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Impact of medication on protein and amino acid metabolism in the elderly: the sulfur amino acid and paracetamol case

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Abstract

The optimisation of nutritional support for the growing number of older individuals does not usually take into account medication. Paracetamol (acetaminophen; APAP) is the first intention treatment of chronic pain that is highly prevalent and persistent in the elderly. Detoxification of APAP occurs in the liver and utilises sulfate and glutathione (GSH), both of which are issued from cysteine (Cys), a conditionally indispensable amino acid. The detoxification-induced siphoning of Cys could reduce the availability of Cys for skeletal muscle. Consequently, APAP could worsen sarcopenia, an important component of the frailty syndrome leading to dependency. The present review provides the rationale for the potential pro-sarcopenic effect of APAP then recent results concerning the effect of chronic APAP treatment on muscle mass and metabolism are discussed. The principal findings are that chronic treatments with doses of APAP comparable with the maximum posology for humans can increase the requirement for sulfur amino acids (SAA), reduce Cys availability for muscle, reduce muscle protein synthesis and aggravate sarcopenia in animals. One clinical study is in favour of an enhanced SAA requirement in the older individual under chronic treatment with APAP. Few clinical studies investigated the effect of chronic treatment with APAP combined with exercise, in nutritional conditions that probably did not affect Cys and GSH homeostasis. Whether APAP can aggravate sarcopenia in older individuals with low protein intake remains to be tested. If true, nutritional strategies based on enhancing Cys supply could be of prime interest to cut down the pro-sarcopenic effect of chronic treatment with APAP.

Key words: **Paracetamol: Acetaminophen: Cysteine: Glutathione: Muscle protein metabolism: Sarcopenia**

Introduction

The number of individuals aged older than 65 years is increasing rapidly, and ageing is associated with alterations in numerous physiological functions. Poor nutritional status is one of the main risk factors for frailty. This geriatric syndrome is associated with alterations in multiple physiological functions and reduced functional reserves[1], in which sarcopenia, the age-related loss of skeletal muscle mass and strength, is considered as a key component of frailty[2]. The decline in nutritional status, functional ability and the increased risk of falls in older adults have been associated with the occurrence of polypharmacy which increases with age[3,4]. However, a causal relationship has not been clearly established, partly because (i) some diseases by themselves promote malnutrition[5] and (ii) the age-associated anorexia could also be a confounding factor. Indeed, reduced food intake can result not only from medication but also from multiple factors including declines in physiological functions (smell and taste, central and peripheral drive to eat, gastric emptying), social factors (poverty, loneliness) and pathological conditions (depression, dementia, somatic diseases, oral-health status)[6,7]. It is nevertheless well documented that many drugs have unpleasant tastes or odours of their own and can further alter the sensory perceptions of dietary products through various mechanisms involving peripheral receptors, chemosensory neural pathways, brainstem and brain or hypo-salivary side effects leading to a poor oral cavity health[8]. These aspects will not be developed in the present review but we will focus on other types of drug–food interactions that could affect intestinal transport and metabolism, systemic transport or tissue/cellular distribution of nutrients[9]. A typical example of drug action on a nutrient bioavailability is paracetamol (acetaminophen; APAP) that interferes with cysteine (Cys).

APAP is the most frequently used analgesic in older adults and is the first-line treatment of a large variety of pain such as headache, muscle pain and chronic pains such as lower back pain and arthritis[10–12]. APAP is usually considered to be safe when administered within the therapeutic range, but in overdosages it can cause severe toxicity in the liver and more rarely in the kidneys[13,14]. A recent meta-analysis including eight observational studies highlighted increases in cardiovascular and gastrointestinal disorders and mortality with regular intake of high therapeutic doses[15]. In connection with nutrition, the

Abbreviations: AA, amino acid; APAP, paracetamol (acetaminophen); Cys, cysteine; GSH, glutathione; IAA, indispensable amino acid; Met, methionine; NAPQI, *N*-acetyl-*p*-benzoquinone imine; PAPS, 3'-phosphoadenosine 5'-phosphosulfate; SAA, sulfur amino acid.

