Occasional Survey

Pharmacology of uricosuric drugs

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Urate deposition and gout

When the level of uric acid, primarily in the form of monosodium urate (Wilcox, Khalaf, Weinberger, Kippen, and Klinenberg, 1972), exceeds the point of maximum solubility, crystals of monosodium urate may then form, particularly in the joints and connective tissues. These crystals initiate attacks of acute gout (Buchanan, Klinenberg, and Seegmiller, 1965; Seegmiller, 1965; Weissmann, 1971), and tophaceous deposits may occur if the hyperuricaemia is allowed to persist. While the drugs colchicine and phenylbutazone are useful in treating the acute attack of gout owing to their anti-inflammatory activity (Smyth, 1972), the most effective approach to the long-term treatment of hyperuricaemia involves reducing the urate level so that the gouty attacks gradually cease and the deposits of urate formed during the hyperuricaemic periods are gradually resorbed.

Urate levels can be lowered by decreasing the rate of production of urate or increasing its rate of elimination. With respect to the first alternative, the drug allopurinol, which blocks the conversion of hypoxanthine and xanthine to uric acid, is now in widespread use either by itself or in combination with one of the uricosurics (Klinenberg, Goldfinger, and Seegmiller, 1965; Scott, Hall, and Grahame, 1966). However, the most common method of reducing urate levels is to use drugs which increase the rate of elimination of urate by the kidneys. The long and fascinating history of the development of uricosuric agents has been reviewed in detail by Gutman (1966).

A short history

The uricosuric properties of salicylate (Fig. 1) were noted before 1890 and its use as a uricosuric continued through the 1950s. As late as 1955, Marson felt that salicylate was superior to probenecid for the long-term treatment of gout. However, for appropriate uricosuric activity, salicylate must be administered in

FIG. 1 Structures of pyrazinoic acid, salicylic acid, and W-2354. Dotted lines show points of in vivo cleavage of W-2354 yielding 5-chlorosalicylic acid, an effective uricosuric agent

doses greater than 5.0 g/day, often resulting in tinnitus, gastric bleeding, and many other serious side effects, so the use of salicylate as a uricosuric gradually waned. During the time that salicylate was in use, a number of other drugs were found to have uricosuric activity and were introduced for clinical use. Cinchophen (2-phenylcinchoninic acid) was introduced by Nicolaier and Dohrn (1908), but its use was discontinued by the late 1940s because of its hepatotoxicity. A number of cinchophen derivatives were also tried, but all showed unacceptable side effects.

In the 1940s, Beyer and his associates at Merck, Sharpe and Dohme found that the drug carinamide could retard the renal excretion of penicillin, thus increasing its effective half-life in the body (Beyer, Miller, Russo, Patch, and Verwey, 1947). Shortly thereafter, it was discovered that carinamide increased the excretion of uric acid (Wolfson, Cohn, Levine, and Huddleston, 1948), and this drug was introduced as a uricosuric. Carinamide was subsequently replaced by probenecid (Fig. 2), which is structurally similar to carinamide but effective as a uricosuric in much lower doses. Probenecid remains one of the two drugs most widely used for the long-term treatment of gout.

The other uricosuric drug currently in wide use is sulphinpyrazone (Fig. 2), a sulphoxide analogue of phenylbutazone. While the anti-inflammatory properties of phenylbutazone are useful in the treatment of

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FIG. 2 Structures of the two most commonly used uricosuric drugs, probenecid and sulphinpyrazone

acute gout, it has only mild uricosuric properties. Sulphinpyrazone, on the other hand, has only minimal anti-inflammatory activity yet it is a potent uricosuric. This drug was found by Brodie, Burns, Gutman, and their associates during an exhaustive study of analogues and metabolites of phenylbutazone (Burns, Yü, Ritterband, Perel, Gutman, and Brodie, 1957; Yü, Burns, and Gutman, 1958).

