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THE EFFECT OF CENTRALLY ACTING DRUG CHLORPROMAZINE ON THE SECRETION OF PROLACTIN IN THE LIZARD, *UROMASTIX HARDWICKII*

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ABSTRACT

This investigation deals with the effect of chlorpromazine, on *Uromastix* hypophyseal prolactin. Administration of the doses 0.125, 0.25, 0.5 and 1 mg chlorpromazine per 3 days per animal resulted in a significant increase pigeon crop-sac response ($p<0.01$). The degree of proliferation of crop-gland showed a dose dependent threshold. Chlorpromazine binds to the target cell specific receptors of PRL and GH, both at the same time.

INTRODUCTION

Overproduction of prolactin (PRL) is associated with the inhibition of the normal release of gonadotrophins. More so PRL is released by the secreting pituitary tumors. Hypothyroidism is another such example. In addition, haloperidol, metoclopramide, methyldopa, cimetidine and monoamine oxidase inhibitors are known to cause excessive secretion of PRL (Girdwood, 1979).

Possibility exists that phenothiazides accelerate PRL secretion. Therefore, chlorpromazine, belonging to this group of drugs, seems to increase PRL concentrations in the plasma (Ayd, 1963).

With the establishment of PRL as a crop-gland stimulating factor in the birds; a number of useful and sensitive bioassay methods (Riddle *et al.,* 1931, 32, 33) employing pigeons and doves have been described.

In recent years *Uromastix hardwickii* has served as a popular experimental animal (Ahmad & Taqawi, 1978, 1979, Ahmad *et al.,* 1980); and the pituitary PRL content of this animal has been extensively studied (Ahmad *et al.,* 2001a, b; 2002a, b).

The present investigation was therefore undertaken to determine the effect of chlorpromazine, on *Uromastix* PRL.

MATERIALS AND METHODS

Assay animals:

Pigeons eight to twelve weeks of age and weighing 250 ± 20 g, belonging to mixed races were used as assay animals. Pigeons were housed one to a cage and were fed grain and water *ad libitum*. The birds were kept in laboratory not more than two days prior to bioassay.

Animals:

For the present investigation pigeons and *Uromastix hardwickii* were obtained from local suppliers and were maintained at a temperature 29 ± 1°C. They were divided into several groups of control and test.

Drug Information:

Chlorpromazine discovered in 1951 belongs to phenothiazine group. Chlorpromazine is a non-selective dopamine antagonists reported as a prolactin (PRL) releaser with weak cholinergic and α-adrenoreceptor blocking activity. Chlorpromazine acts in the hypothalamus, brain stem reticular formation and produces ECG changes. Galactorrhoea and amenorrhoea occurs due to blocking of dopamine mediated prolactin (PRL) inhibiting path in the hypothalamus due to rise in plasma PRL concentration.

The dose of 25 mg given orally is well absorbed from alimentary tract; while intramuscular (IM), or intravenous (IV) administration 4 – 6 hourly with increase in dose every 3 – 4 days is seldom justified. The plasma half-life is about 16 hours. The biological effect of single dose persists for atleast 24 hours. The elimination from plasma is rapid because of its highly lipophilic nature. Its therapeutic effect may be delayed for as long as 4 weeks depending on behaviour. Chlorpromazine accumulates in brain and is highly protein bound. It is metabolized chiefly in liver.

The rate of elimination and of metabolism decreases with advancing age. Individual genetic determinants are also responsible for varied metabolism and the rate of elimination. The use of term "artificial hibernation" in connection with the use of chlorpromazine, with or without other drugs is particularly inappropriate, since there is no general slowing down of bodily processes; in addition the circulation is more, and the individual is not less active. Some central effect on the temperature regulatory mechanism is probable. Chlorpromazine causes heat loss and body temperature may fall as in other long acting vasodilators. The most serious effect is obstructive jaundice; occurring after 2 – 4 weeks of therapy. Recovery occurs after stopping the drug but permanent liver damage has been reported.

Administration of drug:

Uromastix hardwickii were divided at random into 5 equal groups. Individual of one group were administrated, one by one, 0.125 mg chlorpromazine (May and Baker, England) per day for a period of 3 days intravenously through abdominal vein (Ahmad *et al.,* 2001a; 2002b). Individuals of group II received a dose of 0.25 mg similarly; animals of group III were treated with 0.5 mg in the same manner. Animals of group IV were given a dose of 1 mg per day for 3 successive days intravenously. However, untreated animals comprised of a control group were used to obtain normal values.

Removal of Pituitaries:

On the 4^{th} day animals of control and test groups were decapitated one by one. The skull was cleaned and brain was scooped out. The pituitary was extracted from sella turcica by cutting the sella diaphragm. Each pituitary was kept in a marked vial. It was either preserved in the freezing compartment of a refrigerator for later assay or was used for the assay at once. The frozen and fresh pituitaries gave similar results.