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detoxification of APAP requires Cys[16,17], a conditionally indispensable amino acid (IAA)[18]. Cys deficiency has already been shown to be partly responsible for the decreased health and quality of life with ageing[19]. Indeed, Cys deficiency can deplete and oxidise Cys and glutathione (GSH) pools, which promote the progressive increase in ageing-related oxidative stress associated with various chronic diseases and sarcopenia[20–22]. So, it is relevant to question whether APAP treatment could decrease Cys availability necessary to sustain protein reserves, notably in skeletal muscle, and consequently worsen sarcopenia and frailty in older adults. The purpose of the present review was to provide bibliographic data, and evidence leading to our hypothesis; then to discuss recent results concerning the effect of APAP treatment on muscle mass and metabolism.

Sarcopenia: definition, prevalence and mechanisms

The term sarcopenia was first proposed by Rosenberg in 1989[23]. It comes from the Greek *sarx* 'flesh' and *penia* 'poverty'. Nowadays, sarcopenia is defined by a loss of muscle mass, muscle strength and muscle quality[24–27]. It is closely correlated with morbidity and increased mortality[28]. In 2015, one in eight individuals was aged 60 years and over and they will represent more than one in five individuals in 2050[29]. Inevitably with this increase in the ageing population, the prevalence of sarcopenia will increase too and is estimated that it will affect more than 200 million individuals in 2050[30]. Currently, 25–50 % of the elderly aged 65 years and older are probably sarcopenic[31]. In the USA, the cost of sarcopenia has been evaluated to be about $18·4 billion[31]. Sarcopenia is now a major cost in terms of healthcare. It is an important component of the frailty syndrome[2] and could lead to dependency[32,33]. Thus, the prevention of sarcopenia is of prime importance.

Sarcopenia is a multifactorial event affected by intrinsic (for example, age, hormonal change) and extrinsic (for example, disease, nutrition) factors[34]. Muscle loss arises from an imbalance between proteolysis and protein synthesis. Various mechanisms are involved in sarcopenia related to either a decrease in the availability of amino acids (AA) for muscle or an intrinsic impairment of muscle protein metabolism (Fig. 1). In the following, only factors affecting AA availability will be described.

The first major determinant of AA availability for muscle is dietary protein intake. Ageing can be associated with the reduction of nutrient intake, known as 'anorexia of ageing', representing a physiological feature of old age associated with decreased energy expenditure and loss of muscle mass[35]. Epidemiological data have shown that 22–41 % of individuals older than 50 years did not reach the RDA for proteins of 0·8 g/kg body weight per d[36]. The ingestion of a small bolus of IAA (7 g) has been shown to induce a lower muscle protein accretion in the elderly than in young individuals[37]. Furthermore, the quality of ingested protein is of prime importance and is closely linked to its composition of IAA. In fact, IAA are primary stimuli of protein synthesis and some of them have a specific role in muscular anabolism, such as branched-chain AA. This is the case for leucine, nowadays recognised as a regulator of protein renewal, particularly by its action on protein synthesis[38–45] and protein degradation[46,47]. So it appears

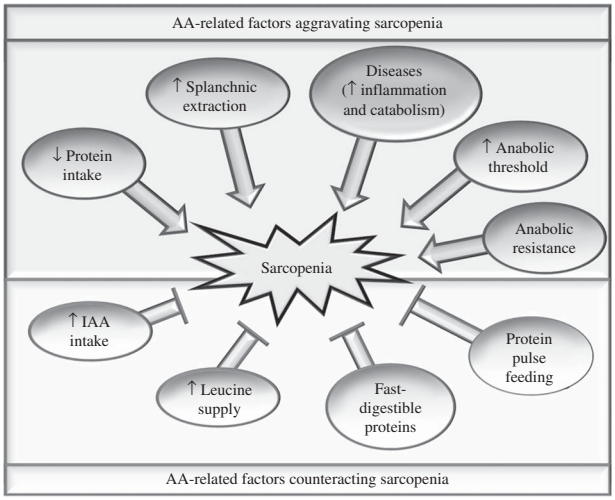

Fig. 1. Amino acid (AA)-related factors affecting skeletal muscle during sarcopenia. IAA, indispensable AA.

of prime importance to recommend the consumption of high-quality proteins, i.e. containing a large proportion of IAA[48–50]. Currently many authors agree on this point and recommend that older adults consume 1–1·5 g proteins/kg per d[51–56] rather than the 0·8 g proteins/kg per d usually recommended for adults whatever their age[57,58].