Over the years a number of other compounds have been shown to have uricosuric activity, but most are not in use owing either to their low potency or to serious side effects. These drugs include zoxazolamine (Burns, Yü, Berger, and Gutman, 1958), *p*-chlorophenoxyisobutyric acid (Trevaks and Lovell, 1965), ACTH (Friedman and Byers, 1950), dicumarol (Hansen and Holten, 1958), ethyl biscoumacetate (Sougin-Mibashan and Horwitz, 1955), 6-azauridine and orotic acid (Fallon, Frei, Block, and Seegmiller, 1961), acetoexamide (Yü, Berger, and Gutman, 1968), chlorprothixene (Healey, Harrison, and Decker, 1965), meclofenamic acid (Robinson and Radcliff, 1972), some mercurial diuretics (Fanelli, Bohn, Reilly, and Weiner, 1973b), and some sulphonamides (Schlosstein, Kippen, Whitehouse, Bluestone, Paulus, and Klinenberg, 1973). Despite the large number of drugs showing uricosuric activity, the ideal uricosuric has still not been found. Probenecid can cause nausea, vomiting, and severe hypersensitivity reactions, and sulphinpyrazone can cause leucopenia and exacerbation of peptic ulceration (Boyle and Buchanan, 1971). Current research is hampered in part by a relative ignorance of the mechanism of action of these drugs.

Current concepts of the mechanism of action of uricosuric drugs

The prevailing view of the renal handling of urate is essentially the one introduced by Gutman and Yü in 1961 and recently reiterated (Gutman and Yü, 1972). This view holds that urate is completely filtered at the glomerulus and mostly reabsorbed in the proximal tubule, and that most of the urate finally excreted derives from tubular secretion. While this concept has been verified in general, certain controversies still exist with regard to some of its finer points.

One major issue involves the completeness of glomerular filtration of urate, and it might be valuable to review the evidence presented by Gutman and Yü in support of the complete filtration theory. The issue at hand is basically whether or not urate exists in the blood in such a state that might preclude free access to glomerular filtration. Thus, urate bound to plasma proteins might not be freely filterable. The older literature, as reviewed by Gutman and Yü, seems to contain about equal numbers of papers for (Adlersberg, Grishman, and Sobotka, 1942; Wolfson, Levine, and Tinsley, 1947) and against (Byers and Friedman, 1949; Yü and Gutman, 1953) binding of urate to plasma proteins. Gutman and Yü concluded that the balance was strongly in favour of no urate binding. However, this conclusion is not supported by present knowledge. First of all, the techniques of compensation dialysis and electrophoresis used in studies quoted by Gutman and Yü would be certain to give negative results because the binding of urate to proteins is weak and reversible and would be disrupted by these techniques. Also quoted as evidence of no urate binding is the famous paper of Bordley and Richards (1933) which showed, by micropuncture, complete filterability of urate in frogs and snakes. However, it has recently been shown by Simkin (1972) that the binding of urate to plasma proteins of snakes and frogs is negligible under conditions showing appreciable binding to plasma proteins of humans. The paper most widely quoted in the literature as evidence of no urate binding to plasma proteins is that by Yü and Gutman (1953) in which they were unable to confirm the data of earlier workers supporting urate binding. Actually, the data reported by Yü and Gutman did indicate a low level of binding (about 3 to 5%) and had they analysed their data from ultrafiltration experiments in a manner similar to that used by Fanelli and Weiner (1973), they would have shown somewhat greater binding. In any case, the fact that they could not duplicate the preceding work does not necessarily mean that work was incorrect.

Several papers in the last few years have reported some degree of urate binding to plasma proteins (Alvsaker, 1966; Klinenberg and Kippen, 1970;

FIG. 3 Schematic drawing of kidney tubule showing sites where uricosuric drugs could act. Displacement of urate from binding sites on plasma proteins could increase the glomerular filtration of urate (A). In the proximal tubule, uricosuric drugs could inhibit reabsorption of urate from the tubular lumen (B), or stimulate secretion of urate from peritubular capillaries into the tubule (C). Little or no urate transport occurs in either direction in the distal tubule (D).

Farrell, Popovich, and Babb, 1971), but it has become clear that to have much meaning these experiments should be carried out under conditions (temperature, ionic strength, etc.) as close to physiological as possible. Recent papers confirm that some binding of urate to plasma proteins does occur under physiological conditions (Campion, Bluestone, and Klinenberg, 1973; Postlethwaite, Gutman, and Kelley, 1973; Kippen, Klinenberg, Weinberger, and Wilcox, 1974). However, it is still not clear whether or not this binding of urate to plasma proteins has any effect on the renal handling of urate. If the binding of urate did retard its glomerular filtration, then uricosuric drugs might increase urate filtration by displacing it from its protein binding sites (Fig. 3). As yet, however, experiments to test this hypothesis have not been done, and the question of the completeness of the filtration of urate must await further data.

