POL. J. PHARMACOL. PHARM., 1975, 27, Suppl. 15—24

WOJCIECH KOSTOWSKI

INTERACTIONS BETWEEN SEROTONERGIC AND CATECHOLAMINERGIC SYSTEMS IN THE BRAIN

Department of Experimental Pharmacology, Institute of Physiological Sciences, Medical Academy 00-927 Warszawa, and Department of Psychopharmacology, Psychoneurological Institute, 00-000 Warszawa

Numerous anatomical data give for the existence of the functional interactions between monoaminergic brain systems. The knowledge of these interactions opens new possibilities for explanation of such brain functions as sleepwaking cycle, emotions and goal-directed behaviour. It is possible that these and other functions are regularly by reciprocal mechanisms including the antagonistic neuronal systems: serotonergic and catecholaminergic — i.e. dopaminergic and noradrenergic. Such organizational model is in general agreement with the model of 5-HT mediated tropotrophic anatagonism of a catecholamine — mediated ergotrophic system proposed by Brodie and Shore [8].

The anatomical organization of neurons containing monoamines such as 5-HT, NA and DA have been mapped thanks to histofluorescence methods and connection of these methods with stereotaxic lesions of discrete brain areas [2,3,4,19,75]. The 5-HT-containing neuronal cell-bodies are located mainly in the raphe area containing three groups of nuclei: anterior, middle and posterior (see 51). Most ascending 5-HT fibres arise from the anterior group (*nuclei raphe*: *medianus*, *dorsalis*, *intermedius*, *linearis* and *centralis superior* of Bechterew). The fibres from these nuclei terminate throughout wide telencephalic and diencephalic regions such as the cerebral cortex, the hippocampus, the thalamus and the hypothalamus [19]. Middle and posterior raphe nuclei (such as *nuclei*; *magnus*, *pontis*, *obscurus* and *pallidus*) project to other structures than the anterior group does. It should be noted that lesions of the middle and the *posterior raphe nuclei* do not affect the concentration of 5-HT in the forebrain [51] whilst lesions of the anterior group induce

marked decrease in the forebrain 5-HT level in cats and rats [35, 38]. Stimulation of the midbrain raphe induces release of 5-HT in the forebrain in rats [1, 39].

NA neurons in the brain form two main ascending systems: dorsal and ventral. Dorsal pathway originates from the dorsolateral part of the *nucleus locus coreruleus* (NLC) and innervates both the paleocortical and the neocortical areas whilst ventral pathway originating from cells located in *pons* and *medulla* (beyond the NLC) projects to the *hypothalamus*, basal forebrain region and amygdaloid complex [57]. Maeda and Shimizu [49] described the "intermediate" NA system originating mainly from the *nucleus locus subcoeruleus* and the anterior portion of the NLC and projecting to the periventricular hypothalamic area. It should be noted that NA fibres from the NLC could be traced into the cerebellar and the telecephalic cortical areas, the *lateral geniculate nuclei* (as well as medial geniculate bodies), the thalamus and the rhombencephalon [70]. It is interesting that ventral NA pathway is resistant to the 6-hydroxydopamine (6OH-DA) whereas dorsal NA pathway could be easily affected by this compound [52]. There is some evidence showing that the NLC and the raphe are anatomically connected [48]. Olson and Fuxe [57] have described a fibre projection from the medial portions of the NLC to the raphe. This system is partly crossed and bilateral lesions of the NLC lead to the disappearance of NA terminals within the raphe area.

The neuronal cell bodies containing DA are located mainly within the substantia nigra (SN, *pars compacta*) and in an area dorsal to the nucleus interpenduncularis. The fibers projeting from the SN innervate mainly the neostriatum *(nucl. caudatus* ans *putamen)* and form so-called nigro-striatal system [2, 3, 4]. This neuronal system plays an important role in the function of the striatal structures and is involved in the control of the motor activity and in the other functions related to the inhibition mediated by the basel forebrain structures [29]. Some DA cell bodies send their axons towards the caudal portion of the raphe and numerous 5-HT terminals have been found within the SN [58]. Thus the anatomical data give support for the existence of the functional interactions between 5-HT, NA and DA systems in the brain. Such interactions were demonstrated on the basis of neurophysiological and neuropharmacological experiments.

