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Drug metabolism and ageing

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Important changes in drug metabolism occur with ageing. Age-associated reductions in function of some but not all cytochrome P450 enzymes (CYPs) have been described. Induction and inhibition of CYPs needs to be revisited in light of recent advances. The function and pharmacology of transporters have not yet been examined for an age-related effect. Finally, the concept of frailty is being underpinned by studies documenting a decline in drug metabolism and changes in disposition in frail older people compared with either healthy elderly or the young.

Introduction

The review will focus on a few key areas where relevant advances in human drug metabolism have emerged and will place them in the context of ageing. Since the discovery in the 1960s and early 1970s that ageing can affect drug metabolism, there has been much work to understand the principles that alter drug metabolism. These include recognition of the central role of the liver, identification of the cytochrome family of enzymes (CYPs), recognition that there are numerous CYPs responsible for metabolism of various drugs, identification of the place of genetics in drug metabolism starting with 2D6, recognition of the central role of 3A4 in drug metabolism, and more recent advances such as isolation of transporter systems in bile caniculi that explain mechanistically many observations about drug metabolism such as the interaction of digoxin with quinidine.

Ageing has a significant effect on many of these phenomena, such as significant reduction in liver volume, significant reduction in activity of some but not all CYPs. There are significant gaps in our understanding. Examples are the effect of age on extrahepatic CYPs and the effect of environment on ageing drug metabolism given the increasing complexity of the CYPs involved in human metabolism. More recently, the concept of frailty has begun to inform our views on drug metabolism in older people, and it may provide a basis for increased individualization of drug therapy in this at-risk population.

CYPs and age

Six subfamilies are now recognized as being responsible for most of human drug metabolism. These are CYPs 1A, 2A, 2C, 2D, 2E and 3A [1]. Within these subfamilies, 1A1, 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 are the most important. CYPs are also found in extrahepatic sites such as the intestine for CYP3A4 and brain for

CYP2D6. Examples of substrates for the subfamilies are listed in Table 1. The effects of age are noted.

Despite an abundant animal literature showing age-related declines in CYP content, activity and inducibility, direct studies in man have failed to show a similar decline in human CYP. Thus, in humans drug clearance is not solely dependent on CYP protein content, functional activity and modulation. However, human studies have been limited by difficulties, including ethical constraints, in obtaining healthy human liver tissue.

Schmucker *et al.* reported that CYP content and the concentration of NADPH cytochrome P450 reductase was not altered with age in man in a study using histologically normal liver samples, obtained mainly at laparotomy [2]. Others have reported an age-related decline in hepatic content of CYPs with selective reduction in 2E1 and 3A4 protein levels in hepatic tissue mainly from patients with chronic liver disease [3]. In contrast, Hunt *et al.* did not detect a decline *in vitro* in CYP 3A activity [4]. The latter study used normal livers obtained from a human transplant pool.

The literature is more consistent in relation to changes in liver size and blood flow with age. Studies using a variety of imaging techniques have shown a reduction in liver volume and blood flow with advancing years of the order of 17–46% [5–7]. These studies have, however, been cross-sectional rather than longitudinal. Drug clearance appears to be reduced in parallel with reduced liver volume in healthy ageing in man [8, 9].

In vivo substrate probes have also been developed to try to estimate specific CYP activities indirectly in man, e.g. debrisoquine and sparteine (2D6); erythromycin, midazolam and nifedipine (3A4/5); chlorzoxazone (2E1); mephenytoin (2C19); caffeine and theophylline (1A2). For some, the literature is consistent about probes for CYPs (CYP2D6, 2C19, and 1A2). However, for CYP3A the ideal *in vivo* probe has not yet been determined [10]. In addition, the effect of age on CYP3A activity remains to be determined (for CYP 2D6 see below).

CYP polymorphisms and age

Little research to date has focused on the effects of polymorphisms of CYPs and ageing. There is no evidence that slow debrisoquine metabolizers are more common in old age [11]. However, one abstract concluded that older people were at greater risk of adverse reactions when deficient in CYP2D6 using propranolol as a probe drug. There was more than a 50% reduction in clearance of total propranolol in older patients deficient in the CYP2D6 pathway compared with young subjects [12]. Other polymorphisms (CYP2C9 and CYP2C18/19) are less characterized, due mainly to accessibility of phenotypes.

