Commentary

The diffuse neuroendocrine system and extrapineal melatonin

I Kvetnoy, A K Sandvik and **H L Waldum**

Two jubilee dates, the 30-year anniversary of Pearse's APUD concept and the 20-year anniversary of the discovery of extrapineal melatonin synthesis in gut are the reason for this commentary.

Thirty years ago, Pearse (1966) first suggested that a specialized and highly organized cell system could exist in which the component cells have as their main feature the capability to produce peptide hormones and biogenic amines. His concept was based on extensive studies on endocrine cells in different organs, including the identification of regulatory substances and a thorough cytochemical and ultrastructural analysis of these cells. He found that so-called 'clear cells' widely dispersed in the organism have a common ability to take up and decarboxylate monoamines to biogenic amines. Thus in 1969 Pearse used the term 'APUD', an acronym for amine precursor uptake and decarboxylation, to designate these cells.

Since identical biogenic amines and regulatory peptides are found both in neurones and in APUD cells located in different organs, those cells can be considered to be part of a common regulatory system – the diffuse neuroendocrine system (DNES) (Waldum *et al*. 1993, Raikhlin & Kvetnoy 1994). Located in practically all organs and producing biologically active substances, DNES cells are regulators of homeostasis acting via neurocrine, endocrine and paracrine mechanisms.

During the last few years attention has especially centred on one of the hormones of the DNES – melatonin (MT) – which plays a key role in the control of biological rhythms. Lerner *et al*. (1958) first identified MT as the pineal substance bleaching frog skin, and MT was found to be the 5-methoxy-N-acetylated derivative of serotonin (ST). The identification of MT stimulated researchers' interest in the physiology of the pineal gland and a wide spectrum of biological activities of pineal MT was shown. However, this organ was still considered to be the only source of MT (Ariens-Kappers 1979, Reiter 1980).

As soon as highly sensitive antibodies to indolealkylamines became available (Grota & Brown 1974) MT could also be identified in extrapineal tissues, primarily those anatomically connected with the visual system such as retina and Harderian gland (Bubenik *et al*. 1974). This was expected because of the well-known influence of light on MT. However, RIA and thin-layer chromatography showed that after the removal of the pineal glands, MT could still be identified in the blood and urine of laboratory animals (Ozaki & Lynch 1976), indicating a significant extrapineal synthesis of MT.

The enterochromaffin (EC) cells are the main ST producing and storing cells of the gastrointestinal tract, and Raikhlin *et al*. (1975) were the first to suggest that MT is produced in the gut mucosa and to localize it to the EC cells.

This started the 'era of extrapineal melatonin'. The pineal gland is clearly not the only site of MT production, and mathematical analysis shows that the total number of EC cells throughout the gut is significantly larger than the possible number of pinealocytes (Raikhlin & Kvetnoy 1994). Huether (1993) showed that the avian and mammalian gastrointestinal tracts contain at least 400 times more MT than the pineal gland. These data, and the fact that EC cells account for 95% of ST suggest that EC cells are the main source of MT in the organism. Moreover, ST and MT have been observed in DNES cells in airway epithelium, liver, kidney, adrenals, thymus, thyroid, pancreas, ovary, carotid body, cerebellum, placenta and endometrium (Bubenik *et al*. 1974, Kvetnoy & Yuzhakov 1993, Raikhlin & Kvetnoy 1994), as well as in non-neuroendocrine cells like mast cells, natural killer cells and eosinophilic leukocytes (Kvetnoy & Yuzhakov 1994).

The discovery of the MT-containing cells in different organs during the last decade is the result of work utilizing ultraspecific rabbit melatonin antiserum for immunohistochemistry (code CIH 102: CIDtech Research Inc, Mississauga, Ontario,

Journal of Molecular Endocrinology (1997) **18,** 1–3 *Printed in Great Britain*
0952–5041/97/018–001 $08.00/0

Canada). This antiserum is produced by rabbits immunized with MT coupled to BSA using formaldehyde; blocking experiments using a variety of indolealkylamines (e.g. serotonin, N-acetylserotonin, 6-hydroxymelatonin, etc.) revealed strong inhibition of binding only with MT (Brown *et al*. 1983). The above list of the cells storing MT indicates that there are considerable prospects for the future search of potential MT-producing cells, and MT has a unique position among the hormones of the DNES, being found in practically all organ systems.

Functionally, MT-producing cells are certain to be part and parcel of the DNES as a universal system of response, control and organism protection. In spite of data showing an active participation of MT in adaptive response, as well as in pathophysiology, the normal functions of extrapineal MT are largely unknown. One interesting hypothesis is that MT may act as a free radical scavenger. The role of free radicals in the pathogenesis of many diseases is well known (Cross *et al*. 1987, Kehrer 1993). It was recently discovered that MT is a potent hydroxyl radical scavenger (Reiter *et al*. 1993), and that it could protect against free radical damage more effectively than the well-known scavenger glutathione (Reiter *et al*. 1994). The free radicals are normal products of aerobic metabolism in cells (Imlay & Linn 1988), and are found in many tissues and organs (Costa *et al*. 1996). In particular, high concentrations of NO were observed in the gut, brain, retina and lung (Brookes 1993, Bruhwyler *et al*. 1993) – in organs where MT-containing cells are also numerous. Moreover, MT was found in significant amounts in the Harderian glands of some mammals (Bubenik *et al*. 1976). The Harderian glands produce large quantities of porphyrins, which induce free radical production and oxidative damage (Hermes-Lima *et al*. 1992). The hypothesis that MT protects the Harderian glands from free radical damage induced by porphyrins (Reiter *et al*. 1994) is supported by the fact that in animals (e.g. Syrian hamsters) where the quantity of porphyrins is widely different between males and females, the amounts of MT in these glands is strongly correlated to the porphyrin content (Menendez-Pelaez & Reiter 1993).