5-HT and DA act reciprocally within the striatum. This area contains both 5-HT and DA terminals originating in the raphe and the SN respectively. There exists a possibility of the conversion of L-DOPA, the precursor of DA, to DA in the serotonergic nerve terminals containing aromatic aminoacids decarboxylase [20]. This mechanism leads to the release of 5-HT and to diminution of the concentration of this amine in the brain. On the other hand, it was found that 5-HTP, the precursor of 5-HT, may release DA from DA

terminals in the striatum. This effect is due to the conversion of 5-HTP to 5-HT since it was blocked by the treatment with MK 485 (D,L,-α-methyl DOPA--hydrazine), the inhibitor of L-aminoacid-decarboxylase [21, 55, 56]. Summing up, the mutual displacement in the storage sites between these two neurotransmitters might be expected.

Pharmacological experiments provide further evidence for the existence of DA-5-HT interaction. Apomorphine, the drug known to stimulate (directly and indirectly) DA receptors [12, 18, 75] increase turnover of 5-HT and increases level of this amine in the brainstem of rats [22]. It was observed by us that stereotyped behaviour (the phenomenon mediated mainly by dopaminergic mechanism) after amphetamine is enhanced after lesions of the midbrain raphe in rats [25]. Drugs blocking DA receptors such as neuroleptics of phenothiazines and butyrophenones groups have been also reported to affect the 5-HT brain system [60, 61]. Moreover, it was recently reported by [41] that intact 5-HT neurons are necessary for the cataleptogenic activity of neuroleptics since lesions of the midbrain raphe in rats markedly reduced effects of both haloperidol and chloropromazine. Both p-chlorophenylalanine (pCPA), the inhibitor of 5-HT biosynthesis, and LSD-25 caused similar effects. Since catalepsy due to neuroleptics is at least partialy related to blockade of DA striatal receptors [67, 77] one may suppose that lesions of the raphe deeply affect the functions of the nigro-striatal system. The general conclusion should be that destruction of 5-HT system leads to the increased activity of DA neurons, further experiments, however, are necessary to confirm this hypothesis and clarify the details of possible interaction.

Recently we have observed that microinjections of DA to the raphe caused strong cortical synchronization in cats [45]. It may indicate that DA increases the activity of synchronizing mechanisms mediated via the raphe.

DA system of the SN and the striatum and serotonergic system of the raphe produce opposite behavioural effects. The destruction of the raphe causes the state of permanent behavioural and EEG arousal and excitation in cats and rats [36, 66]. Insomnia and agitation as well as cortical EEG arousal have been reported after coagulation of the anterior raphe nuclei in rats [38]. Moreover the intensity of the motor agitation was significantly correlated with the decrease in both 5-HT and 5-HIAA levels in the forebrain. pCPA is known to produce insomnia in rats, cats, rabbits, monkeys and men [13, 14, 53, 71 80, 81]. The problem of correlation between the decrease of slow-wave sleep stage (SWS) and the decrease of cerebral 5-HT is still open [11, 65, 80, 81]. Stereotaxic coagulation of DA-cell bodies within the SN leads to akinesia and even to the permanent comatose state in cats [34] although generally normal EEG pattern and EEG arousal were observed. In rats, however, no consistent data have been reported after coagulation of the SN [24, 74]. It appears possible that at least in cats the DA nigro-striatal system is involved

in the maintenacnce of behavioural arousal but not substantially affects the electrical activity of the cortex [36, 37]. The 5-HT system of the raphe is responsible for the inhibition of alertness and for the cortical synchronization as well as for the induction od S-WS [36, 37]. It is known that stimulation of the raphe induces inhibition of motor activity and the .sommnolence in rats [39]. In cats stimulation of the raphe with frequencies of 2/sec. induces cortical synchronization [40]. However in rabbits, stimulation of the bulbar and the pontine raphe produces symptoms of arousal [62]. It may indicate that physiological role of the raphe is more complex.