Not only the quantity and the quality of ingested proteins are of importance, but also the repartition of the dietary protein intake in the course of the day. Indeed, protein pulse feeding (80 % of daily proteins concentrated in one meal) has been shown to be more efficient in stimulating N balance and protein synthesis[59,60]. These results have recently been confirmed in undernourished elderly individuals[61], for whom protein pulse feeding allowed protein mass gain. The efficacy of protein pulse feeding can be explained by the concept of the anabolic threshold[49]. This threshold represents the minimum quantity of AA necessary to trigger protein synthesis stimulation. When compared with healthy young adults, in the elderly, this threshold is thought to be higher, leading to a loss of protein synthesis stimulation for a same amount of ingested proteins. Many studies have indicated that 25 to 30 g of high-quality protein is necessary to pass the anabolic threshold[62–64]. The increase in the anabolic threshold with ageing could be explained by many factors associated with ageing such as inflammation, insulin resistance or oxidative stress that have all been shown to lower the muscle anabolic response following food intake[49,65].

This concept is in accordance with studies performed on the speed of protein digestion, a feature that determines the post-ingestion kinetics of plasma aminoacidaemia. The post-ingestion peak of plasma aminoacidaemia occurs earlier and is higher with fast-digestible proteins than slow-digestible proteins. In young adults, slow digestible proteins were more effective than fast proteins in stimulating postprandial anabolism[66]. In contrast, in the elderly, fast-digested proteins were more effective[67–69]. Indeed, fast-digestible proteins generated a hyperaminoacidaemia that exceeded the anabolic threshold and then allowed a muscle anabolic response to meals in the elderly.

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Another important determinant of AA availability for muscle is the first-pass extraction by the splanchnic area. The splanchnic extraction of AA has been shown to be higher in the elderly than in young adults[70,71]. With ageing a larger amount of AA are sequestrated in the splanchnic area leading to a reduced availability of AA for peripheral tissues such as muscles. Consequently, an increased splanchnic extraction may also contribute to a decreased AA availability for muscle. With a usual amount of protein ingested, the AA level may not reach the anabolic threshold and, as a consequence, muscle anabolism may be reduced in the elderly, compared with younger adults.

Finally, particular conditions can increase the use of AA in the splanchnic area with consequences on the bioavailability of AA for muscle. It is well known that hepatic protein metabolism strongly increases in acute inflammation, for example in sepsis[18]. Detoxification of APAP occurs in the liver and utilises Cys, meaning that the availability of Cys to muscle could be impacted and result in a pro-sarcopenic effect. APAP is a widely used analgesic drug to relieve pain especially in older individuals, a population at risk of low protein intake. The potential negative effects of APAP on Cys homeostasis and on muscle will be developed below.

Prevalence of paracetamol treatment in older individuals

APAP is the first-intention recommended medicine for the treatment of chronic pain especially in older individuals[12,72–77]. Chronic pain is defined as daily pain which persists for 3 consecutive months[73,78]. Pain prevalence varied from 25–40 % for home-dwelling to 28–93 % for the institutionalised elderly[77]. In the USA, at least 50 % of home-dwelling elderly individuals experienced chronic pain[73,78]. In institutionalised elderly individuals this prevalence reached 49–84 %[73,79,80]. The most common cause of chronic pain was arthritis whose prevalence reached 35–57 %[81,82] and low back pain with a prevalence of 49 %[81,83]. The non-management of chronic pain in the elderly can have large repercussions in terms of health and well-being with a high risk of depression, altered physical activity, higher outcomes of falls and malnutrition, and so an altered quality of life[74,84]. APAP is an over-the-counter medicine, which has been recommended by referent organisations such as the WHO, the Food and Drug Administration, the American Geriatrics Society[75,78], the OsteoArthritis Research Society International[85], the European League Against Rheumatism[86,87] and the National Institute for Health and Clinical Excellence[88] to treat pain of small to moderate intensity. APAP has been the most sold and consumed drug for years in the USA and France[89,90].

