to a metabolic or pharmacokinetic interaction between ascorbic acid and LSD and/or apomorphine, since ascorbic acid acts as an antioxidant and, should such a metabolic or pharmacokinetic interaction occur, one would expect the opposite effect, i.e. that ascorbic acid pretreatment would potentiate the effects of LSD and/or apomorphine. Ascorbic acid has been shown to be an essential ingredient in assays demonstrating a high affinity binding of dopamine antagonists, such as haloperidol, to dopamine binding sites in-vitro (Leff et al 1981). The effect of ascorbic acid on the binding of dopamine agonists, on the other hand, would be expected to produce the opposite effect. It is noteworthy that megavitamin therapy including very large doses of ascorbic acid have been shown to be effective in treating certain forms of schizophrenia (Pauling 1974), which appears to be due to the over-stimulation of dopamine receptors in the forebrain.

The fact that pretreatment with ascorbic acid does not change the behavioural response to 5-MeODMT is consistent with the finding that ascorbic acid does not appear to interact with 5-HT binding sites. These latter data also support the hypothesis that the inhibitory effects of ascorbic acid on LSD- and apomorphine-induced behaviours in the cat are not due to a general depression of behaviour by ascorbic acid. This hypothesis is further substantiated by the fact that ascorbic acid alone produced no significant behavioural changes in these animals.

In conclusion, our data support the hypothesis that LSD and related hallucinogens act by a combined action at central 5-HT and dopamine receptors. The fact that LSD-induced behaviours are partially blocked by ascorbic acid suggests that large doses of ascorbic acid may be a new method for treating LSD overdose.

REFERENCES

Aghajanian, G. K., Foote, W. E., Sheard, M. H. (1970) J. Pharmacol. Exp. Ther. 171: 178–184

Axelrod, J., Brody, R. O., Witkop, B., Evarts, E. V. (1957) Ann. N.Y. Acad. Sci. 66: 435–444

Leff, S., Silby, D. R., Hamblin, M., Creese, I. (1981) Life Sci. 29: 2081–2087

Pauling, L. (1974) Am. J. Psychiatry 131: 1251–1254

Rebec, G. V., Centore, J. M., White, L. K., Alloway, K. D. (1985) Science 227: 438–440

Symes, A. L., Lal, S., Sourkes, T. L. (1975) J. Pharm. Pharmacol. 27: 947–956

Trulson, M. E. (1985) Pharmacol. Biochem. Behav. in press

Trulson, M. E., Crisp, T. (1982) Eur J. Pharmacol. 80: 295–309

Trulson, M. E., Keltch, G. F. (1985) Ibid. 108: 33–37

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Letter to the Editor

A hypothesis for the mode of action of anti-rheumatic drugs in a model of cartilage destruction

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We have been using as a model rats and mice with air pouches which develop lining cells closely resembling synovium (Edwards et al 1982; Sedgwick et al 1983). These pouches when sufficiently mature, i.e. 6 days, will respond to a variety of stimuli both immune and non-immune with long lasting exudates containing many migrated leucocytes (Sedgwick et al 1983, 1984a).

We examined the breakdown of cartilage in both inflamed and non-inflamed pouches and have found that inflammation protected the rate of loss of proteoglycan from cartilage (Sedgwick et al 1984b, 1985; Willoughby et al 1985). Invariably the cartilage in the inflamed air pouch would float free in exudate while cartilage, in the non-inflamed pouch would adhere to the pouch wall in close proximity to the macrophages and fibroblasts of the lining cells. Unpublished findings from this department (de Brito) have shown that the presence of granulation tissue in close proximity to cartilage will speed proteoglycan loss.

Implantation of rat femoral head cartilage into pouches of rats treated with indomethacin (3 mg kg^{-1}) showed protection against loss of proteoglycan, unlike xiphisternum cartilage which showed no protection (Sin et al 1984; Sedgwick et al 1984b). This drug treatment caused suppression both of cells and volume of exudate in inflammation induced by carrageenan. It seems unlikely that the protection afforded by indomethacin could be due to its anti-inflammatory effect since this would be expected to enhance cartilage breakdown. A more likely explanation could be that in granulomatous inflammation indomethacin has previously been shown to induce macrophages to engage in autophagocytosis, where lysosomes are seen adjacent to mitochondria, fusing with them (Di Rosa et al 1971). This self-

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destructive process could lead to impaired macrophage function, thus the cells would be unable to instruct the fibroblasts to secrete their enzymes which would normally contribute to cartilage breakdown (Vaes 1980). This instructive process could be, and probably is, mediated by interleukin 1 (IL1).

Dexamethasone also protected the implanted cartilage and was the most potent anti-inflammatory drug used in that it completely suppressed the inflammatory exudate. Here too, the protection of cartilage could not be attributed to the drug's anti-inflammatory activity but the thickness of the pouch wall was reduced, thereby causing it to revert to a younger, less reactive state. Similarly, the macrophages still residing within the unusually thin wall, would not be secreting products such as catabolin/IL1 (Dingle 1979; Sheppeard et al 1982; Rainsford 1985). Therefore the action of dexamethasone could be due to its anti-proliferative activity and its ability to inhibit cellular secretion products rather than a direct anti-inflammatory effect. This is similar to the inhibitory effect of steroids on wound healing where macrophages fail to instruct fibroblasts (Leibovich & Ross 1975).