With respect to our knowledge of reabsorption and secretion of urate, a major problem is the great variation among experimental animals in the handling of urate and in responses to uricosuric drugs. For example, the mongrel dog shows net reabsorption of urate while the Dalmatian coach hound shows net secretion (Kessler, Hierholzer, and Gurd, 1959). Probenecid is uricosuric in man, yet decreases urate excretion in the rabbit (Poulsen, 1955). For a short review of this question see Mudge (1965), and for an exhaustive review see Gutman and Yü (1972). It is generally accepted that in man urate is both secreted and reabsorbed and that this bidirectional transport occurs primarily in the proximal tubule (Gutman and Yü, 1972). However, there is still controversy over the precise locations of these transport processes.

The most direct technique for determining the location of the renal transport processes is micropuncture. However, this method cannot be used in human subjects. Recent micropuncture experiments with rats have suggested that the site of net urate reabsorption in the rat may be distal to the site of net secretion (Greger, Lang, and Deetjen, 1971; Lang, Greger, and Deetjen, 1972). Experiments in humans have relied primarily on the use of combinations of drugs to provide clearance data from which inferences about transport sites for urate can be made. Both Steele and Boner (1973) and Diamond and Paolino (1973) have suggested, on this basis, that there is a urate reabsorptive site distal to the secretory site in man. However, their studies do not rule out the possibility that urate reabsorption and secretion are coextensive. Fanelli and Weiner (1973) have also concluded that, at least in the chimpanzee, secretion is not distal to reabsorption. The current consensus thus appears to be that urate is secreted at a site coextensive with and/or more proximal to the reabsorptive site.

Uricosuric drugs could act either by stimulating secretion of urate or by inhibiting reabsorption of urate. The most probable mechanism of action of uricosurics is inhibition of urate reabsorption by competition with urate for the reabsorptive transport mechanism. A number of uricosuric drugs also compete for secretory transport as well, leading to a biphasic response. Thus salicylate inhibits secretion in low doses leading to urate retention, and inhibits reabsorption to a greater extent in large doses causing uricosuria (Yü and Gutman, 1955). Pyrazinamide (or pyrazinoic acid, Fig. 1) acts primarily to inhibit secretory transport, but has been shown to cause uricosuria in large doses in the chimpanzee (Fanelli and Weiner, 1973). The glycoside phloridzin has also been shown to increase the excretion of urate (Skeith, Healey, and Cutler, 1970).

It has been suggested that certain uricosuric drugs, including iopanoic acid (Fig. 4) (Postlethwaite and Kelley, 1971), benziodarone (Vinay, Gougoux, Michaud, and Lemieux, 1972), and azapropazone (Frank, 1971), act by stimulation of secretion of urate. The reason given for this conclusion is usually that the uricosuric effect of the drug is abolished by prior administration of pyrazinamide, the main action of which is considered to be selective inhibition of urate secretion. However, Weiner and Tinker (1972) have presented a detailed argument showing that it is hazardous to make assumptions based on the so-called 'pyrazinamide suppression test'. Furthermore, Postlethwaite and Kelley (1971) have shown that at least two of the radiocontrast agents thought possibly to stimulate urate secretion are capable of displacing urate from its binding sites on plasma proteins *in vitro*, and the same has been shown for azopropazone (Whitehouse, Kippen, and Klinenberg,

FIG. 4 Structures of benziodarone, iopanoic acid, and halofenate. The dotted line indicates point of *in vivo* cleavage of halofenate

1971). This probably indicates, as discussed elsewhere (Whitehouse and others 1971), that these drugs are capable of competing with urate for tubular reabsorption, so it is improbable that their effect is solely due to stimulation of urate secretion. Furthermore, it is quite difficult to understand how the radio-contrast agents, for example, might stimulate an active transport process. It is most unlikely that they are supplying energy to the transport system. So far none of the authors suggesting stimulation of secretion of urate by uricosurics has provided a plausible hypothesis as to how this might occur. In any case, it is clear that much still needs to be learned about urate receptors and transport processes within the kidney before the mechanisms of uricosuric activity will be satisfactorily understood.

