Formation of Active Metabolites of Psychotropic Drugs
An Updated Review of Their Significance

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Summary

Most of the currently available psychotropic drugs form 1 or more active metabolites during in vivo biotransformation in humans and/or animals. In some cases these metabolites are rapidly conjugated and excreted, but in others they attain blood and/or brain concentrations within the same range as, or even higher than, those of the parent drug, thus being potential biologically active compounds.

The formation of metabolites with their own biological activity in addition to that of the parent compound may result in a complex situation where different chemical species participate in the final effects. These chemical species may have different pharmacokinetic properties of distribution and clearance. They may act by similar mechanisms, by different mechanisms or even antagonistically. The formation of active metabolites may be important not only for the therapeutic outcome but also for explaining the toxicity of particular drugs.

The examples given, although limited, provide evidence that studies on drug metabolites are essential for an understanding of the mechanism of action of psychotropic drugs, and for extrapolating pharmacological and toxicological findings from animals to humans. The development of any new psychotropic agent requires knowledge of the pharmacology and toxicology of all active species as well as their pharmacokinetic profile, including the extent to which they reach the central nervous system.
With a few exceptions psychotropic drugs such as antidepressants, antipsychotics and anxiolytics are highly lipophilic compounds which are almost entirely eliminated from the body by biotransformation. Like most xenobiotics, their biotransformation involves mainly 2 phases. The first (phase I) prepares the drug for conjugation (phase II) by providing polar groups. In phase II the metabolic product(s), or the parent drug if it has a polar group that allows conjugation, react with an endogenous substrate (glucuronic acid, sulphate, glutathione or other molecules) to yield water-soluble conjugated metabolites that are easily excreted in urine or bile. Phase II reactions are usually detoxifying, reducing the biological properties of the original compound.

Phase I reactions consist of oxidations, reductions and hydrolyses and may result in the formation of 'biologically active metabolites', with oxidation particularly prominent. Almost all the oxidations are mediated by hepatic enzyme microsomal systems; they are usually the rate-limiting step, being affected by species, age, sex, diseases and inducing and inhibitory agents, and their primary activity is determined by an individual's genetic makeup and environmental factors. This variability is partly clarified by the relatively recent recognition of multiple forms of cytochrome P450, the haemoprotein enzymes that bind and metabolise drugs (see the reviews of Coon 1981; Kato 1983; Nebert et al. 1981).

Relevant to the role of oxidation in the production of active metabolites is the observation that these may behave either similarly to or differently from the parent compound, as regards both pharmacodynamics and pharmacokinetics. Accordingly, the present review underlines the importance, in the overall evaluation of the clinical effects and efficacy of several psychotropic agents (and drugs in general), of considering the pharmacokinetics and biological activity not only of the drug but also of its metabolite(s). In this context, biological activity must be taken in a broad sense to include both pharmacological and toxic activity (Drayer 1976, 1982; Garattini 1985).

A number of reviews have dealt with the metabolism of antidepressants (Amsterdam et al. 1980; Blackwell & Simon 1986; Coccaro & Siever 1985; Hollister 1986; Rudorfer & Potter 1987), antipsychotics (Dahl 1982; Balant-Gorgia & Balant 1987; Jorgensen 1986), benzodiazepines (Caccia & Garattini 1985; Garattini & Reggi 1984; Garattini et al. 1977; Greenblatt & Shader 1987; Jochemsen & Breimer 1984; Kaplan & Jack 1983) and anxiolytics in general (Kaplan & Jack 1981; Mennini et al. 1987). Therefore, this review confines itself to summarising the present knowledge about metabolites that may be partly or totally responsible for the biological activity obtained on administration of the parent compound.

The review is based mostly on human studies but animal studies of particular relevance, for example in clarifying the mechanism of action of specific psychotropic drugs, have also been considered. Obviously, if the activity of the metabolite has been demonstrated only in animal models, caution must be used in extrapolating these data to clinical situations until species differences in drug metabolism, drug efficacy and toxicity are clearly elucidated.

1. Main Metabolic Pathways

1.1 Antidepressants

To this class belong 'first-generation' antidepressants exemplified by the tricyclic derivatives, monoamine oxidase (MAO) inhibitors (hydrazides and nonhydrazides) and lithium, and a number of new compounds with a variety of chemical structures and pharmacological profiles, generally classified as 'second-generation' antidepressants. Recent reviews by Amsterdam et al. (1980), Rudorfer and Potter (1987) and Ereshefsky et al. (1988) give detailed information about the pharmacokinetics and metabolism of tricyclic antidepressants. In addition, Coccaro and Siever (1985), Blackwell and Simon (1986) and Rudorfer and Potter (1989) have briefly reviewed the pharmacokinetics and metabolism of some second-generation antidepressant drugs. With a few exceptions such as lithium (which is excreted unchanged in the urine) and fluvoxamine and viloxazine [which, although extensively biotransformed, do not ap-