The maximum therapeutic dose of APAP is 4 g/d (four doses of 1 g each spaced by at least 4 h) for adults, whatever their age, and without hepatic or renal insufficiencies. At therapeutic doses APAP is usually considered safe even in long-term treatment. Notably, no sign of hepatotoxicity was reported when 4 g/d APAP was administered for up to 12 months to adult patients with osteoarthritis pain[91]. However, a recent meta-analysis including eight observational studies revealed increases in cardiovascular and gastrointestinal disorders, and in mortality with regular intake of high therapeutic doses[15].

Paracetamol detoxification induces an irreversible loss of cyseine

After oral ingestion, APAP is rapidly absorbed at the intestinal level[92]. APAP half-life varies from 90 min to 3 h after a unique dose[17,93] with a maximum concentration reached at 60 to 90 min. These values depend on the fed state (i.e. post-absorptive or post-prandial) and the ingested dose[94]. APAP undergoes an intense hepatic metabolism followed by renal elimination. APAP detoxification mainly occurs in the liver through phase I and II reactions[16,17]. Briefly, APAP metabolism consists mainly (up to 90 %) of phase II reactions: direct sulfate (sulfation) or glucuronide conjugations (Fig. 2). The obligate coenzyme of the sulfotransferase reaction responsible for sulfation is the activated form of endogenous inorganic sulfate that

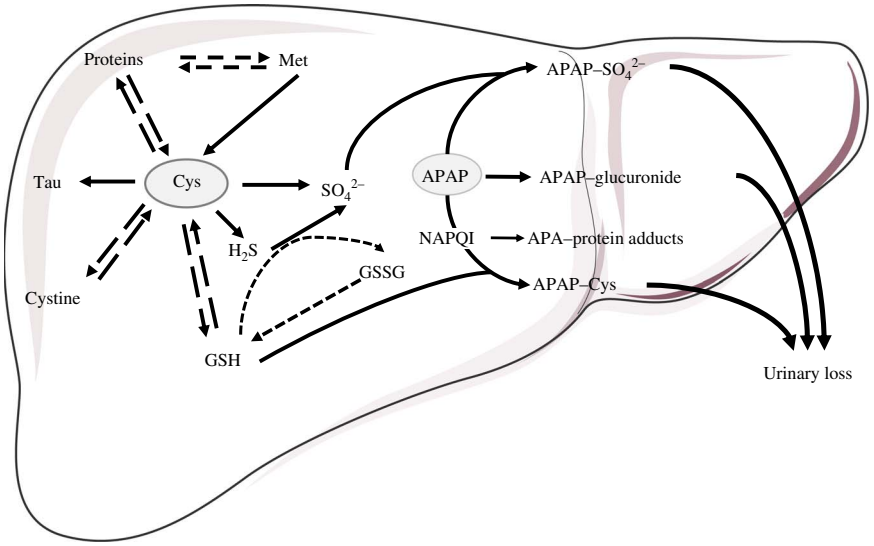

Fig. 2. Cysteine (Cys) and paracetamol (acetaminophen; APAP) hepatic metabolism. Met, methionine; SO_4^{2-}, sulfate; Tau, taurine; H_2S, hydrogen sulfide; GSH, glutathione; GSSG, glutathione disulfide; NAPQI, *N*-acetyl-*p*-benzoquinone imine.

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is named PAPS (3'-phosphoadenosine 5'-phosphosulfate). PAPS synthesis depends on sulfate availability and sulfotransferase activities[95]. A marginal (about 10 %) phase I reaction consists of conjugation with GSH (γ-glutamyl-cysteinyl-glycine)[16,17]. In this phase, APAP is converted by cytochrome P450 into a highly reactive compound (*N*-acetyl-*p*-benzoquinone imine; NAPQI). NAPQI is neutralised by GSH and then metabolised through the mercapturate pathway.

