis of group ferences.

Results

Distribution of 5-HT and 5-HIAA in the Human Brain

The distribution of 5-HT and 5-HIAA in various parts of the rain is shown in Table 1. The highest values of 5-HT were found in ıe mesencephalon, while the putamen, globus pallidus and medulla longata showed somewhat lower concentrations and the neocortex ıe lowest values. The limbic cortical structures showed higher

concentrations than the neocortex and the different neocortical areas did not differ from each other.

Table 1. *Mean and standard deviation values of the concentration of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) (μg/g wet tissue) in various parts of the brain. n indicates the number of cases*

	5-HT			5-HIAA		
Part of brain	m	S.D.	n	m	S.D.	n
Hypothalamus	0.12	±0.07	20	1.31	±0.58	20
Caudatus	0.12	±0.05	40	0.55	±0.20	40
Putamen	0.17	±0.06	40	1.00	±0.35	40
Globus pallidus	0.18	±0.08	20	1.60	±0.53	20
Thalamus	0.13	±0.05	44	1.05	±0.27	45
Mesencephalon	0.37	±0.18	25	3.50	±1.15	45
Pons	0.05	±0.03	23	0.86	±0.43	25
Medulla oblongata	0.17	±0.06	24	1.39	±0.54	40
Hippocampus	0.05	±0.03	20	0.31	±0.14	25
Cortex lobus frontalis	0.01	±0.02	35	0.13	±0.12	41
Cortex lobus occipitalis	0.01	±0.01	35	0.17	±0.09	36
Cortex gyrus cinguli	0.03	±0.03	39	0.29	±0.11	36
Cortex gyrus hippocampus	0.03	±0.03	34	0.24	±0.10	35
Cortex lobus parietalis	0.02	±0.02	15	0.19	±0.22	16
Cortex lobus temporalis	0.01	±0.01	16	0.17	±0.15	16
Cortex cerebellum	0.01	±0.01	14	0.04	±0.02	16

The distribution of 5-HIAA corresponds largely to that of 5-HT. The mesencephalon showed the highest concentrations and the globus pallidus, medulla oblongata and hypothalamus were also rich in 5-HIAA. The lowest values were found in the cerebellum and neocortex. Limbic cortical structures showed higher values of 5-HIAA than the neocortex (Table 1).

The correlation of 5-HT values between different brain parts was positive in 83 of 93 computable correlations and 33 of these were significant ($p < 0.05$, Table 2). Most of these significant positive correlations were found in the basal ganglia and the limbic structures. For 5-HIAA (Table 3) all the correlations except one were positive. Seventy-five out of 93 correlations showed a significant positive correlation ($p < 0.05$). The most pronounced correlations were found between the same brain parts as for 5-HT. Thus, high levels of 5-HT and 5-HIAA in one area of the brain match high levels in other areas.

The correlations between 5-HT and 5-HIAA values in the same brain part were positive in 12 of the 16 analyzed parts but only significant in 3 out of 16. The four negative correlations were in cortical regions and the cerebellum.

Influence of Brain Weight

The brain weight seems to influence both 5-HT and 5-HIAA concentrations. There is a negative correlation between 5-HT and brain weight in 12 of he 16 investigated brain parts, four being significant, namely the hypothalamus, caudatus, mesencephalon and medulla oblongata. For 5-HIAA all the analyses except one show a negative correlation with the brain weight, at a significant level in no less than nine brain parts.

Influence of Time Between Death and Autopsy

The time between death and autopsy varied from 4.5—148 hours. There was a weak negative correlation between the time variable and 5-HT concentration in the various brain parts. For 5-HIAA the negative correlation was much stronger for the time elapsed between death and autopsy. A significant decrease of 5-HIAA concentrations was found in the hypothalamus, caudatus, putamen, thalamus, mesencephalon, pons and medulla oblongata. An interesting but confusing finding is that all the cortical regions investigated show a positive correlation between 5-HIAA concentrations and time between death and autopsy. Three of these are significant—the parietal, temporal and cerebellar cortex.

Influence of Time Between Autopsy and Freezing of the Samples

The time between autopsy and freezing of the samples up to 30 min does not seem to influence our values.

