Zeitschrift: Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: 34 (1978)

Artikel: Dopaminergic control of prolactin secretion

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DOI: https://doi.org/10.5169/seals-308150

Bull. Schweiz. Akad. Med. Wiss. 34, 191-196 (1978)

Medical and Biological Research, SANDOZ LTD., Basel

DOPAMINERGIC CONTROL OF PROLACTIN SECRETION

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Abstract

A brief summary is given about present-day knowledge and views on the control of prolactin secretion in mammals. This is followed by the presentation of the evidence that dopamine is the inhibitory hypothalamic transducer controlling hormone release by prolactin cells. Most of the evidence is pharmacological in nature. It is only very recently that dopamine has been found in a meaningful concentration in the blood flowing from the median eminence to the pituitary. Although the dopamine concept of an inhibitory control of prolactin secretion seems quite satisfactory, the possibility of another unrelated inhibitory control system is not excluded.

Zusammenfassung

Nach einem kurzen Abriss unserer heutigen allgemeinen Kenntnisse und Ansichten über die Steuerung der Prolaktin-Sekretion bei Säugetieren folgt eine Darstellung und Diskussion der Befunde, die auf Dopamin als den Prolaktin sekretionshemmenden Ueberträgerstoff des Hypothalamus hinweisen. Diese Hinweise sind mehrheitlich pharmakologischer Natur. Erst kürzlich gelang der Nachweis, dass Dopamin im Portalblut, zwischen Eminentia mediana und Hypophysenvorderlappen, in für die Prolaktinsekretionshemmung genügender Konzentration vorkommt. Obschon das Dopamin-Konzept der Prolaktinsekretionssteuerung befriedigt, ist das Vorhandensein eines weiteren, andersartig wirkenden Hemmsystems nicht auszuschliessen.

Prolactin secretion by the mammalian pituitary, in contrast to most other anterior pituitary hormones, is under a predominantly inhibitory influence of the CNS. Thus the pituitary secretes increased amounts of prolactin if the hypophyseal stalk is severed or if the isolated pituitary is incubated in vitro.

PASTEELS (1961) and TALWALKER et al. (1963) were the first to demonstrate the presence of an extractable fraction in the hypothalamus which, when incubated in vitro with pituitaries, attenuated the release of prolactin. Thus the CNS exerts its inhibitory influence on prolactin secretion by the release of one or several prolactin inhibitory factors (PIFs) into the hypothalamo-pituitary portal system. NICOLL et al. (1970) and VALVERDE et al. (1972) produced evidence that the hypothalamus contains in addition extractable fractions which enhance the release of prolactin. The CNS may thus exert a stimulatory influence by releasing one or several prolactin stimulatory factors (PRFs), TRH being the first candidate for such a function.

Because the isolated pituitary secretes prolactin autonomously, physiologists and pharmacologists in general consider the inhibitory aspects of prolactin control more important than the stimulatory aspects. Our present-day understanding of prolactin control in mammals hardly considers the possible involvement of PRFs but explains changes in prolactin secretion mainly by modulation of the inhibitory tone.

The neuronal network which controls the secretion of prolactin comprises cholinergic, noradrenergic, serotoninergic, GABA-ergic and dopaminergic elements (CLEMENS 1976). Disregarding control mechanisms for PRF, the final common pathway is composed of dopaminergic neurones plus presumably postsynaptic neurones producing PIF. The dopaminergic neurones belong to the group of tubero-infundibular neurones which terminate in the median eminence adjacent to the primary capillary plexus of the portal vessels connecting the median eminence and the anterior pituitary. Although there are many questions implicit to such a neuronal network, we shall concentrate on the dopaminergic control of prolactin secretion.

VAN MAANEN and SMELIK postulated in 1968 that the tubero-infundibular neurones could exert their inhibitory control on prolactin secretion "via the release of the inhibitory neurotransmitter into the portal vessel system". Thus prolactin secreting cells are postulated to have monoamine receptors which when stimulated depress prolactin secretion.

The pharmacological evidence for the existence and characterization of such inhibitory monoamine receptors is as follows. MACLECD and LEHMEYER (1972) using incubated rat pituitary fragments, demonstrated that dopamine, l-noradrenaline, l- and d-adrenaline inhibit prolactin release, but that metanephrine and 3,4-dihydroxymandelic acid are inactive at 10^{-5}M. Dopamine was found to be more active than noradrenaline and to be active even at 10^{-9}M. CLEMENS (1976) found dopamine to be at least 10 times more potent than noradrenaline in dose-response studies in vitro. The inhibitory action of dopamine on prolactin secretion can be antagonized in vitro by drugs known to block catecholamine receptors. MACLEOD

