Upsala J Med Sci 91: 283–288, 1986

Melanin Affinity of Xenobiotics

Nils Gunnar Lindquist

National Board of Health and Welfare, Department of Drugs, Division of Pharmacology and Toxicology, Box 607, S-751 25 Uppsala, Sweden

The pigment melanin has been found to accumulate several foreign compounds, and to keep them bound for very long periods (22,25,26,34,35). Ionic binding seems to be of great importance for the interaction as melanin contains a number of functional groups such as carboxyls, o-hydroquinones and o-semiquinones, thereby acting as a cation-exchange polymer, but other binding mechanisms may also be involved (13,22,23). This unique property of melanin has been suggested to be involved in the pathogenesis of chronic lesions in melanin containing tissues (25,34).

It was earlier known (34-35) that phenothiazines were accumulated in the pigmented uveal tract of the eye - thus causing chorioretinopathy. Also certain drug-induced pigmentations of the skin and inner ear lesions have been related to melanin binding (12,15). Melanin affinity may be a toxicological mechanism that also involves the brain stem. Autoradiographic in vitro investigations using specimens from human brains have shown accumulation of isotope labelled chlorpromazine in the melanin containing nerve cells in substantia nigra and locus coeruleus (24). The melanin affinity of neuroleptic drugs has also been demonstrated by use of pigment preparations from beef eyes and synthetic dopamine melanin, which has been reported to be structurally similar to the melanin present in the pigmented cells in the human substantia nigra (10,28). Due to their high melanin affinity these drugs most likely accumulate in the pigmented neurons, which may be the cause of degeneration and depigmentation of these cells (7,14,36). Manganese, which is known to cause parkinsonism in man (33) and degeneration of pigmented neurons in substantia nigra in monkeys (16), has also shown high affinity for melanin (4,8,29). The neurotoxic compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been found to produce parkinsonian-like symptoms, similar to those seen in idiopathic Parkinson's disease, through the destruction of nigrostriatal neurons in primates, including man (5,11,20, 21). Interestingly, primates have shown much higher sensitivity to MPTP than smaller laboratory animals such as guinea

pigs, rats (6) and mice (17,18). Primates have melanin containing nerve cells in the substantia nigra whereas rodents lack melanin in the catecholaminergic neurons of the brain (3,32). It has been shown that MPTP and two of its main metabolites have melanin affinity in vitro (9,30,31); whole body autoradiography (37,38) of ^{3}H-MPTP in mice showed accumulation and retention in melanin containing tissues such as the eyes (31) (Fig. 1).