Influence of Storage Time for Frozen Samples

The samples were stored frozen at —20 °C for 13—290 days before determination of 5-HT and 5-HIAA. No correlation between 5-HT and storage time was found. Ten of the 16 analyses between 5-HIAA and storage time were positive with four on a significant level.

Influence of Age

5-HT concentrations showed 9 positive and 7 negative correlations to age in the 16 investigated brain parts, two being significantly positive: the mesencephalon and medulla oblongata, and two significantly negative: the pallidus and the cortex of the gyrus hippocampus. 5-HIAA concentrations showed 11 positive and 5 negative correlations with only one being significant positive (the hippocampus) (Table 4).

Table 2. *Product-moment correlations between the concentration of 5-hydroxytryptamine (5-HT) (μg/g wet tissue) in different parts of the brain. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$. Number of cases in brackets*

	Hypothalamus	Nucleus caudatus	Putamen	Globus pallidus	Thalamus	Mesencephalon	Pons	Medulla oblongata	Hippocampus	Cortex lobus frontalis	Cortex lobus occipitalis	Cortex gyrus cinguli	Cortex gyrus hippocampus	Cortex lobus parietalis	Cortex lobus temporalis	Cortex cerebellum
Hypothalamus		0.35 (20)	0.16 (20)	0.01 (20)	0.29 (19)	0.28 (20)	0.24 (19)	0.46* (20)	0.29 (20)	0.08 (20)	0.17 (19)	−0.22 (19)	0.06 (19)			
Nucleus caudatus			0.50*** (40)	0.28 (20)	0.47*** (20)	0.38* (20)	0.19 (19)	0.24 (20)	0.43* (20)	0.33 (20)	0.38 (19)	0.60** (19)	0.58** (19)			
Putamen				0.15 (20)	0.40** (39)	0.28 (20)	0.17 (19)	0.23 (20)	0.45* (20)	−0.18 (20)	0.20 (19)	0.58** (19)	0.64** (19)			
Globus pallidus					0.19 (19)	0.02 (20)	0.43* (19)	−0.11 (20)	0.04 (20)	0.36 (20)	0.12 (19)	0.21 (19)	0.46* (19)			
Thalamus						0.45* (24)	0.05 (22)	0.07 (23)	0.37 (19)	0.13 (19)	0.08 (18)	0.43* (23)	0.50* (19)			
Mesencephalon							0.17 (23)	0.50** (24)	0.64*** (20)	−0.02 (20)	0.16 (19)	0.52** (23)	0.33 (19)			
Pons								0.14 (23)	0.12 (19)	0.18 (19)	0.19 (18)	0.17 (22)	0.14 (18)			
Medulla oblongata									0.43* (20)	−0.18 (20)	−0.02 (19)	0.36* (23)	0.17 (19)			
Hippocampus										0.15 (20)	0.42* (19)	0.56** (19)	0.49* (19)			
Cortex lobus frontalis											0.05 (34)	−0.06 (34)	0.06 (33)	−0.30 (14)	0.28 (15)	−0.21 (13)
Cortex lobus occipitalis												0.21 (34)	0.43** (33)	0.82*** (15)	0.73*** (16)	0.52* (14)
Cortex gyrus cinguli													0.52*** (34)	0.67** (15)	0.24 (16)	−0.06 (14)
Cortex gyrus hippocampus														0.66** (14)	0.38 (15)	0.50* (13)
Cortex lobus parietalis															0.73*** (15)	0.38 (13)
Cortex lobus temporalis																0.41 (14)
Cortex cerebellum																

Table 3. *Product-moment correlations between the concentration of 5-hydroxyindoleacetic acid (5-HIAA) (μg/g wet tissue) in different parts of the brain. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$. Number of cases in brackets*