Table 1
Cytochrome P450s involved in drug metabolism and chemical detoxification

CYP	Typical substrate	Clinical relevance to drug metabolism in humans	Genetics	Location	Effects of age
1A1	Polycyclic hydrocarbons	?Cancer risk linked with mutations	15q22 polymorphic	Extrahepatic	Not known
1A2	Caffeine, theophylline, paracetamol	Bioactivation of carcinogens	15q22 polymorphic	Hepatic	Reduced
2A	Warfarin	Polymorphic	19q13.1 polymorphic	Hepatic	?Reduced
2C9 & 10	Tolbutamide, hexobarbital	Autoimmune hepatitis	10q24 polymorphic	Hepatic	Reduced
2C18 & 19	mephenytoin, diazepam, omeprazole	Drug toxicity and lack of efficacy	10q24 polymorphic	Hepatic	Reduced
2D6	Debrisoquine, sparteine, β-blockers, tryciclic antidepressants, codeine	Drug toxicity and lack of efficacy, lung cancer, Parkinson's disease	22q13.1 Polymorphic	Hepatic, brain	No change over many studies
2E1	Chloroxazone Paracetamol	Cancer, drug toxicity	10 ?Polymorphic	Hepatic and extrahepatic	?Reduced
3A3/4	Nifedipine, erythromycin, ciclosporin, terfenadine	Exaggerated effects	7q22	Hepatic and gut	Reduced in some studies but not all amiodarone

Induction and inhibition of CYPs in ageing

Induction and inhibition in response to age need re-examining because of the increased number of isoforms of CYP recognized as being involved in drug metabolism. The original studies on induction determined the inducibility of metabolizing enzymes indirectly using antipyrine and propranolol as probe drugs in subjects with and without a smoking history. The data suggest a loss of inducibility occurred with age [13, 14]. In contrast, direct studies on the *in vitro* induction of aryl hydrocarbon hydroxylase (CYP1A) in monocytes from old and young volunteers have shown that the inducibility of this enzyme is not affected by age [15]. This would be consistent with differential selective inducibility of various enzymes based on our increased understanding of the complexity of CYPs. The effects of age on inhibition are also not well characterized [16]. Theophylline has also been extensively studied as a model drug for the effects of age on drug metabolism. Specific studies in older subjects have not documented a reduction in the extent and degree of inhibition using cimetidine compared with the young [17].

Diet and drug metabolism

Insufficient studies have been conducted either in young or elderly volunteers to determine in a consistent manner the effects of diet and food on drug metabolism. Changes in diet may lead to significant alterations in drug metabolism [18, 19]. Substituting protein for carbohydrate in diets induces oxidative metabolism [20, 21]. Some dietary constituents such as caffeine [22] and cruciferous vegetables [23] can induce oxidative metabolism, whereas others, most notably grapefruit juice, can inhibit it [24]. Given the variety of known dietary influences on drug metabolism, and the high prevalence of protein calorie malnutrition in sick elderly hospitalized patients, the interactions between diet and drug metabolism in the elderly deserve further study.

Phase II reactions and age

There have been few studies examining age effects on conjugation. While our understanding of phase 2 metabolism of individual drugs has improved, there have been no major advances in our knowledge of phase 2 metabolism in ageing humans. Much of the current database is old (lorazepam, oxazepam and paracetamol). The clearance of lorazepam and oxazepam is not significantly reduced with age [25, 26].

P-glycoprotein and transporters

Transporters have contributed significantly to our understanding of drug disposition in the last decade. Active transport of bile-excreted drugs and molecules was confirmed with the determination of anion and cation transporter proteins in bile caniculi. Our increasing knowledge of P-glycoprotein (Pgp) function has begun to lead directly to enhanced understanding of drug disposition and drug interactions.

