Biochemical Pharmacology, Vol. 22, pp. 3141-3143. Pergamon Press, 1973. Printed in Great Britain.

In vitro inhibition of the biosynthesis of a prostaglandin by gold and silver

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(Accepted 25 July 1973)

Organic gold salts are used since many years in the treatment of rhumatoïd arthritis (1). According to a recent well substanciated theory, the action of anti-inflammatory agents is essentially due to an inhibition of prostaglandins synthesis which plays a major role in the process of inflammation (2-5). We have tested the action of gold salts on this synthesis and compared their effects with those of other metals of the gold family or of close atomic weight.

Material and methods : The techniques adopted by Deby et al. (6) were used with the exception that bull seminal vesicles were extracted instead of sheep vesicles. The partially purified enzymatic system is incubated for 25 min. with tagged arachidonic-5, 6, 8, 9, 11, 12, 14, 15-^{3}H (New England Nuclear) in presence of glutathione and hydroquinone. Reaction is stopped by addition of citric acid. In the controls the amount of PGE_2 formed increases regularly until a plateau is reached after about 12 minutes. At 25 minutes one measures the level of this plateau. We have seen that the shape of the curve remains the same after addition of one of the inhibitors dealt with in this paper. After addition of cold PGE_2 (Upjohn) 100 µg, the system is extracted

three times by 10 ml of ethyl ether; the fractions evaporated to dryness in nitrogen, dissolved in ethylacetate (0.1 ml) and chromatographed (TLC) on silicagel Merck with $CHCl_3/CH_3OH/CH_3COOH/H_2O$ (90 : 6 : 1 : 0.75). The spots of prostaglandins (E_2 and $F_{2\alpha}$) are scraped, extracted with a small volume of chloroform, pipetted on small columns, eluated by ether/methanol (9 : 1) in vials for β spectrometry; after evaporation to dryness, the residues are dissolved in 10 ml of Instagel Packard and counted at the Packard Tricarb. The metals tested were : $AuCl_3.HCl.3H_2O$ (Merck); sodium aurothiopropanolsulfonate (Allochrysine$^{(R)}$ Lumière); strong silver proteins (= protargol) containing 8 per cent of silver (one cannot have Ag^+ at pH 8.0); $HgCl_2$; platinium chloride (BDH) $H_2PtCl_6.6H_2O$. The results (Table 1) are expressed after substraction of the blank as per cent of the final radioactivity of the controls in optimal conditions. Concentrations 10^{-5} to 10^{-6} M of gold and silver preparations have a marked inhibitory effect. At 10^{-7} M, silver is still active. If one discards as non specific due to various classical effects on protein solutions the results observed with the metals at the higher concentration (10^{-4} M), it is clear that Hg^{2+} has no effect and that Pt inhibits only at rather high concentration. Thus, as far as gold is concerned, the general theory elaborated by Vane and associates in order to explain the wide-spread actions of anti-inflammatory agents is confirmed by our observations. One wonders why silver which seems such a good inhibitor of prostaglandin synthesis has not been used in the same therapeutic indications as gold salts. Is it the importance of secondary effects of silver preparations ? It is illogical to interpret the well known antidiarrheic actions

of protargol as the result of decreased prostaglandin synthesis, just as the anticholeric actions of the classical anti-inflammatory agents (7).

Table 1 : Synthesis of prostaglandins by a partially purified system of bull seminal vesicles in presence of various metals. The results are expressed in per cent of the radioactivity of the controls.

Mol. Cns.	$HgCl_2$	$AuCl_3$	H_2PtCl_6	Allochrysine(R)	Protargol
10^{-4}	67.5 ± 7.5	43.0 ± 2.6	72.0 ± 4.6	57.5 ± 4.94	19.0 ± 2.66
10^{-5}	100.0 ± 11.6	60.5 ± 3.4	82.0 ± 6.3	73.0 ± 8.5	31.5 ± 2.94
10^{-6}	100.0 ± 8.2	79.0 ± 6.4	93.0 ± 7.4	96.0 ± 7.6	53.5 ± 3.32
10^{-7}	100.0 ± 9.4	89.0 ± 7.3	100.0 ± 8.2	100.0 ± 6.8	78.3 ± 4.50

References :

1. The Pharmacological Basis of Therapeutics. Goodman L.S. and Gilman A., edit., p. 961, Macmillan Co., (1965).
2. Vane J.R., Nature-New Biology, 231, 232 (1971).
3. Flower R., Gryglewski R., Herbaczynska-Cedro K., Vane, J.R., Nature-New Biology, 238, 104 (1972).
4. Collier H.O.J., Nature, 232, 17 (1971).
5. Collier H.O.J., Nature, 223, 35 (1969).
6. Deby C., Descamps M., Binon F., Bacq Z.M., C.R. Soc. Biol., 165, 2465 (1971).
7. Finck A.D., Nature, 238, 273 (1972).

Acknowledgement : Mr Pike (Upjohn Co.) generously provided the the prostaglandins utilised in this piece of work.