	Hypothalamus	Nucleus caudatus	Putamen	Globus pallidus	Thalamus	Mesencephalon	Pons	Medulla oblongata	Hippocampus	Cortex lobus frontalis	Cortex lobus occipitalis	Cortex gyrus cinguli	Cortex gyrus hippocampus	Cortex lobus parietalis	Cortex lobus temporalis	Cortex cerebellum
Hypothalamus		0.36 (20)	0.20 (20)	0.44* (20)	0.49* (20)	0.52** (20)	0.57** (20)	0.25 (20)	0.41 (20)	0.30 (20)	0.29 (20)	0.44* (20)	0.40* (20)			
Nucleus caudatus			0.75*** (40)	0.76*** (20)	0.58*** (40)	0.63*** (40)	0.47* (20)	0.64*** (40)	0.83*** (20)	0.71*** (20)	0.36 (20)	0.61** (20)	0.68*** (20)			
Putamen				0.80*** (20)	0.50*** (40)	0.57*** (40)	0.65*** (20)	0.57*** (40)	0.69*** (20)	0.43* (20)	0.34 (20)	0.51* (20)	0.44* (20)			
Globus pallidus					0.60** (20)	0.88*** (20)	0.50* (20)	0.53** (20)	0.69*** (20)	0.47* (20)	0.48* (20)	0.64*** (20)	0.59** (20)			
Thalamus						0.61*** (45)	0.54** (25)	0.56*** (40)	0.51** (25)	0.38* (25)	0.39* (20)	0.45* (20)	0.43* (20)			
Mesencephalon							0.42* (25)	0.51* (40)	0.60*** (25)	0.41* (25)	0.36 (20)	0.59** (20)	0.50* (20)			
Pons								0.67*** (20)	0.45* (25)	0.39* (25)	0.22 (20)	0.41* (20)	0.30 (20)			
Medulla oblongata									0.56** (20)	0.30 (20)	0.46* (20)	0.57** (20)	0.45* (20)			
Hippocampus										0.71** (25)	0.51** (20)	0.71*** (20)	0.80*** (20)			
Cortex lobus frontalis											0.45** (36)	0.66*** (36)	0.17 (35)	0.94*** (16)	0.94*** (16)	0.48* (16)
Cortex lobus occipitalis												0.62*** (36)	0.51*** (35)	0.68*** (16)	0.68*** (16)	0.44* (16)
Cortex gyrus cinguli													0.45** (35)	0.80*** (16)	0.79*** (16)	0.31 (16)
Cortex gyrus hippocampus														−0.09 (15)	0.01 (15)	0.29 (15)
Cortex lobus parietalis															0.96*** (16)	0.36 (16)
Cortex lobus temporalis																0.43* (16)

Table 4. *Product-moment correlations between the concentrations of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) (μg/g wet tissue) and age. n indicates the number of cases.* * = $p < 0.05$; ** = $p < 0.01$

Part of brain	5-HT/age		5-HIAA/age	
	n	r	n	r
Hypothalamus	20	0.36	20	0.14
Caudatus	40	0.05	40	0.25
Putamen	40	0.08	40	0.05
Pallidus	20	–0.46*	20	0.09
Thalamus	44	–0.06	45	–0.06
Mesencephalon	25	0.48**	45	0.22
Pons	23	0.001	25	–0.001
Medulla oblongata	24	0.44*	40	0.22
Hippocampus	20	0.22	25	0.39*
Cortex lobus frontalis	35	0.08	41	0.09
Cortex lobus occipitalis	35	–0.10	36	–0.01
Cortex gyrus cinguli	39	–0.03	36	0.24
Cortex gyrus hippocampus	34	–0.39*	35	0.26
Cortex lobus parietalis	15	–0.26	16	–0.05
Cortex lobus temporalis	16	0.01	16	–0.04
Cerebellum	14	–0.07	16	0.39

Influence of Sex

Forty-two males (mean age 57, range 18—95) and 19 females (mean age 62, range 23—79) were investigated. There is no significant difference between the two groups concerning the concentrations of 5-HT in various parts of the brain. For 5-HIAA the concentration in the males was lower in 10 out of 16 brain regions than for the females, although this difference was only significant in the gyrus hippocampus ($p < 0.05$).

Influence of Arteriosclerosis and Final Hypoxia

A significant lower 5-HT concentration was found in the cortex of the gyrus hippocampus between stage 2 arteriosclerosis compared with stage 0 ($p < 0.01$). The concentrations of 5-HIAA in various brain parts showed a more complex picture. In general the different brain regions from patients with arteriosclerosis stage 1 showed lower concentrations than those from both stage 0 and 2. The difference in most areas was significant. Stage 3 contained only 1 case.

With increasing hypoxia 5-HT concentrations were significantly lowered in the frontal and occipital cortex. A significant increase was found in the medulla oblongata. 5-HIAA concentration increased with

increasing hypoxia in 12 of the 16 investigated brain parts, reaching significance only in the mesencephalon.