There is also evidence for the existence of interaction between NA and 5-HT systems in the brain. The most conclusive are results of biochemical experiments. The depletion of brain NA as a result of the inhibition of the DA hydroxylase was accompanied by an increase in the rate of 5-HT synthesis [32, 33]. The destruction of the catecholaminergic neurons by 6-OH-DA injected intracisternally in rats produces a substantial increase of 5-HT synthesis rate as well an increase of the concentration of 5-HIAA in the forebrain [7]. In cats the synthesis of 5-HT is markedly increased after treatment with α-methyl-tyrosine, the inhibitor of catecholamines biosynthesis [37]. Furthermore, the electrolytic lesions of the caudal portions of the NA dorsal pathway or the rostral part of the NLC induced a significant increase of telencephalic tryptophan and 5-HIAA levels in cat [59]. We have studied [42] the changes in the concentration of 5-HT, NA and their metabolits: 5-HIAA and 3-methoxy-4-hydroxy-phenethylenglycol sulphate (MOPEG-SO_4), respectively, after lesions of raphe and NLC in rats. Bilateral lesions of the NLC produced a substantial increase in the forebrain 5-HIAA level. On the other hand, lesion of the raphe *(nucl. raphe medianus)* caused an increase in the concentration of MOPEG-SO_4 in the cortex and hippocampus — i. e. in areas innervated by the NLC. The maximal effects were found 3-4 days after lesion. These data indicate that the function of the raphe and the function of the NLC may reciprocaly inhibit one another.

Lesions of the raphe produce well known insomnia, the motor hyperactivity and the persistent cortical desynchronization in cats and rats. It may be postulated that these phenomen are at least partially due to the predominance and the hyperactivity of NA system (and/or DA system) since it can be blocked by α-methyl-tyrosine as reported by Jouvet [36] and observed by us (Kostowski, Domańska and Tarchalska, to be published). We have also recently found that bilateral lesions of the NLC inhibit hyperactivity of the raphe lesioned rats, the role, however, of DA system in this hyperactivity remains unexplained. It is postulated [36] that DA system controls motor hyperactivity, during waking, and excitation whilst NA system controls the bioelectrical phenomena (such as desynchronization and some phasic events) accompanying the waking and the rapid-eye-movement sleep (REM).

As already mentioned, the interaction between 5-HT and catecholaminergic systems plays an essential role in the sleep-waking cycle. It is particular interest that the spontaneous bioelectrical activity of the raphe cells is highest during SWS as observed by some suthors (see 17). On the other hand, some raphe units are inhibited during REM and in S-WS preceding waves in the *lateral geniculate nucleus* (vide infra, 50). The bioeletrical activity of some cells within the NLC is markedly decreased during S-WS [47]. Thus, the activity of both NLC and *raphe* seems to be opposite during S-WS and PS.

REM is accompanied by phasic electrical phenomena such as the *ponto-geniculo-occipital* waves (*PGO*). *PGO* waves similar to those recorded during sleep have been registered after administration of drugs which affect brain monoamines. Some drugs decreasing brain 5-HT concentration are able to induce in cat the occurrence of *PGO* waves disconnected from the sleep-waking cycle [13, 36, 37]. RESP * given at the doses of 0·5—1·0 mg/kg induces the continuous *PGO*-like waves (called *PGO*-res). Similar effect is produced by pCPA [30]. Furthermore, the effect of reserpine and pCPA can be reversed by 5-HTP ** [15, 16, 30]. Lesions of the raphe system, similarly to reserpine and pCPA increase or induce *PGO* waves. Thus, 5-HT appears to inhibit the occurence of *PGO* [17, 36]. On the other hand lesions of the *dorsolateral pontine tegmentum* at the level of NLC supress the cortical and geniculate *PGO* [9]. According to Jouvet [36, 37] catecholamine-containing neurons are responsible for generation and maintenance of *PGO* due to the release of some deaminated metabolites of NA which trigger postsynaptic responses in the vestibular and the oculomotor nuclei leading to rapid eye movements during REM. Similar events occur in the lateral geniculate nucleus and the occipital cortex. It is supposed that 5-HT system of the raphe exerts tonic inhibition upon catecholaminergic mechanisms triggering phasic phenomena during REM [36]. There exist, however, many conflicting data with such model. α-MT is known to increase the amount of *PGO* [5]. Both 5-HT and NA system inhibit "pacemaker" and/or "generator" cells for *PGO*-activity, located in the dorsal pontine reticular formation [26, 31]. It is also possible that other mechanisms (related for instance to the cholinergic systems) play a role in both triggering and maintenance of *PGO*-activity. The discussion of this problem is, however, beyond the frame of this rewiev.