and LEHMEYER (1974a) found phentolamine at $4x10^{-5}$M to antagonize only weakly the action of $5x10^{-7}$M dopamine on rat pituitary fragments, but perphenazine antagonized dose-dependently the inhibitory action of $5x10^{-7}$M dopamine at concentrations between 10^{-9} and 10^{-8}M. Perphenazine alone did not influence prolactin secretion. Haloperidol and pimozide acted similarly to perphenazine (MACLEOD and LEHMEYER 1974b; MACLEOD 1976). These observations favour the idea that dopamine receptors are involved in the inhibitory action of dopamine on prolactin release. A further approach to the characterization of the prolactin secretion inhibitory receptors was made by the use of dopaminomimetic drugs instead of the labile biogenic amines. It was found that apomorphine also inhibits prolactin release in vitro (MACLEOD and LEHMEYER 1974a). This effect is antagonized by pimozide but not by phentolamine or propranolol (SHAAR and CLEMENS 1974), indicating that α-adrenoceptors and β-adrenoceptors are probably not involved in the apomorphine effect, but that dopamine receptors are. In addition, certain ergot alkaloids and their derivatives have been used successfully to inhibit the release of prolactin from pituitary fragments or cells (PASTEELS et al. 1971; LU et al. 1971; MACLEOD and LEHMEYER 1972; TASHJIAN and HOYT 1972). The inhibitory action of $3x10^{-9}$M α-ergokryptine was antagonized dose-dependently by $2,5x10^{-9}$M haloperidol (MACLEOD and LEHMEYER 1974a). Similar antagonisms were noted with bromocriptine plus haloperidol (MACLEOD, personal communication), as well as with lergotrile plus pimozide, but not with lergotrile plus phentolamine or lergotrile plus propranolol (CLEMENS 1976). Thus there is clear pharmacological evidence that prolactin cells are equipped with dopamine receptors, stimulation of which leads to attenuation of prolactin release. Further evidence of dopamine receptors on pituitary cell membranes was provided recently by ligand binding studies by LABRIE's group using cell membranes isolated from beef pituitaries. Membrane bound (^{3}H)-dihydroergokryptine was displaced competitively by haloperidol, both compounds showing similar affinity to the binding sites. The affinities of phentolamine and propranolol were several orders of magnitude lower than that of haloperidol (CARON et al. 1976).

It is thus evident that the end-apparatus for a dopaminergic inhibitory control of prolactin secretion exists. What is then the evidence that dopamine is released in the median eminence to act at the pituitary as the physiological inhibitory transmitter in the sense of the hypothesis of VAN MAANEN and SMELIK (1968)?

It seems clear from the receptor studies described above that any hypothalamic extract containing catecholamines will show prolactin inhibitory activity when incubated with pituitary fragments. Accordingly SHAAR and CLEMENS (1976) noted a close correlation between pro-

lactin inhibitory activity in hypothalamic extracts and their catecholamine content. Unfortunately such findings cannot prove the physiological role of the catecholamines. SCHALLY's group (TAKAHARA et al. 1974) first showed that dopamine, freshly prepared in isotonic glucose solution, suppressed prolactin secretion when infused into the hypothalamo-pituitary portal system of the rat. Recently PORTER's group (BEN-JONATHAN et al. 1977) pointed out that whereas noradrenaline is the major catecholamine in the hypothalamus, dopamine is the catecholamine present in portal blood. The highest dopamine concentration measured was 18 - 19 ng/ml plasma or about $1,3 \times 10^{-7}$ M. Dopamine incubated at this concentration with pituitary fragments produced near maximal inhibition of prolactin release in the experiments reported by MACLEOD (1976) and CLEMENS (1976). Thus for the first time there is evidence for dopamine travelling in a meaningful concentration in the blood flowing from the median eminence to the pituitary. The results of the work by PORTER's group may be taken as good evidence that the tubero-infundibular neurones which end in the vicinity of the capillaries of the primary portal plexus are capable to release dopamine in such amounts that it could act as PIF on the prolactin secreting cells.

Summarizing, we can state that VAN MAANEN and SMELIK's (1968) original hypothesis of a direct monoaminergic inhibitory control of prolactin secretion by the hypothalamus via the portal system is well substantiated by the demonstration of a dopamine-sensitive inhibitory apparatus for prolactin release on the prolactin cells, and by the demonstration of dopamine in meaningful concentrations in portal blood. We might conclude that there is no necessity to postulate the existence of PIF other than dopamine. However, recent findings suggest that at least one other factor may be involved. SCHALLY's group (SCHALLY et al. 1977) working with hypothalamic extracts with PIF-like activity but devoid of catecholamines have recently succeeded in identifying the active principle as GABA. In vitro inhibition of prolactin secretion by GABA which, on a molar basis, seems much less potent than dopamine (ARIMURA and SCHALLY 1977) could not be antagonized by perphenazine. GABA then acts on the prolactin secreting cell but not by stimulating a catecholamine receptor. We are thus faced with the likelihood of a second inhibitory system, probably unrelated to the dopaminergic control mechanism.