Influence of Cancer

Sixteen patients died from cancer, 3 with leukemia, 3 with pulmonary cancer, 4 with ovarian cancer, 2 with carcinoma of the kidney, 2 with ventricular cancer and 1 with urinary bladder and 1 with rectal cancer. The cancer patients were compared with patients who died from other causes. The 5-HT concentration in the cancer group was found to be significantly lowered in two brain parts: the thalamus and the hypothalamus.

5-HIAA concentrations were found to be higher in the cancer group in 14 of the 16 investigated brain parts and were significant in the putamen, pons and medulla oblongata.

Influence of Drugs

Nineteen patients were treated with opiates and 8 with neuroleptics and of these, five were treated with a combination of opiates and neuroleptics the last days and weeks before death. Neuroleptic drug treatment was only used to potentiate the effect of analgesics or to reduce a high body temperature. The concentrations of 5-HT were found to decrease with the opiate treatment. In 15 of the 16 investigated brain parts the 5-HT concentration was lower in the opiate group and significantly so in the thalamus and the cortex gyrus hippocampus. The 5-HIAA concentrations were found to be higher in the opiate group in all investigated brain parts with the exception of the hypothalamus and on a significant level in the mesencephalon, medulla oblongata and cortex of the frontal lobe, occipital lobe, gyrus cinguli and the temporal lobe (Table 5). We could not judge the influence of neuroleptics as too few patients had been treated with them. With a combination of opiates and neuroleptics all 16 investigated areas showed a slight decrease in the concentration of 5-HT, though none were on a significant level. 5-HIAA concentrations were higher in all 16 investigated parts of the brain and on a significant level in the caudatus, medulla oblongata, hippocampus and cortex of the frontal lobe, occipital lobe, gyrus cinguli and gyrus hippocampus.

Circadian Variation

The patients were grouped according to time of death into four 6-hour periods (midnight—6 a.m., 6 a.m.—noon, noon—6 p.m.,

Table 5. *Influence of opiates on the concentrations of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) (μg/g wet tissue) in various parts of the brain. Mean(m) and standard deviation (S.D.). n indicates number of cases.* * = $p < 0.05$; ** = $p < 0.01$

	5-HT							5-HIAA						
	no opiates			opiates				no opiates			opiates			
Part of brain	m	S.D.	n	m	S.D.	n	p <	m	S.D.	n	m	S.D.	n	p <
Hypothalamus	0.14	±0.07	10	0.11	±0.08	10	0.36	1.45	±0.65	10	1.16	±0.49	10	0.28
Caudatus	0.13	±0.05	25	0.10	±0.06	15	0.07	0.51	±0.14	25	0.62	±0.25	15	0.12
Putamen	0.18	±0.06	25	0.15	±0.05	15	0.25	0.95	±0.30	25	1.09	±0.42	15	0.22
Pallidus	0.18	±0.08	10	0.17	±0.09	10	0.88	1.46	±0.43	10	1.74	±0.62	10	0.27
Thalamus	0.15	±0.05	30	0.10	±0.04	14	0.01**	1.02	±0.29	30	1.09	±0.24	15	0.48
Mesencephalon	0.38	±0.20	15	0.34	±0.05	10	0.53	3.26	±0.93	30	3.97	±1.41	15	0.05*
Pons	0.06	±0.03	14	0.05	±0.02	9	0.37	0.78	±0.41	15	0.98	±0.44	10	0.26
Medulla oblongata	0.17	±0.07	14	0.17	±0.05	10	1.0	1.18	±0.41	25	1.73	±0.56	15	0.01**
Hippocampus	0.04	±0.03	10	0.05	±0.03	10	0.87	0.27	±0.11	15	0.37	±0.16	10	0.07
Cortex lobus frontalis	0.01	±0.02	16	0.01	±0.01	19	0.29	0.09	±0.04	22	0.18	±0.16	19	0.04*
Cortex lobus occipitalis	0.01	±0.01	17	0.01	±0.02	18	0.39	0.13	±0.05	17	0.20	±0.10	19	0.01**
Cortex gyrus cinguli	0.03	±0.04	21	0.03	±0.02	18	0.69	0.25	±0.08	17	0.33	±0.13	19	0.04*
Cortex gyrus hippocampus	0.04	±0.03	17	0.02	±0.02	17	0.05*	0.21	±0.06	16	0.26	±0.12	19	0.10
Cortex lobus parietalis	0.02	±0.03	6	0.01	±0.02	9	0.24	0.10	±0.03	7	0.26	±0.28	9	0.13
Cortex lobus temporalis	0.012	±0.012	7	0.004	±0.01	9	0.11	0.09	±0.02	7	0.23	±0.18	9	0.05*
Cerebellum	0.01	±0.01	7	0.01	±0.01	7	0.64	0.03	±0.02	7	0.05	±0.03	9	0.12