Pituitary Suspension:

A suspension was made by grinding the pituitaries with an agate and a mortar in a small but fixed quantity of pyrogen free distilled water. This was then with the help of a hypodermic syringe, transferred into serum bottle and stored in refrigerator for administration during the bioassay period.

Assay Procedure:

Assay procedure was essentially the same as that of Ahmad *et al.* (2001a, b). Feathers were

plucked off the skin overlying the crop gland Ahmad *et al.,* (2001a, b; 2002b). A normal suspension of pituitary was injected intradermally on one side of the crop in volume of 0.1 cc per day for four days. An identical volume (0.1 cc) of the pyrogen free water was injected on other side of the crop in the same bird served as control. The suspension prepared of the pituitaries of the drug-treated *Uromastix* was similarly injected intradermally on one side of the crop. The injections were made with a 1 ml hypodermic syringe and a 27 gauge needle inserted at the geometrical centre of each crop-gland (Ahmad *et al.,* 200la, b; 2002b) the site of which had been marked previously with a non-toxic marker dye for subsequent reference. The injections were made in such a way that the intradermal bleb was always formed.

The birds were killed on day 5, twentyfour hours after the last injection. The skin was separated from the underlying crop-sac and the whole crop-sac was removed and bisected. The lining of each half was rinsed with running tap water and adherent fat was removed. Each half was stretched by one person against light of a table lamp fitted with a 100 watt bulb as a source; while another measured in centimeters with a caliper, the diameter of the proliferated area. When the stretched crop-gland was viewed against light, the proliferated epithelium appeared as an essentially circular opaque area of parallel epithelial strands which was easily measurable.

RESULTS

Table-1 indicates that chlorpromazine is lactogenic and produces PRL in excessive amounts. A comparison of different experimental groups showed a significant difference between the mean diametric crop-sac response when analyzed by the single factor ANOVA ($p< 0.01$, Table-2). The daily doses showed increased response proportional to the rise of drug amount in the respective doses (Fig.1).

Table-1
Response of pigeon crop-gland to homogenates of *Uromastix* pituitaries of normal and four different dose groups (II– V) following administration of chlorpromazine

No. of Groups	Animals/Group	Dose injected (mg)	Total drug injected/ individual (mg)	*Mean crop-sac response (cm) ± SD
I	5	Normal	Nil	1.20 ± 0.18
II	5	0.125	0.375	1.28 ± 0.18
III	5	0.25	0.75	1.39 ± 0.07
IV	5	0.50	1.50	1.41 ± 0.15
V	5	1	3	1.54 ± 0.01

*The mean of five measurements of crop-sac diameter with ± SD.

DISCUSSION

PRL is exceptional among the hormones of pituitary is being greatly influenced by the hypothalamus (Meites and Nicoll, 1966). Thus, disturbance due to disease process or drug effect in or near the pituitary or hypothalamic area can interrupt the normal connections between

hypothalamus and anterior pituitary and produces excessive release of PRL by simultaneously causing deficiencies in release of one or more of the hormones of the anterior pituitary (Turkington *et al.,* 1972a; Tolis *et al.,* 1974).

Many drugs for example ACTH, dexamethasone (Ahmad *et al.,* 2001a,b) and especially those that affect the central nervous system (e.g. phenothiazine, reserpine, L-DOPA) can produce hyperprolactinemia (Turkington *et al.,* 1972a; Kleinberg *et al.,* 1977). Also in the present study chlorpromazine produced the same results in *Uromastix hardwickii*. This indicates that the drug disrupted the pituitary-hypothalamic relationship and resulted in excess PRL release from normal secretory cells. Finally, it will not be inappropriate to mention that chlorpromazine, in addition to affecting the PRL secretion also promotes growth hormone (GH) secretion. Thus it exerts these effects at the target cells by binding to both types of specific receptors to produce the effect of hypersecretion of both hormones (Chadwick *et al.,* 1961; Ferguson and Wallace, 1961; Lesniak *et al.,* 1977).

Table-2

Comparison of the effect of different doses of chlorpromazine on the pigeon crop-sac

ANOVA

Source of Variation	SS	Df	MS	F	P-value	F crit
*Between Groups	0.34	4	0.09	4.46	0.01	2.87
Within Groups	0.39	20	0.02	-	-	-
Total	0.73	24				

*Between groups; Doses of chlorpromazine (0.125, 0.5, 0.5 and 1.0 mg/day)

