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# Effect of Chlorpromazine and Other Drugs on the Disposition of Circulating Melatonin

THE mammalian pineal gland has the unique ability to synthesize methoxyindoles such as melatonin[1,2] and methoxytryptophol[3]. It has been suggested that these compounds function as hormones[4,5]: melatonin is secreted into the circulation[4,6] and efficiently extracted from the blood by most tissues[7,8]; both compounds inhibit gonad function[4,5,9], and it has also been claimed that melatonin acts on the thyroid[10,11], gut[12], pituitary[13], skin[14] and brain[15].

The physiological disposition of circulating melatonin has been investigated by injecting isotopically labelled material of high specific activity[7,8]. It has been shown that melatonin disappears rapidly from the circulation[7]. Most of the hormone is inactivated by 6-hydroxylation within the liver, followed by conjugation and excretion as the sulphate or glucuronide[7]. We have investigated the effects of a group of widely used drugs on the disposition of circulating melatonin. It will be shown that chlorpromazine markedly prolongs the disappearance of this hormone from the blood and the tissues.

Tritiated melatonin (200 μc./μmole) was synthesized from *N*-acetylserotonin and tritiated acetic anhydride (New England Nuclear Co., Boston, Massachusetts) by a method described previously[7]. Groups of Sprague–Dawley rats weighing 180–200 g were given the labelled hormone intravenously, in doses ranging from 8 to 63·6 μc., and killed by neck fracture 30 min later. (The fate of the hormone was found to be unrelated to the magnitude of the amount injected, in this range of dosages.) Tissues were rapidly dissected and homogenized in 3 volumes of cold 0·4 normal perchloric acid; the unchanged tritiated melatonin was then extracted into 8 ml. of chloroform, and measured as described before[8]. Blood was collected by cardiac or vena caval puncture.

Thirty minutes before receiving the melatonin, groups of rats were treated with reserpine, chlorpromazine, serotonin, or methoxytryptamine (Table 1). Reserpine pretreatment caused a significant fall (by about one-third) in the content of labelled hormone in the brain and the heart; it did not interfere with the accumulation of melatonin by the ovaries (Table 1). Chlorpromazine markedly enhanced the accumulation of tritiated melatonin by all the organs studied: brain, ovary and heart each contained more than three times as much hormone as the organs of control animals, 30 min after its injection. Neither serotonin nor methoxytryptamine pretreatment

altered the accumulation of tritiated melatonin in tissue, although both compounds are similar to melatonin in chemical structure (Table 1).

Phenothiazines are known to influence membrane transport mechanisms[16]. The ability of chlorpromazine to enhance the accumulation of circulating melatonin by the tissues could thus have resulted from changes in the uptake of the indole from the blood. If so, it might be expected that the ratio of tritiated melatonin in brain to that in the blood would be increased by chlorpromazine treatment. If, on the other hand, chlorpromazine acted by inhibiting the metabolism of the indole, it would be anticipated that the levels of labelled hormone would

Table 1. Effect of Pretreatment with Drugs on the Levels of Tritiated Melatonin in Tissues

| Drug | Dose | $^3$H-melatonin content (m$\mu$c./g) Brain | Ovary | Heart |
|---|---|---|---|---|
| Control | – | 19·1 ± 2·0 | 23·7 ± 2·4 | 25·8 ± 2·7 |
| Reserpine | 3 mg/kg | 12·5 ± 1·7* | 23·8 ± 3·1 | 17·6 ± 1·2* |
| Chlorpromazine | 20 mg/kg | 64·9 ± 7·7† | 76·5 ± 10·7† | 71·2 ± 8·5† |
| Serotonin | 20 mg/kg | 17·3 ± 1·9 | 31·7 ± 5·4 | 21·6 ± 4·2 |
| Methoxytryptamine | 20 mg/kg | 21·7 ± 2·5 | 32·2 ± 3·9 | 22·2 ± 2·7 |

Groups of six rats were given the drug intraperitoneally 30 min before receiving 63·6 $\mu$c. of $^3$H-melatonin intravenously. They were killed 30 min after the melatonin was injected.

* Differs from control, $P < 0.05$.

† Differs from control, $P < 0.001$.

Table 2. Effect of Chlorpromazine on the Tritiated Melatonin Contents of Blood and Tissues

| Treatment | $^3$H-melatonin content (m$\mu$c./g) Brain | Skin | Eye | Blood |
|---|---|---|---|---|
| Control | 3·68 ± 0·39 | 2·27 ± 0·06 | 1·50 ± 0·04 | 3·29 ± 0·30 |
| Chlorpromazine | 10·00 ± 1·06* | 7·40 ± 0·18* | 3·57 ± 0·09* | 8·76 ± 0·71* |

Rats were given chlorpromazine (20 mg/kg) or its diluent 30 min before receiving $^3$H-melatonin (8 $\mu$c. intravenously). Thirty minutes later they were killed. "Skin" represents both ears; "Eye" represents both whole eyes.

* $P < 0.001$.

rise in both the tissues and the blood. To determine which mechanism was operating, rats were pretreated with chlorpromazine, and then given tritiated melatonin intravenously; 30 min later the levels of hormone were determined in both blood and tissues. It was found (Table 2) that chlorpromazine treatment elevated the levels of melatonin in both the brain and the circulation. The drug also increased the accumulation of the hormone in the skin and the eye.

Chlorpromazine and melatonin appear to exert physiological actions on several common structures: they have both been reported to alter electroencephalograph patterns[15,17], to interfere with the ovulatory or oestrous cycle of rats[9,18], to block some of the effects of serotonin on smooth muscle[12,19], and to alter mammalian pigmentation[14,20]. On the basis of the results reported here, it seems possible that one mechanism by which chlorpromazine might produce some of its effects is by elevating the levels of melatonin in the tissues. Melatonin has been found in human urine and in bovine sciatic nerve, albeit

in very small quantities[6]. It should be of interest to determine whether humans who have been treated chronically with chlorpromazine have higher than normal levels of melatonin or its metabolites in their urine and tissues.

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