6 p.m.—midnight). The 5-HT and 5-HIAA concentrations in each group were compared. Each value was statistically corrected to the age 50 and to the mean brain weight. In some brain parts a striking circadian variation was found. In the hypothalamus 5-HT concentration showed a maximum between midnigt—6 a.m. and a sharp decline to the time period 6 a.m.—noon and then showed a slow increase during the afternoon and night. The values of the concentrations between 6 a.m.—noon and noon—6 p.m. are significantly lower than between midnight—6 a.m. (Fig. 1). The concentration of

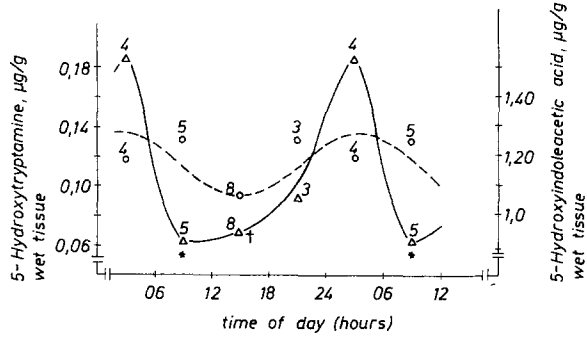

Fig. 1. Concentrations of 5-HT (△) and 5-HIAA (○) in hypothalamus in relation to hour of death. Shown are means of pooled values of four 6-hour periods. * = $p < 0.05$; † = $p < 0.10$ vs. maximum. Numbers inside the figure indicate number of patients. Standard error was not drawn in order to simplify the figure

5-HIAA shows a similar circadian variation although we do not find any significant difference between the time groups. In the mesencephalon the circadian variation is less pronounced but here the maximum for both 5-HT and 5-HIAA lies in the time period 6 a.m.—noon. In the hippocampus (Fig. 2) there is a maximum between midnight—6 a.m. and a minimum between 6 p.m.—midnight and this difference is significant. The cortex of the gyrus hippocampus shows a similar circadian variation (Fig. 3). In the frontal lobe a 5-HT maximum occurs between 6 p.m.—midnight and a minimum between 6 a.m.—noon, this difference being on a significant level (Fig. 4). In this region 5-HIAA shows a maximum between noon to 6 p.m. but the difference between the time groups is not significant. In the medulla oblongata a smaller and inconsistent 5-HT variation was found during the 24-hour period. There is a striking covariation between 5-HT and 5-HIAA in all investigated brain parts with the exception of the medulla oblongata.

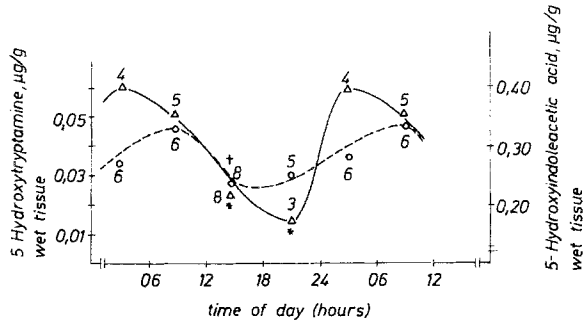

Fig. 2. Concentrations of 5-HT (△) and 5-HIAA (○) in hippocampus in relation to hour of death. Shown are means of pooled values of four 6-hour periods. * = $p < 0.05$; † = $p < 0.10$ vs. maximum. Numbers inside the figure indicate number of patients