Thus, taking into account the large number of MT-producing cells in many organs, the wide spectrum of biological activities of MT and especially its main property as a universal regulator of biological rhythms, we suppose that extrapineal melatonin may play a key role as a paracrine signal molecule for the local co-ordination of intercellular relationships. Extrapineal MT may also act as a typical hormone, reaching widely spread target cells through the bloodstream. It has now been shown that many cells in different organs have MT receptors (Pang *et al*. 1993). In both cases, some non-endocrine cells such as mast cells and eosinophilic leukocytes may take up MT from the blood or intercellular space for transport to sites where it exerts its effects.

We must underline that these ideas on the significance of extrapineal MT as a general neuroendocrine regulator are speculative. However, we wish to bring those views forward to stress once more the great significance of Pearse's APUD concept; his theory revealed new perspectives in many different fields of biology and medicine, and also for the ongoing elucidation of the functions of extrapineal MT.

REFERENCES

Ariens-Kappers J 1979 *Progress in Brain Research* **52** 3–22.

Brookes SJH 1993 *Journal of Gastroenterology and Hepatology* **8** 590–603.

Brown GM, Grota LJ, Pulido O, Burns TG, Niles LP & Snieckus V 1983 *Pineal Research Review* **1** 207–246.

Bruhwyler JU, Chleide E, Liegegois JF & Carreer F 1993 *Neuroscience and Biobehavioral Reviews* **17** 373–384.

Bubenik GA, Brown GM & Uhlir I 1974 *Brain Research* **81** 233–242.

Bubenik GA, Brown CM & Grota LJ 1976 *Brain Research* **119** 417–427.

Costa A, Poma A, Navarra P, Forsling ML & Grossman A 1996 *Journal of Endocrinology* **149** 199–207.

Cross CE, Halliwell B, Borish ET, Pryor WA, Ames BN, Saul RL, McCord JM & Harman D 1987 *Annals of Internal Medicine* **107** 526–545.

Grota LJ & Brown GM 1974 *Canadian Journal of Biochemistry* **52** 196–200.

Hermes-Lima M, Castillo RF, Valle VGR, Bechara EJH & Vercesi AE 1992 *Biochimica et Biophysica Acta* **1180** 201–206.

Huether G 1993 *Experientia* **49** 665–670.

Imlay JA & Linn S 1988 *Science* **240** 1302–1309.

Kehrer JP 1993 *Critical Reviews in Toxicology* **23** 21–48.

Kvetnoy IM & Yuzhakov VV 1993 *Microscopy and Analysis* **15** 27–29.

Kvetnoy IM & Yuzhakov VV 1994 In *Advances in Pineal Research* 7, pp 199–212. Eds GJM Maestroni, A Conti & RJ Reiter. London: John Libbey.

Lerner AB, Case J & Takahashi J 1958 *Journal of the American Chemical Society* **80** 2587–2589.

Menendez-Pelaez A & Reiter RJ 1993 *Journal of Pineal Research* **15** 59–69.

Ozaki Y & Lynch HJ 1976 *Endocrinology* **99** 641–644.

Pang SF, Dubocovich ML & Brown GM 1993 *Biological Signals* **2** 177–180.

Pearse AGE 1966 *Veterinary Records* **79** 587–590.

Pearse AGE 1969 *Journal of Histochemistry and Cytochemistry* **17** 303–313.

Raikhlin NT & Kvetnoy IM 1994 *Physiology and General Biology Reviews* **8** 1–44.

Raikhlin NT, Kvetnoy IM & Tolkachev VN 1975 *Nature* **255** 344–345.

Reiter RJ 1980 *Endocrine Reviews* **1** 109–131.

Reiter RJ, Poeggler B, Tan DX, Chen LD, Manchester LC & Gurrero JM 1993 *Neuroendocrinology Letters* **15** 103–116.

Reiter RJ, Tan DX, Poeggler B, Chen LD & Menendez-Pelaez A 1994 In *Advances in Pineal Research* 7, pp 211–228. Eds GJM Maestroni, A Conti & RJ Reiter. London: John Libbey.

Waldum HL, Sandvik AK, Syversen U & Brenna E 1993 *Acta Oncologica* **32** 141–147.

I Kvetnoy,
Laboratory of Pathomorphology,
Medical Radiological Research Center,
Obninsk 249020, Russia

A K Sandvik,
Department of Physiology and
Biomedical Engineering,
University of Trondheim,
N-7005 Trondheim, Norway

H L Waldum,
Department of Medicine,
University of Trondheim,
N-7005 Trondheim, Norway