Molecular properties of uricosuric drugs

The first and most obvious feature is that most uricosurics are weak acids which bind more strongly than urate to the common binding sites on plasma proteins. This association is not purely Coulombic, i.e. attraction of opposite charges, but also involves Van der Waal's binding and other lipophilic forces of attraction. The drugs must have sufficient lipophilicity to bind firmly to the urate receptor but not so much that they partition extensively into the fat depots, CNS, etc., leaving the urate receptors appreciably devoid of drug. For this reason, highly lipophilic anions such as barbiturates may be poor uricosurics even though they may bind to albumin and effectively displace urate *in vitro*. The converse

of lipophilicity, i.e. hydrophilicity, ensures that drugs once absorbed remain principally in the plasma and renal compartments. This, too, is probably important in determining uricosuric activity *in vivo*, paradoxical though it may seem. The uricosuric activity of salicylate and phenylbutazone is expressed *in vivo* partly because the major primary metabolites of the two drugs (salicylurate, γ - and p -hydroxyphenylbutazones) are themselves relatively efficient displacers of urate from its receptors (Schlosstein and others, 1973). Thus, a fine balance between lipophilicity and hydrophilicity may qualitatively determine when some drug anions may be effective uricosurics and others are not. Some preliminary attempts to assess this balance mathematically have been made for the prime urate/DNSA binding site on albumin (Dunn, 1973). Quantitative considerations are also important, for unless sufficient drug anion is available to ensure that a considerable proportion of all urate receptors (in the kidney and/or plasma) are effectively blocked, even an ideal drug may fail to show uricosuric activity *in vivo*. It has been calculated that blood levels of drug $\geq 10 \mu\text{g/ml}$ must be attained to show uricosuric activity (Whitehouse and others 1971).

With the benefit of such hindsight, it is perhaps understandable why so few drugs have proved efficient uricosurics. To ensure adequate uricosuric levels, the drugs must either be acceptable in massive doses (salicylate, probenecid) or have long half-lives, and perhaps also pathways of metabolism and elimination that ensure that sufficient pharmacologically active metabolites are presented to the urate receptors in lieu of the original drug when its plasma concentration declines below the threshold for efficacy.

Current research on uricosurics

The search for uricosuric drugs has been hampered in the past partly by the lack of a suitable animal model for testing these drugs. However, it has become apparent in the last few years that certain primates, including the chimpanzee and *Cebus* monkey, are similar enough to man in their response to uricosurics that they may be used for *in vivo* screening of potential uricosuric drugs. Using the *Cebus* monkey, Blanchard, Maroske, May, and Weiner (1972) found that certain 2-substituted analogues of probenecid were about 10 times more potent than probenecid itself. Fanelli and his co-workers have used both the *Cebus* monkey and the chimpanzee to study the uricosuric activity of mercurial diuretics and other drugs (Fanelli, Bohn, and Reilly, 1973a; Fanelli and others 1973b).

Another study of uricosuric drugs was based on the hypothesis that uricosuric compounds can be identified by the strength of their activity in displacing urate

from its binding sites on human albumin (Whitehouse and others, 1971). By screening a large number of potential uricosurics, several compounds potent in displacing urate from albumin were identified. A subsequent clinical trial confirmed the uricosuric activity of these compounds (Schlosstein and others, 1973), which included diflumidone, sulphaethidole, and 5-chlorosalicylic acid (as the metabolite of W-2354, Fig. 1).

Other compounds currently being investigated for

their uricosuric activity include benziodarone (Fig. 4) and benzbromarone (Delbarre, Auscher, Olivier, and Rose, 1967; Zöllner and Gröbner, 1969) and halofenate (Fig. 4) (Jain, Ryan, Hague, and McMahon, 1970; Fanelli, Bohn, Reilly, and Baer, 1972). However, probenecid and sulphinpyrazone currently remain the uricosuric agents of choice. It is nevertheless probable that they will be supplemented by other compounds in the future as research on uricosuric drugs progresses.

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