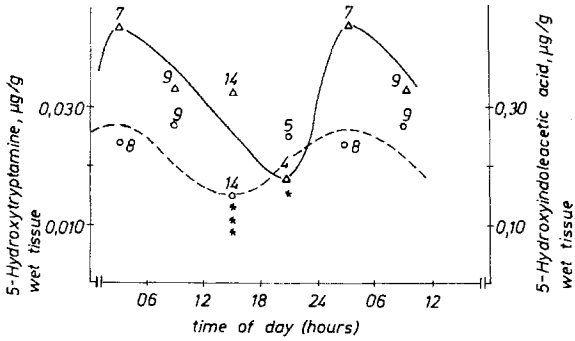

Fig. 3. Concentrations of 5-HT (△) and 5-HIAA (○) in cortex gyrus hippocampus in relation to hour of death. Shown are means of pooled values of four 6-hour periods. * = $p < 0.05$; *** = $p < 0.001$ vs. maximum. Numbers inside the figure indicate number of patients

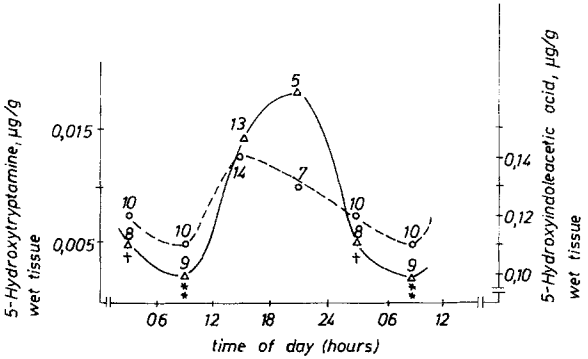

Fig. 4. Concentrations of 5-HT (△) and 5-HIAA (○) in cortex lobus frontalis in relation to hour of death. Shown are means of pooled values of four 6-hour periods. † = $p < 0.10$; ** = $p < 0.01$ vs. maximum. Numbers inside the figure indicate number of patients

Discussion

The concentrations of 5-HT and 5-HIAA in this study agree well with those reported by *Gottfries et al.* (1974). The values are essentially lower than those found by *Lloyd et al.* (1974), *Cochran et al.* (1976), *Crow et al.* (1979) and *Joseph et al.* (1979). The present material includes some cases from the study by *Gottfries et al.* (1974) and the same preparation and analytical methods were used for all new cases included, which probably explains the similar results. When preparing and storing the samples we were careful to prevent evaporation, which could be an explanation for the differences between our study and the above mentioned studies. The highest concentrations of 5-HT and 5-HIAA were found in the mesencephalon and the basal ganglia. Significantly higher concentrations of 5-HT and 5-HIAA were found in the phylogenetically older cortical parts, that is the limbic cortex, than in the neocortex. It should be noted that all investigated areas had measurable concentrations of 5-HT and the low values of 5-HT in the cortical regions might well be of biological importance. This is in line with animal studies (*Mac Lean*, 1962). A similar distribution between different brain parts has been reported for DA (*Adolfsson et al.*, 1979). The correlation of 5-HT and 5-HIAA values in different brain parts must be carefully interpreted because the values are affected by many variables.

There is a negative correlation between the brain weight and the concentrations of 5-HT and 5-HIAA in various brain parts. A possible explanation for this is post-mortem brain oedema. However, there is a loss of brain weight and a neuronal cell loss in normal aging (*Henderson et al.*, 1980). In our study as well as in earlier studies (*Gottfries et al.*, 1974; *Livrea et al.*, 1978) we do not find any striking influence of age on the concentrations of 5-HT and 5-HIAA in the brain. Thus, one could imagine a compensatory mechanism of higher concentrations of 5-HT and 5-HIAA in the remaining neurons explaining this negative correlation. Our finding of a positive correlation between 5-HT concentration in the brain-stem and age is in line with the findings of *Carlsson et al.* (1980 b). An interesting finding is that age seems to be positively correlated to the CSF-5-HIAA-concentration (*Bowers* and *Gerbode*, 1968; *Gottfries et al.*, 1971). This high level of 5-HIAA in CSF in advanced age may be due to a decreased active outflow, while the transport between brain tissue and CSF is either only a passive diffusion or, if an active process, is not disturbed in old age.