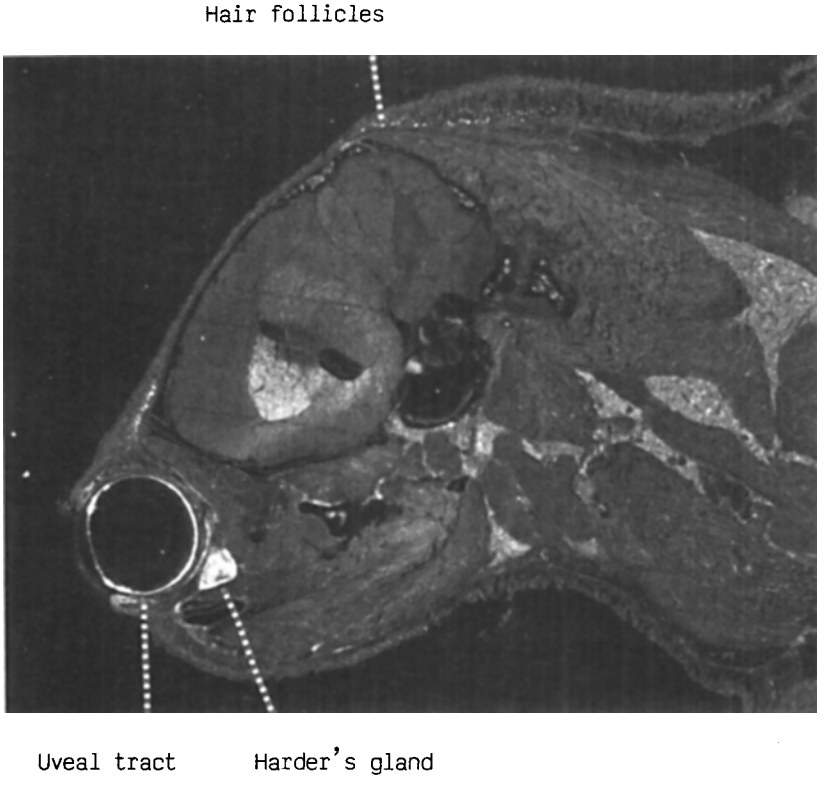

Fig.1. Detail of an autoradiogram of a pigmented mouse 1 hour after an intravenous injection of ^{3}H-MPTP. There is high accumulation in the uveal tract, eye-lids, Harder's gland and hair follicles.

Barbeau et al (1,2) have recently demonstrated that amphibians (frogs and salamanders) may be as sensitive as monkeys to the effects of MPTP and related substances on the central nervous system. Amphibians do have neuromelanin in certain neurons in the efferent regions of the brain (19), and by means of whole body autoradiography of ^{3}H-MPTP in frogs a high accumulation and retention was seen in the melanin bearing neurons (27) (Fig. 2).

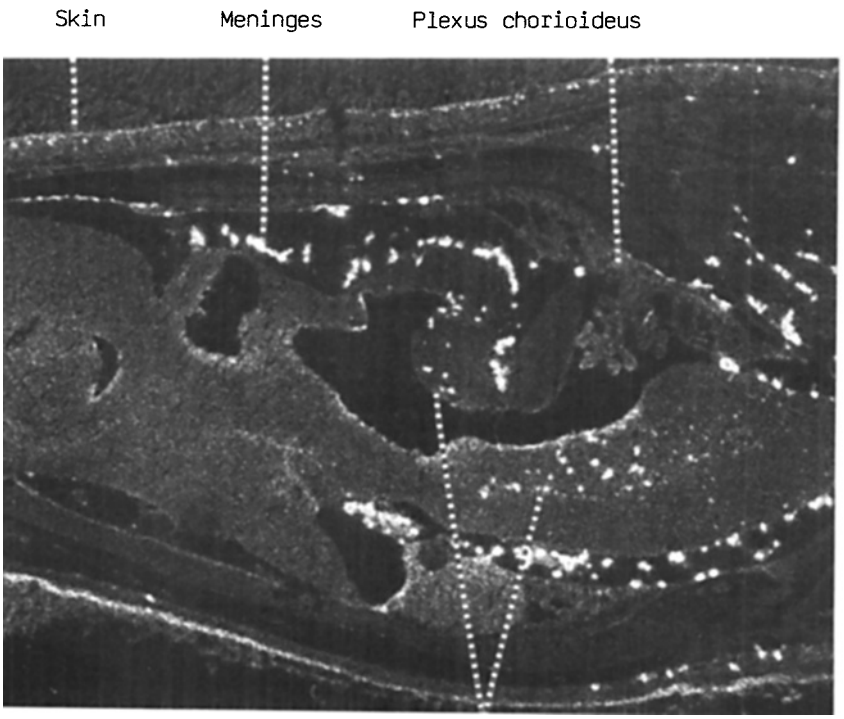

Fig. 2. Detail of an autoradiogram of a frog (Rana temporaria) 4 hours after an intraperitoneal injection of ^{3}H-MPTP. Accumulation is seen in neuromelanin containing neurons and in other melanin bearing tissues such as in skin and meninges.

The MPTP-induced destruction of the pigmented cell bodies in the neurons of the substantia nigra which has been observed in man and monkeys may be due to the affinity of MPTP and its metabolites for melanin, causing high concentrations of these compounds in the neuromelanin-bearing neurons. This mechanism may be involved also in other forms of chemically induced parkinsonism and possibly also in idiopathic Parkinson's disease, although the offending agent remains to be discovered.