Recently we have found [43] that microinjections of 5-HT or quipazine (the 5-HT like compound, see 68) inhibited or decreased the *PGO*-res. This effect was accompanied by increased cortical synchronization which lasted, however, longer than decrease in *PGO*-res frequency was observed.

According to model proposed by Routtenberg the raphe controls and is controlled by the LC. On the other hand the neocortex is controlled by the raphe and controls the raphe. Such model recurs to the original theories of

* RESP = reserpine, ** 5-HTP = 5-hydroxytryptophan.

Hernandez-Peon [27, 28], Clemente et al [10] and Nauta et al [54] of forebrain--brain stem circuits regulating sleep and waking states. Routenberg [69] postulates that oscillations within 5-HT and catecholamines levels lead to oscillations in the stages of the sleep. According to this model waking state — by inhibition the S-WS-system leads to "boild-up" of 5-HT within the raphe perikarya and terminals. Then 5-HT after reaching a "cortical" level begins to suppress the neocortical activity. NA system of the NLC is suppressed during this state due to the negative feedback from the raphe. Then the NLC would begin to extent an inhibitory influence on the raphe and thus initiating REM. Since, the activity of raphe cells would be decreased, a "build-upt" of 5-HT begins and again reaches a critical level for releasing and maintaining S-WS,

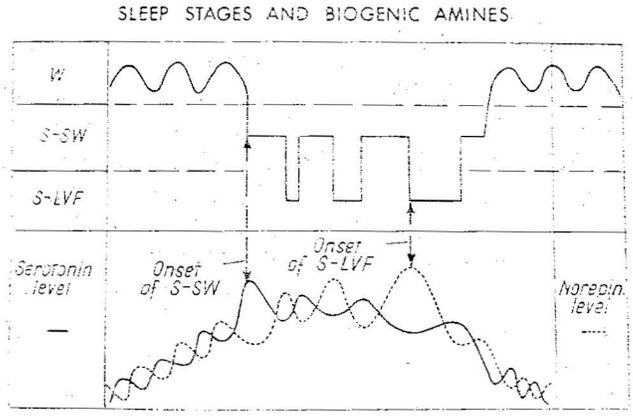

Fig. 1. Oscillations within levels of serotonin and norepinephrine as related to stages of wakefulness (W), slow-wavesleep (S-WS) and rapid-eye-movent sleep (S-LVF) (for details see text, according to Routtenberg [69].

and the sleep cycle begins over again. This interesting model needs further confirmations. It should be, however mentioned that increased turnover of NA have been demonstated by Pujol et al [64] during REM in rats. The model proposed by Routtenberg [Fig. 1) does not describe the role of cholinergic neurons and DA systems in the sleep-waking cycle. It is known, as already mentioned, that DA nigrostriatal system is involved in responsiveness and behavioural arousal. We believe that possible inhibitory influence from the LC on the raphe and inhibition of DA nigro-striatal system by the raphe are involved in mechanisms regulating sleep-waking cycle. The complexity of the sleep-waking cycle may be at least partly explained by interactions between these three monoaminergic systems. The model I wish to propose is summarized schematically in Fig. 2 and 3. The inhibition of 5-HT system of raphe by NLC reduces the signs of S-WS and consequently releases nigro-striatal DA system from inhbitory influence of raphe. Thus, both waking system and REM system might be active during REM, however, well-organized motor behaviour

(characteristic for waking stage) is inhibited by muscular relaxation mediated probably by caudal portion of the NLC [17, 36]. Such model needs obviously further studies, particularly interactions between 5-HT and DA systems should be analysed using biochemical, bioelectrical and behavioural methods.