Sulfation being a capacity-limited process, glucuronidation and, more significantly, oxidation to NAPQI increase at a supra-therapeutic dose of APAP[16,17]. NAPQI is the compound responsible for the potential hepatic toxicity of APAP. After an APAP overdose, i.e. more than 7·5 g[17], the hepatic GSH pool is strongly depleted and NAPQI forms APAP–protein adducts causing important mitochondrial damage leading to cell death[96]. APAP overdoses have been treated with *N*-acetylcysteine for 40 years[97]. Standardised administration of *N*-acetylcysteine should be started within 8 h of an acute overdose[17]. *N*-acetylcysteine is a drug that replenishes GSH stores *in vivo*[98]. Co-administration of APAP and *N*-acetylcysteine could prevent acute APAP toxicity, as has been shown in a preclinical study[99].

We and others have recently shown that the formation of hepatic APAP–protein adducts occurs also at doses below the toxic level and even at therapeutic dosages. APAP–protein adducts do not lead to cell toxicity when they remain a small amount. APAP–protein adducts were present in serum from patients who received the maximum daily therapeutic dose of 4 g/d, for 10 d[100]. APAP–protein adducts were also present in liver 1 h after a single injection of a very low dose of APAP (15 mg/kg) in overnight fasted mice[101]. In both studies there was no relationship between APAP–protein adducts and toxicity. APAP–protein adducts were also observed without GSH depletion. As recently questioned[93], it seems that NAPQI simultaneously binds to GSH and proteins. We showed in a rat model that a 0·5 or 1 % APAP diet, equivalent to 2 and 4 g/d for humans, respectively[102], during 17 d led to the formation of APAP–protein adducts[103]. APAP–protein adducts were formed in the absence of hepatotoxicity and were detected with a large increase (218 %) with the 1 % dose compared with 0·5 %. So, even at low therapeutic dosage and before hepatic GSH depletion, APAP–protein adduct formation occurred and increased more than the increase in the dose.

After hepatic metabolism, all endproducts of APAP detoxification are excreted in the urine, 55–60 % as glucuronide, 20–30 % as sulfate conjugates and up to 10 % as GSH-dependent conjugates[16,17]. As Cys is both the main source of sulfate and the limiting AA in GSH synthesis[104,105], APAP metabolism leads to an extensive use of Cys that is diverted from its physiological uses and finally definitively lost in the urine (Fig. 2). Based on the respective proportions of APAP metabolites, it appears that 30–40 % of the dose is metabolised using Cys-derived compounds (sulfate or GSH)[17]. By equimolarity, the maximum therapeutic dose of 4 g/d APAP represents a net loss of 1·3 g Cys/d. Cys siphoned under APAP treatment is highly significant as it represents 20 % of the sulfur AA (SAA) intake in the elderly treated with 3 g/d APAP[106]. The requirement in AAS could be not achieved due to the low amount of ingested food in the elderly individuals chronically treated with APAP. The average SAA intake of the elderly was estimated to be 1·8 g/d, meaning that APAP detoxification would lead to urinary loss of the major part of SAA ingested, and that the main SAA metabolic needs would be uncovered[107].

Cysteine, a conditionally indispensable amino acid

Cys and methionine (Met) are the two SAA used for protein synthesis but only Met is indispensable. Cys is provided by dietary proteins, GSH and protein degradation, with its endogenous synthesis occurring mainly in the liver from Met and serine[108] (Fig. 2). Cys becomes indispensable when its endogenous synthesis cannot be sufficient to cover all metabolic needs[18]. Both Cys supplied preformed in the diet and Cys formed from Met are equally partitioned toward the synthesis of taurine, sulfate and GSH[108] (Fig. 2), the last two compounds being key players in APAP detoxification.

Sulfate can be synthesised by two different pathways from Cys (Fig. 2). Sulfate is one of the endproducts of the cysteine sulfinate-dependent pathway of Cys catabolism, whose first step is catalysed by cysteine dioxygenase, a highly regulated enzyme[109]. Other Cys catabolic pathways produce sulfide that is then oxidised into sulfate within the mitochondria[110]. A significant depletion of GSH limits the production of sulfate through the sulfide oxidative pathway; and thiosulfate, an intermediate in this pathway, accumulates[111]. This observation highlights the importance of GSH, another Cys-related compound, in sulfate synthesis.