CONCLUSIONS

Accumulation of certain chemical compounds in melanin-containing tissues has been suggested to be an important factor in the pathogenesis of chronic lesions in the skin, eye, inner ear and brain stem. The pigment melanin is very stable in the body, except for the epidermal melanin. Therefore a long term retention, even for years, of compounds with high melanin affinity, may

be seen in melanin containing tissues. The risk for development of lesions may be due to the degree and nature of the melanin binding, the distribution and toxicity of the different compounds, and the sensitivity of the different melanin containing tissues.

REFERENCES

1. Barbeau, A., Dallaire, L., Buu, N.T., Veilleux, F., Boyer, H., de Lanney, L.E., Irwin, I., Langston, E.B. & Langston, J.W.: New amphibian models for the study of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Life Sci 36:1125-1134, 1985.
2. Barbeau, A., Dallaire, L., Buu, N.T., Poirier, J. & Rucinska, E.: Comparative behavioral, biochemical and pigmentary effects of MPTP, MPP+ and paraquat in Rana pipiens. Life Sci 37:1529-1538, 1985.
3. Barden, H. & Levine, S.: Histochemical observations on rodent brain melanin. Brain Res Bull 10:847-851, 1983.
4. Bruenger, F.W., Stover, B.J. & Atherton, D.R.: The incorporation of various metal ions into in vivo - and in vitro-produced melanin. Radiat Res 37:1-12, 1967.
5. Burns, R.S., Chiueh, C.C., Markey, S.P., Ebert, M.H., Jacobowitz, D.M. & Kopin, I.J.: A primate model of parkinsonism: Selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci USA 80:4546-4550, 1983.
6. Chiueh, C.C., Markey, S.P., Burns, R.S., Johannessen, J., Jacobowitz, D.M. & Kopin, I.J.: N-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a parkinsonian syndrome causing agent in man and monkey, produces different effects in guinea pig and rat. Pharmacologist 25:131, 1983.
7. Christensen, E., Moller, J. & Faurbye, A.: Neuropathological investigation of 28 brains from patients with dyskinesia. Acta Psychiatr Scand 46:14-23, 1970.
8. Cotzias, G.C., Papavasiliou, P.S., van Woert, M.H. & Sakamoto, A.: Melanogenesis and extrapyramidal diseases. Fed Proc 23:713-718, 1964.
9. D'Amato, R.J., Lipman, Z.P. & Snyder, S.H.: Selectivity of the parkinsonian neurotoxin MPTP: Toxic metabolite MPP+ binds to neuromelanin. Science 231:987-989, 1986.
10. Das, K.C., Abramson, M.B. & Katzman, R.: Neuronal pigments: spectroscopic characterization of human brain melanin. J Neurochem 30:601-606, 1978.
11. Davis, G.C., Williams, A.C., Markey, S.P., Ebert, M.H., Caine, E.D., Reichert, C.M. & Kopin, I.J.: Chronic parkinsonism secondary to intravenous injection of meperidine analogues. Psychiatry Res 1:249-254, 1979.
12. Dencker, L. & Lindquist, N.G.: Distribution of labelled chloroquine in the inner ear. Arch Otolaryngol 101:185-188, 1975.
13. Felix, C.C., Hyde, J.S., Sarna, T. & Sealy, R.C.: Interactions of melanin with ions. Electron spin resonance evidence for chelate complexes of metal ions with free radicals. J Am Chem Soc 100:3922-3926, 1978.
14. Forrest, F.M., Forrest, I.S. & Roizin, I.: Clinical and biochemical and postmortem studies on a patient treated with chlorpromazine. Agressologie 4:259-265, 1963.
15. Greiner, A.C. & Berry, K.: Skin pigmentation and corneal and lens opacities with prolonged chlorpromazine therapy. Can Med Assoc J 90:663-665, 1964.
16. Gupta, S.K., Murphy, R.C. & Chandra, S.V.: Neuromelanin in manganese-exposed primates. Toxicol Lett 6:17-20, 1980.