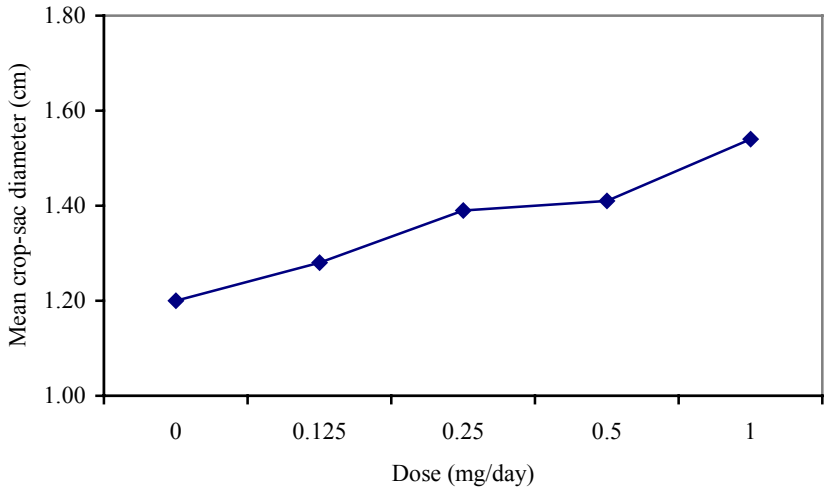

Fig. 1: A direct dose dependent mean crop-sac diametric response to chlorpromazine.

REFERENCES

Ahmad, M., Adeeba, S. and Humera, A. (1980). The effect of hypothalamic lesion on the thrombocytes of the lizard, *Uromastix hardwickii. Z.mikrosk-anat. Forsch*. **91**(2): S. 343-352.

Ahmad, M., Mahmood, I., Hasan, R., Javaid, A., Naim, T., Fatima, H. and Ahmad, M. (2001a). *In vitro* effects of ACTH on pigeon crop-sac epithelium. *Pak. J. Pharm. Sci*. **14**(1): 19-23.

Abmad, M., Mahmood, I., Hasan, R., Fatima, H. and Ahmad, M. (2001b). Effect of dexamethasone on pituitary prolactin in the lizard, *Uromastix hardwickii. Pak. J. Pharm. Sci*. **14**(2): 43-46.

Ahmad, M., Humera, A., Hasan, R., Fatima, H., Javaid, A., Naim, T. and Ahmad, M. (2002a). The effect of Hypothalamic lesion on blood cholesterol in the lizard, *Uromastix hardwickii. Pak. J. Pharmacol*. **19**(1): 53-56.

Ahmad, M., Mahmood, I., Hasan, R., Naim, T., Javaid, A., Fatima, H. and Ahmad, M. (2002b). Bioassay of pituitary prolactin of the lizard, *Uromastix hardwickii. Pak. J. Pharmacol*. **19**(2): 7-11.

Ahmad, M. and Taqawi, I. (1978). Radiation induced leukemia and leukopenia in the lizard, *Uromastix hardwickii. Radiobiol. Radiother.* **19**: 353-360.

Ahmad, M. and Taqawi, I. (1979). The clinical sequence of hematological effects in the lizard, *Uromastix hardwickii* subjected to gama-radiation. *Radiobiol. Radiother*. **20**: 769-776.

Ayd, F. J. (1963). Chlorpromazine: Ten years Experience. *J. Am. Med. Ass.* **184**: 51-62.

Chadwick, A., Folley, S.J. and Gemzell, C. A. (1961). Lactogenic activity of human pituitary growth hormone. *Lancet*. **2**: 241-243.

Ferguson, K.A. and Wallace, A.L.C. (1961). Prolactin activity of human growth hormone. *Nature* (London). **190**: 632-633.

Girdwood, R.H. (1979). In: Clinical Pharmacology (Dilling) 24th Ed., Bailliere Tindall London, pp.394.

Kleinberg, D.L., Noel, G.L. and Frantz, A.G. (1977). Galactorrhoea: A study of 235 cases, including 48 with pituitary tumors. *N. Engl. J. Med*., **296**: 589-600.

Lesniak, M.A., Gorden, P. and Roth, J. (1977). Reactivity of non-primate growth hormones and prolactins with human growth hormone receptors on cultured human lymphocytes. *J. Clin. Endocrinol. Metab*. **44**: 838-849.

Meites, J. and Nicoll, C.S. (1966). Adenohypophysis: Prolactin. *Ann. Rev. Physiol.* **28**: 57-88.

Riddle, O. and Brancher, P.F. (1931). Studies on the Physiology of reproduction in birds. *Am. J. Physiol*. **97**: 617- 626.

Riddle, O., Bates, R.W. and Dykshorn, S.W. (1932). Prolactin, a new and third hormone of the anterior pituitary. *Anat. Rec.* **54**: 25.

Riddle, O., Bates, R.W. and Dykshorn, S.W. (1933). The preparation, identification and assay of prolactin, a hormone of the anterior pituitary. *Am. J. Physiol*. **105**: 191-216.

Tolis, G., Somma, M., Compenhaut, J.V. and Friesen, H. (1974). Prolactin secretion in sixty-five patients with galactorrhoea. *J. Obstet. Gynecol.* **118**: 51-101.

Turkington, R.W. (1972a). The clinical endocrinology of prolactin. *Adv. Intern. Med.*, **18**: 363-387.