The third drug used, levamisole, also protected cartilage from degradation but lacked anti-inflammatory activity. This suggests that the inflammatory response is dissociated from the process of cartilage destruction. Levamisole, in given circumstances, will enhance 'T' suppressor cell activity (Symoens 1977; Symoens & Rosenthal 1977); it is known that T-cell activity is a prerequisite for granuloma formation—essentially a process involving both macrophages and fibroblasts. Indeed it has previously been shown that thymectomized rats cannot develop normal granulomas (Rothwell & Spector 1972; Giroud et al 1972). In addition, in man, treatment with levamisole leads to a fall in acute phase proteins (Symoens 1977). Billingham (1985) has suggested that acute phase reactants in the rat are a good marker of IL1 production (see also Dinarello 1984). It seems reasonable to postulate that levamisole could be inhibiting IL1 formation and thus fibroblast secretion of enzymes.

D-Penicillamine, which causes a significant potentiation of the inflammatory response with increased numbers of cells and volume of exudate, surprisingly affords good protection of the cartilage, which could not be attributed to its pro-inflammatory effect, since this does not occur in man in whom it has been proposed as one of the disease modifying drugs (Huskisson 1974).

It seems that for this drug, too, there is a similar mode of action to that proposed for the other diverse compounds examined, and that in man it is the ability to lower acute phase reactants. If the Billingham suggestion is correct, a drop in IL1 levels and subsequently a failure of the macrophage to instruct the fibroblast to destroy the cartilage is implied. However D-penicillamine increases the release of catabolin from porcine synovial tissue in-vitro (Sheppeard et al 1982).

In summary, implantation of cartilage into an inflamed air pouch causes slower loss of proteoglycan than in a non-inflamed pouch. Indomethacin and dexamethasone both inhibit cell migration and exudate formation protects cartilage breakdown. In contrast D-penicillamine potentiates cell migration and exudate formation yet also protects cartilage as does levamisole which has no effect on the inflammatory process.

The findings support the suggestion that anti-inflammatory effects are not relevant to the phenomenon of cartilage protection. Instead, the inhibition of an IL1-like messenger seems the more important action in this model. This concept is highly speculative but could have relevance for those who search for new therapeutic agents to treat arthropathies. For too long such therapeutic agents have been anti-inflammatory drugs treating signs or symptoms of the disease but not the process. Most of the disease modifying drugs have been discovered by serendipity—the present speculation may provide clues for a more rational approach.

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REFERENCES

Billingham, M. E. J. (1985) Br. J. Rheumatology 24: (suppl. 1) 25–28

Dinarello, C. A. (1984) New Engl. J. Med. 311: 1413–1418

Dingle, J. T. (1979) Ann. Rheum. Dis. 38: 201–221

Di Rosa, M., Papadimitriou, J. M., Willoughby, D. A. (1971) J. Path. 105: 239–245

Edwards, J. C. W., Sedgwick, A. D., Willoughby, D. A. (1982) Annals Rheum. Dis. 41: 282–286

Giroud, J. P., Papadimitriou, J. M., Dunn, C. J., Willoughby, D. A. (1972) J. Path. 108: 335–347

Huskisson, E. C. (1974). Reports on Rheumatic Diseases No. 54. Arthritis & Rheumatism Council

Leibovich, S. S., Ross, R. (1975) Am. J. Path. 78: 71–100

Rainsford, K. D. (1985) Int. J. Tiss. React. VII (2): 123–6

Rothwell, T. L. W., Spector, W. G. (1972) J. Path. 108: 15

Sedgwick, A. D., Sin, Y. M., Edwards, J. C. W., Willoughby, D. A. (1983) Ibid. 141: 483–496

Sedgwick, A. D., Sin, Y. M., Mackay, A. R., Al-Duaij, A., Willoughby, D. A. (1984a) J. Pharm. Pharmacol. 36: 171–174

Sedgwick, A. D., Moore, A. R., Al-Duaij, A., Sin, Y. M., Landon, B., Willoughby, D. A. (1984b) Ibid. 36: 709

Sedgwick, A. D., Moore, A. R., Al-Duaij, A., Edwards, J. C. W., Willoughby, D. A. (1985) Br. J. Exp. Path. 66: 445–453

Sheppeard, H., Pilsworth, L. M. C., Hazleman, B., Dingle, J. T. (1982) Ann. Rheum. Dis. 41: 463–469.

Sin, Y. M., Sedgwick, A. D., Willoughby, D. A. (1984) J. Path. 142: 22–31

Symoens, J. (1977) in: Willoughby, D. A., Giroud, J. P., Velo, G. P. (eds) Perspectives in Inflammation. MTP Lancaster, p. 11

Symoens, J. Rosenthal, M. (1977) J. Reticuloendothel. Soc. 21: 175

Vaes, G. (1980) Agents and Actions, 10/6: 474–485

Willoughby, D. A., Al-Duaij, A., de Brito, F., Sedgwick, A. D. (1985) Int. J. Immunopharm. 7: 411–412