17. Hallman, H., Olson, L. & Jonsson, G.: Neurotoxicity of the meperidine analogue N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine on brain catecholamine neurons in the mouse. Eur J Pharmacol 97:133-136, 1984.
18. Heikkila, R.E., Hess, A. & Duvoisin, R.C.: Dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine in mice. Science 224: 1451-1453, 1984.
19. Kemali, M. & Gioffrè, D.: Anatomical localisation of neuromelanin in the brains of the frog and tadpole. Ultrastructural comparison of neuromelanin with other melanins. J Anat 142:73-85, 1985.
20. Langston, J.W., Ballard, P., Tetrud, J.W. & Irwin, I.: Chronic parkinsonism in humans due to a product of meperidine analog synthesis. Science 219:979-980, 1983.
21. Langston, J.W., Forno, L.S., Rebert, C.S. & Irwin, I.: Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in the squirrel monkey. Brain Research 292: 390-394, 1984.
22. Larsson, B.: Mechanisms of accumulation of foreign substances in melanin. Binding to preformed melanin and incorporation into growing melanin. Acta Universitatis Upsaliensis, 43, 1979.
23. Larsson, B. & Tjälve, H.: Studies on the mechanism of drug-binding to melanin. Biochem Pharmacol 28:1181-1187, 1979.
24. Lindquist, N.G.: Accumulation in vitro of ^{35}S-chlorpromazine in the neuromelanin of human substantia nigra. Arch Int Pharmacodyn Ther 200: 190-195, 1972.
25. Lindquist, N.G. & Ullberg, S.: The melanin affinity of chloroquine and chlorpromazine studied by whole body autoradiography. Acta Pharmacol Toxicol (Copenh) 31: Suppl 2, 1972.
26. Lindquist, N.G.: Accumulation of drugs on melanin. Acta Radiol (Diagn) (Stockh) Suppl 325, 1973.
27. Lindquist, N.G., Lydén-Sokolowski, A. & Larsson, B.S.: Accumulation of a parkinsonism inducing neurotoxin in melanin-bearing neurons: Autoradiographic studies on ^{3}H-MPTP. Acta Pharmacol Toxicol (Copenh) 59: 161-164, 1986.
28. Lydén, A., Larsson, B. & Lindquist, N.G.: Studies on the melanin affinity fo haloperidol. Arch Int Pharmacodyn Ther 259:230-234, 1982.
29. Lydén, A., Bondesson, U., Larsson, B.S. & Lindquist, N.G.: Melanin affinity of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine, an inducer of chronic parkinsonism in humans. Acta Pharmacol Toxicol (Copenh) 53:429-432, 1983.
30. Lydén, A., Larsson, B.S. & Lindquist, N.G.: Melanin affinity of manganese. Acta Pharmacol Toxicol (Copenh) 55:133-138, 1984.
31. Lydén, A., Bondesson, U., Larsson, B.S., Lindquist, N.G. & Olsson, L.-I.: Autoradiography of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): Uptake in the monoaminergic pathways and in melanin containing tissues. Acta Pharmacol Toxicol (Copenh) 57:130-135, 1985.
32. Mardsen, C.D.: Brain melanin. In: Pigments in pathology (ed. M. Wollman). Academic Press, New York, pp 395-420, 1969.
33. Mena, I., Mann, O., Fuenzalida, S. & Cotzias, C.: Chronic manganese poisoning. Clinical picture and manganese turnover. Neurology (NY) 17: 128-136, 1967.
34. Potts, A.M.: The concentration of phenothiazines in the eye of experimental animals. Invest Ophthalmol Vis Sci 1:522-530, 1962.
35. Potts, A.M.: The reaction of uveal pigment in vitro with polycyclic compounds. Invest. Ophthalmol Vis Sci 3:405-416, 1964.
36. Roizin, L.: Chemogenic lesions: A multifactor pathogenic concept. In: Neurotoxicology (eds. L. Roizin., H. Shirakt & N. Grcevic) pp. 613-648. Raven Press, New York, 1977.
37. Ullberg, S.: Studies on the distribution and fate of ^{35}S-labelled benzylpenicillin in the body. Acta Radiol. (Diagn) (Stockh) Suppl 118, 1-110, 1954.

38. Ullberg, S.: The technique of whole body autoradiography. Cryosectioning of large specimens. Science Tools (The LKB Instrument J.) 2-29, 1977.

Address for reprints:
Nils Gunnar Lindquist
National Board of Health and Welfare
Department of Drugs
Division of Pharmacology and Toxicology
Box 607
S-751 25 Uppsala, Sweden