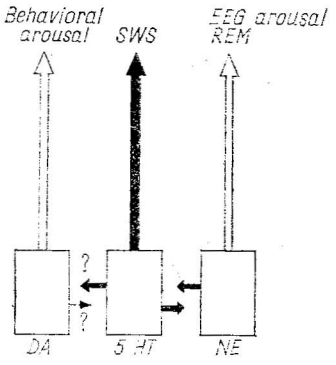

Fig. 2

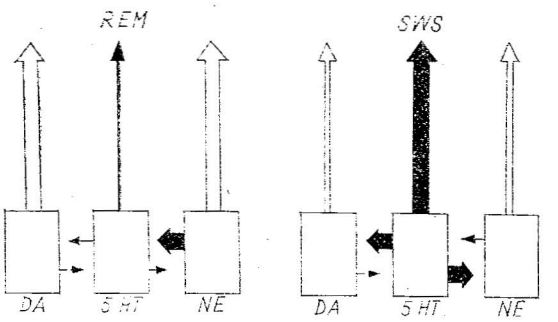

Fig. 3.

Fig. 2. Model of brain stem mechanisms regulating sleep and wakefulness. Dopaminergic nigro-striatal system (DA) controls behavioural arousal and responsiveness [36, 37], serotonergic system of raphe (5-HT) is involved in behavioural inhibition and cortical synchronization and controls slow wave sleep (S-WS) whilst noradrenergic system of the locus coeruleus and related cells (NE) controls electrocortical activation during REM sleep and waking [36, 37]. 5-HT system of raphe exerts an inhibitory influence upon NE system and probably inhibits DA nigro-striatal system (for details see text). It is also supposed that DA system activates 5-HT system of raphe [45] but details of this interactions are unknown. White arrows — activation, black arrows — suppression.

Fig. 3. Proposed brain stem mechanisms of SWS and REM-sleep (for explanations see Fig. 2). During SWS raphe inhibits both DA and NA systems. During REM-sleep serotonergic system of raphe is inhibited by NA system of NLC and DA system is probably released from inhibitory control of raphe. Well organized motor activity is however blocked by muscular relaxation mediated probably by caudal protion of NLC [17, 36, 37].

Actions of 5-HT and catecholaminergic systems may be antagonistic in respect to operant conditions situations and aggressive behaviour. It is proposed [73, 78, 79] that noradrenergic reward system facilitates behaviour whilst 5-HT punishment system inhibits it. These systems seem to act reciprocally in the control of goal-directed behaviour (Fig. 4). Evidence that NA system controls the reward mechanism has been extensively summarized by Stein [73] and Wise and Stein [78]. It is known that intraventricular administration of NA facilitated hypothalamic self-stimulation. The role of NLC in positive reinforcing mechanism has been recently established [5]. Depletion of 5-HT by pCPA is known to facilitate self-stimulation [63] whilst ivc injections of 5-HT and adrenergic receptors blocking drugs cause suppression of self stimulation [79]. Recently, DA receptors have been reported to play a role in the reward mechanism *.

* See: Clavier R., Routtenberg A.: Brain Res., 1974, 72, 25.

Catecholamines and 5-HT seem to play an opposite role in the regulation of aggressive and sexual behaviour. Depletion of brain 5-HT icreases aggressiveness and facilitates sexual behaviour in rats [23, 46, 71, 76]. It was observed by Benkert and co-workers [6] that fighting and mounting behaviour was