Arimura, A., Schally, A.V.: Prolactin release inhibiting and stimulating factors in the hypothalamus. Adv.Exper.Med.Biol. 87, 237-252 (1977).

Ben-Jonathan, N., Oliver, C., Weiner, H.J., Mical, R.S., Porter, J.C.: Dopamine in hypophysial portal plasma of the rat during the estrous cycle and throughout pregnancy. Endocrinology 100, 452-458 (1977).

Caron, M.G., Drouin, J., Raymond, V., Kelly, P.A., Labrie, F.: Specificity of the catecholaminergic effect on prolactin secretion and (3H) dihydroergocryptine binding. Clin.Res. 24, 656A (1976).

Clemens, J.A.: Neuropharmacological aspects of the neural control of prolactin secretion, p. 283-302 in: Labrie, F., Meites, J., Pelletier, G. (edts): Hypothalamus and Endocrine Functions, Plenum Press, New York, London, 1976.

Lu, K.H., Koch, Y., Meites, J.: Direct inhibition by ergocornine of pituitary prolactin release. Endocrinology 89, 229-233 (1971).

Macleod, R.M.: Regulation of prolactin secretion. Frontiers Neuroendocrinology 4, 169-194 (1976).

Macleod, R.M., Fontham, E.H., Lehmeyer, J.E.: Prolactin and growth hormone production as influenced by catecholamines and agents that affect brain catecholamines. Neuroendocrinology 6, 283-294 (1970).

Macleod, R.M., Lehmeyer, J.E.: Regulation of the synthesis and release of prolactin, p. 53-82 in: Wolstenholme, G.E.W., Knight, J. (edts): Lactogenic Hormones. Churchill Livingstone, London (1972).

Macleod, R.M., Lehmeyer, J.E.: Studies on the mechanism of the dopamine-mediated inhibition of prolactin secretion. Endocrinology 94, 1077-1085 (1974a).

Macleod, R.M., Lehmeyer, J.E.: Restoration of prolactin synthesis and release by administration of monoaminergic blocking agents to pituitary tumor-bearing rats. Cancer Res. 34, 345-350 (1974b).

Nicoll, C.S., Fiorindo, R.P., Mckennee, C.T., Parsons, J.A.: Assay of hypothalamic factors which regulate prolactin secretion, p. 115-150 in: Meites, J. (edt): Hypophysiotropic Hormones of the Hypothalamus: Assay and Chemistry. Williams and Wilkins, Baltimore, 1970.

Pasteels, J.L.: Sécrétion de prolactine par l'hypophyse en culture de tissu. C.R.Acad.Sci. (D) Paris 253, 2140 (1961).

Pasteels, J.L., Danguy, A., Frérotte, M., Ectors, F.: Inhibition de la sécrétion de prolactine par l'ergocornine et la 2-Br-α-ergocryptine: action directe sur l'hypophyse en culture. Ann.Endocr. (Paris) 32, 188-192 (1971).

Schally, A.V., Redding, T.W., Arimura, A., Dupont, A., Linthicum, G.L.: Isolation of gamma-amino butyric acid from pig hypothalami and demonstration of its prolactin release-inhibiting (PIF) activity in vivo and in vitro. Endocrinology 100, 681-691 (1977).

Shaar, C.J., Clemens, J.A.: The role of catecholamines in the release of anterior pituitary prolactin in vitro. Endocrinology 95, 1202-1212 (1974).

Shaar, C.J., Clemens, J.A.: A catecholamine as a prolactin inhibitory factor (PIF). Fed.Proc. 35, 305 (1976).

Takahara, J., Arimura, A., Schally, A.V.: Suppression of prolactin release by a purified porcine PIF preparation and catecholamines infused into a rat hypophyseal portal vessel. Endocrinology 95, 462-465 (1974).

Talwalker, P.K., Ratner, A., Meites, J.: In vitro inhibition of pituitary prolactin synthesis and release by hypothalamic extracts. AmJ.Physiol. 205, 213-218 (1963).

Tashjian, A.H., Hoyt, R.F.: Transient control of organ specific functions in pituitary cells in culture, p. 353-387 in: Sussman, M. (edt): Molecular Genetics and Developmental Biology, Prentice Hall Inc., Englewood Cliffs, N.J. 1972.

Valverde, R.C., Chieffo, V., Reichlin, S.: Prolactin-releasing factor in porcine and rat hypothalamic tissue. Endocrinology 91, 982-993 (1972).
Van Maanen, J.H., Smelik, P.G.: Induction of pseudopregnancy in rats following local depletion of monoamines in the median eminence of the hypothalamus. Neuroendocrinology 3, 177-186 (1968).

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