In an *in vitro* model of normal hepatic tissue a 40-fold variation in transporter mRNA was found supporting the emergence of transporters as a new variable contributing to interindividual variability in metabolism [27]. Pgp pumps protease inhibitors out from sanctuary sites (brain and testes), reducing their potential efficacy in HIV disease [28]. Inhibition of Pgp in a mouse model has given proof of concept that such modulation could increase drug efficacy [29].

To date, drug development has been undertaken in the face of substantial variation in drug absorption and disposition. Such findings are now interpretable in the light of transporter pharmacology. In particular, Pgp is found in human intestine, where it has been implicated in the efflux of many compounds [30]. For example, transporter pharmacology now provides an explanation for digoxin–quinidine-induced bradycardia (quinidine inhibits Pgp efflux of digoxin) and lofepramine–quinidine-induced nausea and respiratory depression (inhibition of brain efflux function of Pgp pump) [31, 32].

Transporter mutations also explain hereditary cholestatic liver disease [33]. For example, ingestion of macrolide antibiotics makes occult dysfunction clinically manifest because of enhanced Pgp inhibition.

The effect of ageing on Pgp function throughout the body is as yet unknown. There is evidence both in mice and humans that ageing is associated with increased expression/function of Pgp in lymphocytes [34, 35]. Because Pgp is expressed in such a variety of tissues and cells, altered expression of Pgp with advancing age may underlie many drug interactions and altered drug effects in older people. Further research in this field could well impact on the burden of adverse drug reactions in elderly patients.

Frailty, esterases and ageing

Heterogeneity increases in older populations whatever the physiological variable being studied, so that the biggest difference between young and old is often a marked increase in the scatter of data in the elderly rather than a substantial shift in the mean. This heterogeneity has been explored in drug metabolism *in vivo* by undertaking drug metabolism studies in healthy young, 'fit' elderly and 'frail' elderly patients or volunteers. For the purposes of these studies, frailty was defined in terms of function rather than disease as 'persons over 65 years

who are not independently mobile and are dependent on others for activities of daily living' [36].

Esterases, a phase 1 enzyme class mainly located in liver, plasma and specific organs such as the brain, have been studied by the Cardiff Group. These studies have demonstrated that frailty is associated with a decline in metabolic activity of plasma aspirin esterase [37–39].

Other reported frailty-associated findings include a reduction in the conjugation of paracetamol [40]. Similar findings have been reported with metoclopramide [41] not seen in the fit elderly and additional decrements in acetanilide clearance [42]. Furthermore, increased variability in frail elderly compared with 'fit' elderly women has been demonstrated for theophylline clearance [43]. More recent studies of benzoyl, butyryl, and acetylcholinesterases have also demonstrated no decline *in vivo* with age [44].

This goes some way to explain the increased heterogeneity in drug handling and response in older people. In addition to the effects of frailty, trauma and ill health can also have substantial effects on enzymes of drug metabolism in older people. Plasma aspirin esterase activity is significantly reduced in elderly people either following emergency and elective hip fracture patients on admission to hospital and improves towards normal during subsequent recovery [45]. The effect of trauma on enzymes of drug metabolism may be related to the amount of injury, as relatively minor surgical interventions such as inguinal hernia repair are not associated with decrements in drug metabolism in man [46]. Other illnesses, which cause substantial acute inflammatory responses such as pneumonia, have also been found to be associated with reduced esterase activities in older patients [47]. Given the variability within the older population in terms of physical fitness/frailty and their burden of illness/comorbidities, there is a need to individualize prescribing within this population.

Conclusions

The increasing interindividual variability in drug metabolism, drug action and adverse reactions is a feature of advancing age. This should alert the prescriber to the increasing heterogeneity that occurs in treating older people. Frailty is easy to recognize clinically and increasingly should be considered when using drugs in older people. Changes in drug disposition with ageing can be inferred as being due to changes in conventional physiological changes such as liver volume and intrinsic enzyme capacity. Transporters clearly play a fundamental role in the elimination of drugs and in getting drugs to and from target sites of action, and in the future will enhance our understanding of drug disposition in old age. To date there is no unifying method of estimating hepatic capacity to metabolize compounds analogous to renal clearance that has found clinical utility. This remains a challenge for current research.

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