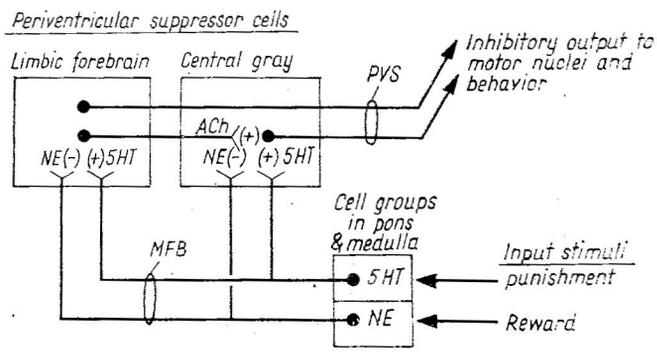

Fig. 4. Diagram showing hypothetical relationship between reward and punishment mechanism and behaviour. Cholinergic periventricular system (PVS) supresses behaviour. NA decrease activity of PVS. Reduction of PVS inhibitory influence facilitated behaviour. Signals of punishment increase behavioural suppression by activation of the 5-HT raphe system. MFB — medial forebrain bundle [79].

noted at high catecholamine level and greatly reduced 5-HT content in the brain. pCPA increases mouse-killing attitude in rats [70, 71, 72], lesions of the raphe system, however, produce no clear effects [44, 71, 72] in this type of aggressive behaviour but increase mutual aggressiveness [44]. We have recently found that catecholamines and 5-HT exert in some conditions opposite effects on aggressive behaviour in ants *genus Formica*. The investigations of aggressive and sexual behaviour in future would elucidate the nature of the antagonistic role of 5-HT and catecholamines in the brain.

REFERENCES

1. Aghajanian, G. K., Rosecrans, J. A. and Sheard, M. H.: Science, (Washington) 1967, 156, 402.
2. Anden N-E, Carlsson A., Dahlström A., Fuxe K., Hillarp N. A., and Larsson K.: Life Sci. 1964, 3, 523.
3. Anden N-E., Dahlström A., Fuxe J. and Larsson K.: Life Sci., 1965, 4, 1275.
4. Anden N-E., Dahlström A., Fuxe K., Larsson K., Olson L. and Ungerstedt U.: Acta Physiol. Scand., 1966, 67, 313.
5. Arbuthnott G., Fuxe K. and Ungerstedt U.: Brain Res., 1971, 27, 406.
6. Benkert O., Gluba H., Matussek N.: Neuropharmacol., 1973, 12, 177.
7. Blondaux C., Juge A., Sordet F., Chouvet G., Jouvet M., Pujol J. F.: Brain Res., 1973, 50, 101.
8. Brodie B., Shore P. A. In: Hormones, Brain Function and Behaviour (ed. H. Hoagland), Academic Press — New York, 1957, pp. 161—176.
9. Buguet A., Petitjean F., Jouvet M.: C. R. Soc. Biol., 1970, 164, 2293.
10. Clemente C. D., Sterman M. B., Wyrwicka W.: Exp. Neurol., 1963, 7, 404.