We could not find any sex differences for 5-HT, but 5-HIAA

shows higher concentrations in the females in most brain regions investigated. This agrees with the findings of *Gottfries et al.* (1974). The increased 5-HIAA concentrations in some parts of the female brain could be explained by lower mean brain weight in females. Studies on 5-HIAA in the CSF in normals do not show any sex differences (*Bowers* and *Gerbode,* 1968; *Gottfries et al.,* 1971). In pathological states, however, a sex difference has been demonstrated (*Sjöström* and *Roos,* 1972; *Sedvall et al.,* 1974), which indicates a higher turnover rate of 5-HT in the female brain or more plausibly may be attributed to the difference in height rather than in sex (*Wode-Helgodt* and *Sedvall,* 1978).

An estimation of final hypoxia from the records and post-mortem findings is rather difficult and contains many possible sources of error. Our finding of a slight decrease of 5-HT with increasing hypoxia is in line with animal experiments (*Davis* and *Carlsson,* 1973 a, b; *Hedner,* 1978). The decrease in 5-HT is not very large, but the cortical regions seem to be more susceptible to hypoxia than deeper situated parts of the brain.

The degree of arteriosclerosis does not appear to influence the 5-HT concentrations to any great extent. For 5-HIAA, however, lower concentrations were found in the group with slight to moderate arteriosclerosis. Upon further examination of the case histories of the patients in this group it turned out that 13 out of 15 patients had died from heart disease with terminal cardiac insufficiency. This group of patients had suffered a more severe hypoxia and had also received more analgesic drugs than the other groups. These variables should lead to an increase in 5-HIAA. The patients' different times of death are also scattered evenly throughout the day. Thus, we cannot find any plausible explanation for our finding of low 5-HIAA with a moderate arteriosclerosis.

The decrease of 5-HT and the increase of 5-HIAA after opiate treatment have not previously been reported in human studies. However, there are numerous animal studies with varying results. Among others, *Haubrich* and *Blake* (1973), reported an increase in the brain concentrations of 5-HIAA in rats after both acute and chronic administration of morphine. *Perez-Cruet et al.* (1975) showed the same effect for heroin in rats. This indicates the possibility of an increased 5-HT turnover in the brain after opiate treatment. The underlying mechanism for this effect of opiates is still under debate. *Larson* and *Takemori* (1977) tried to explain the morphine induced increase in 5-HT turnover in terms of changes in the uptake of tryptophan or 5-hydroxytryptophan from the blood by the brain. A decreased activity of tryptophan hydroxylase after acute morphine

administration has also been reported (*Knapp* and *Mandell*, 1972).

Our patients were treated with a variety of opiate drugs, most of them morphine analogues and pentacozine. Our findings of decreased concentration of 5-HT and increased concentrations of 5-HIAA are in line with most of the animal studies. We do not think that the circadian variation of 5-HT and 5-HIAA in some brain regions could explain our findings, because when plotting the values for the opiate patient, they are found to be evenly scattered over the day.

Sixteen patients died of cancer. They showed lowered amounts of 5-HT and increased amounts of 5-HIAA. When going through the case histories we could not find any form of cancer associated with especially low 5-HT levels or high 5-HIAA levels. However, 13 of the 16 patients had received opiates before death and we are inclined to interpret the changes in 5-HT and 5-HIAA concentrations as being the result of opiate treatment rather than being an effect of different cancer diseases.

The most pronounced circadian variation of 5-HT was seen in the hypothalamus, hippocampus, cortex frontalis and gyrus hippocampus. 5-HT is believed to play an important role in sleep-wakefulness (*Jouvet* and *Pujol*, 1974; *Koella*, 1974) and a sleep center has been postulated (*Kleitman*, 1963) in the hypothalamus and the neighbouring parts of the mesencephalon. The high concentrations of 5-HT in the hypothalamus during the night could mean that 5-HT plays a role in inducing and maintaining sleep. Other parts of the brain show peaks of 5-HT at different times during the day and this neurotransmitter may then have entirely different functions. Whether 5-HT like NA may play a role in the regulation of corticotropin releasing hormone (CRH) (*Carlsson et al.*, 1980 a) is still an open question. 5-HT concentration shows a circadian variation during the day that is similar to that of NA. Evidence both for an inhibitory and excitatory effect on CRH has been presented (*Jones et al.*, 1976; *Azmitia*, 1978).

In addition to what was previously known about the influence of various factors on 5-HT and 5-HIAA concentrations in post-mortem human brain, this investigation shows that circadian variation and the influence of opiates must be carefully controlled.

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