11. Cohen H., Ferguson J., Henriksen S., Stolk J., Zarcone V., Barches J., Dement W.: Proc. Amer. Psychol. Ass., 1970, 78, 831.
12. Costall B., Naylor R. J., Olley J. E.: Eur. J. Pharmacol. 1972, 18, 95.
13. Delorme F., Jeannerod M., Jouvet M.: C. R. Soc. Biol. (Paris), 1965, 150, 900.
14. Delorme F., Froment J. L., Jouvet M.: C. R. Soc. Biol. (Paris), 1966, 160, 2347.
15. Dement W. C. In: Sleep, Physiology and Patology (ed. A. Kales), Lippincot, Philadelphia, 1969, pp. 245—265.
16. Dement W., Mitler M., Henriksen S.: Rev. Canad. Biol. 1972, 31 suppl., 239.
17. Dement W. C., Henriksen S., Jacobs B., Mitler M. In: Pharmacology and the Future of Man. Proc. 5th Int. Congr. Pharmacol., San Francisco, 1973, 4, pp. 74—79 Ed. Karger-Basel.
18. Ernst A. M.: Psychopharmacol. (Berl.), 1967, 10, 316.
19. Fuxe K., Hökfelt T., Ungerstedt U.: Int. Rev. Neurobiol., 1970, 13, 93.
20. Fuxe K., Buchter L., Engel J.: J. Pharm. Pharmacol. 1971, 23, 420.
21. Goldstein M., Anagnoste B., Battiasta A. F., Owen W. S., Nakatani S.: J. Neurochem., 1969, 16, 645.
22. Grabowska M., Michaluk J.: Pharmacol. Biochem. Behav., 1974, 2, 263.
23. Grant L. D., Coscina D. V., Grossman S. P., Freedman D. X.: Pharmacol. Biochem. Behav., 1963, 1, 77.
24. Gumułka W., Ramirez-dell Angell A., Samanin R., Valzelli L.: Eur. J. Pharmacol., 1970, 10, 79.
25. Gumułka W., Kostowski W., Członkowski A.: Pharmacol., 1973, 10, 363.
26. Haefely W., Jalfre M., Ruch-Monachon M. A. In: 3rd International Catecholamine Symposium, Strasbourg, May 20—25, 1973.
27. Hernandez-Peon R.: Excerpta Med. 1965, 93, 123.
28. Hernandez-Peon R. In: Neurophysiologie des étáts du sommeil (ed. M. Jouvet), C. N. R. S., 1965 , 127, 63.
29. Hornykiewicz O. In: The Structure and Function of the Nervous Tissue (ed. G. Bourne), Academic Press — New York, 1972, vol. 6.
30. Jacobs B., Henriksen S., Dement W. C.: Brain Res., 1972, 48, 406.
31. Jalfre M., Ruch-Monachon M. A., Haefely W.: Adv. bioch. Psychopharmacol., 1974, 10, 121.
32. Johnson G. A., Kim E. G., Boukma S. J.: J. Pharmacol. exp. Ther., 1972, 180, 539.
33. Johnson G. A. and Kim E. G.: J. Neurochem., 1973, 20, 1761.
34. Jones B. E., Bobillier P., Jouvet M.: C. R. Soc. Biol. (Paris), 1969, 163, 176.
35. Jouvet M., Bobillier P., Pujol J. F. and Renault J.: C. R. Soc. Biol. (Paris), 1966, 160, 2343.
36. Jouvet M. In: Ergebnisse der Physiologie (ed. R. H. Adrian et al.), Springer Verlag-Berlin, 1972, pp. 158—307 Ed. Karger-Basel.
37. Jouvet M. In: Pharmacology and the Future of Man, Proc. 5th Int Congr. Pharmacol., SanFrancisco, 1973, vol. 4, pp. 103—107, Ed. Karger, Basel.
38. Kostowski W., Giacalone E., Garattini S., Valzelli L.: Eur. J. Pharmacol., 1968, 4, 371.
39. Kostowski W., Giacalone E., Garattini S., Valzelli L.: Eur. J. Pharmacol., 1969, 7, 170.
40. Kostowski W.: Brain Res. 1971, 31, 151.
41. Kostowski W., Gumułka W., Członkowski A.: Brain Res. 1972, 48, 443.
42. Kostowski W., Samanin R., Bareggi S., Marc V., Garattini S., Valzelli L.: Brain Res. 1974, 82.
43. Kostowski W., Gumułka W., Domańska M. In Comm. Meeting: Symposium: Serotonin Brain, Drugs, Kazimierz, 1974, 23.
44. Kostowski W., Członkowski A., Markowska L.: Pharmacology, in press.
45. Kostowski W., Gumułka S.: Pol. J. Pharmacol., Pharm., 1974, 26, 351.
46. Karli P., Vergnes M., Didiergeorges F. in: Aggressive Behaviour (ed. S. Garattini and E. B. Sigg), Excerpta Medica-Amsterdam, 1969, pp. 47—55.

47. Lindbrink P., Corrodi K., Fuxe K., Olson L. In: Pharmacology and the Future of Man, Proc. 5th Int. Congr. Pharmacol. San Francisco, 1973, vol. 4, pp. 90—102, Ed. Karger-Basel.
48. Loizou L. A.: Brain Res. 1969, 15, 563.
49. Maeda T., Shimizu N.: Brain Res., 1972, 36, 19.
50. McGinty D., Harper R.: Sleep Res. 1973 (in press) (see 17).
51. Morgane P., Stern W. C. In: Serotonin and Behavior (ed. J. Barchas and F. Usdin), 1973, pp. 427—442, Academic Press — New York.
52. Malmfors T., Thoenen H. (Eds): 6-Hydroxydopamine and Catecholamine Neurons, North Holland Publ. — Amsterdam, 1971.
53. Mouret J. R., Bobillier P., Jouvet M.: Eur. J. Pharmacol., 1968, 5, 17.
54. Nauta W. J. H., Koella W. P., Quarton G. C.: Neurosci. Res. Programm Bull., 1966, 4, 5.
55. Ng K. Y., Chase T. N., Colburn R. W., Kopin I. J.: Science (Washington), 1971, 172, 487.
56. Ng K. Y., Chase T. N., Colburn R. W., Kopin I. J.: Brain Res., 1971 , 45, 499.
57. Olson L., Fuxe K.: Brain Res., 1971, 28, 165.
58. Parizek J., Hassler R., Bak I. J.: Z. Zellforsch. Abt. Histochem., 1971, 115, 137.
59. Petitjean F., Jouvet M.: C. R. Soc. Biol. (Paris), 1970, 164, 2288.
60. Pletscher A., Bartolini G., Bruderer R., Burkhard W. O., Gey F. K.: J. Pharmacol. Exp. Ther., 1964, 145, 344.
61. Pletscher A., Daprada M., Bartholini G., Burkard W. P., Bruderer H.: Life Sci., 1965, 4, 2301.
62. Polc P., Monnier M.: Brain Res., 1970, 22, 47.
63. Poshel B. P., Niteman F. W.: Physiol. Behav., 1971, 7, 39.
64. Pujol. J. F., Buguet A., Froment J., Jones B., Jouvet M.: Brain Res., 1971, 29, 195.
65. Rechtschaffen A., Lovell R. A., Freedman D. W., Whitehead P. K., Aldrich M.: Psychopharmacol. (Berl.), 1969, 6, 223.
66. Renault J.: Monoamines et sommeils. III. Ed. J. Tixier et Fils — Lyon, 1967, pp. 79—86.
67. Rossum v. J. M.: Arch. Int. Pharmacodyn. Ther., 1966, 160, 493.
68. Rodriguez R., Rojas-Ramirez J. A., Drucker-Colin R. R.: Eur. J. Pharmacol., 1973, 24, 164.
69. Routtenberg A. In: Brain Systems and Circuitry Concerned with Sleep-Waking Behaaviou (ed. P. J. Morgane and W. C. Stern), Brain Information Service, Res. Report Nr 2, Univ. California — Los Angeles, 1973, pp. 33—38.
70. Sachs Ch., Jonsson G., Fuxe K.: Brain Res., 1973, 63, 249.
71. Sheard M. H.: Brain Res., 1969, 15, 524.
72. Sheard M. H.: Physiol. Behav., 1973, 10, 809.
73. Stein L. In: Psychopharmacology: a Review of Progress (ed. D. H. Efron), U. S. Goverment Printing Office-Washington, 1968, pp. 105—123.
74. Simpson B. A., Iversen S. D.: Nature (London), 1971, 230, 30.
75. Ungersted U.: Acta physiol. scand., 1971, suppl. 367, 1—48.
76. Vergnes M., Mack G., Kempf F.: Brain Res., 1973, 57, 67.
77. Vogt M.: Br. J. Pharmacol., 1969, 37, 325.
78. Wise C. D., Stein L.: Science (Washington), 1969, 163, 299.
79. Wise C. D., Berger B. D., Stein L.: Biol. Psychiatry, 1973, 6, 3.
80. Wyatt R. J., Engelman K., Kupfer D. J., Sjoerdsma A., Snyder F.: Electroenceph. clin. Neurophysiol., 1969, 27, 529.
81. Wyatt R. J., Engelman K., Kupfer D. J., Fram D., Sjoerdsma A., Snyder F., Lancet, 1970, 11, 842.

Received: 15 October 1974.
Author's address: 26/28, Krakowskie Przedmieście, 00-927 Warszawa, Poland.