Biosynthesis of GSH, which is tightly regulated, occurs in two steps catalysed by glutamate–Cys ligase and GSH synthetase[112]. Key factors of GSH synthesis are the activity of the rate-limiting enzyme, glutamate–Cys ligase, and the availability of Cys. GSH translocated out of the cells is degraded through the γ-glutamyl cycle, playing an important role in the inter-organ transport of Cys[112]. In the case of low SAA supply, GSH is used as a Cys supplier[113,114]. Other studies have shown that the tissue GSH pool was depleted whereas protein synthesis was maintained in the case of low SAA supply[115,116]. These results highlight that protein synthesis has priority over GSH synthesis. In addition to its role in detoxification processes, GSH serves several vital functions including antioxidant protection. Indeed, GSH/GSSG (reduced GSH:glutathione disulfide ratio) is the major redox couple that determines the anti-oxidative capacity of cells, and GSH deficiency contributes to oxidative stress[117]. Total plasma Cys is also known as an indicator of the oxidative status[118–121]. The liver is quantitatively the most important organ in the metabolism of SAA and GSH[122]. The liver plays a key role in the regulation of peripheral plasma SAA/GSH and their bioavailability for peripheral tissues such as skeletal muscle[122]. Direct provision of Cys and indirect supply through GSH are indispensable for the muscle because Cys cannot be synthesised within muscle due to the lack of the enzymes necessary to synthesise Cys from Met[123,124].

At the whole-body level, Cys can be synthesised from Met. Therefore, the total SAA requirement is defined as the Met intake, in the absence of Cys, that is needed to support all metabolic requirements of both Met and Cys[108,125]. Nevertheless, Cys has been clearly demonstrated to have a sparing

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effect of 60 % of Met requirement when present in the diet. This sparing effect is clearly associated with a change in Met metabolic flux leading to the endogenous synthesis of Cys[126–132]. Other studies have shown that sulfate can also act as a sparing agent on Cys[133–135]. However, the sulfate sparing of Cys, observed under Cys deficiency and very low sulfate ingestion, has been considered of primarily academic interest[136]. The mean requirement of total SAA is 12–15 mg/kg per d[108] and the population-safe intake is 21–27 mg/kg per d[137,138]. The range of daily intake of SAA has been estimated from 6·8 g/d in the case of a high-protein diet to only 1·8 g/d in elderly individuals with low energy intake[107].

Of note, SAA metabolism seems to be modified with ageing towards a higher SAA requirement[139,140]. Furthermore, Cys and GSH oxidation increases with age[19] as shown in human plasma and erythrocytes[141] and in rat liver and kidney[142], and Cys supplementation improves skeletal muscle function[19]. Keeping in mind that APAP treatment leads to a significant irreversible loss of Cys, chronic treatment could further impair GSH and Cys homeostasis and muscle mass in the elderly.

Effects of long-term paracetamol treatment on glutathione and cysteine homeostasis

It is well known that acute APAP administration induces a time- and dose-dependent decrease in liver GSH concentration in mice or rats[143,144]. Decreases in liver concentrations of Cys and PAPS, as well as in serum sulfate, occur too[145]. A mathematical model of the dynamics of cellular changes in GSH homeostasis induced by APAP was recently built and tested *in vitro* using human liver-derived cells[146].

Chronic administration of APAP also decreases liver GSH content in mice, the effect being dependent not only on APAP dose but also on the quantity of food ingested and SAA dietary content[102,147,148] (Table 1). Long-term ingestion of APAP increases the Met requirement of mice for growth, and the maintenance of GSH level and protein synthesis in the liver[149]. Similarly, feeding rats with a 1 % APAP diet inhibits growth[150]. The dose of APAP provided by the 1 % APAP diet is considered as an equivalent to the maximum therapeutic dose of 4 g/d for humans. Indeed, as the mean daily dry food ingested by humans is approximately 400 g/d, the 4 g of APAP represents 1 % of the daily DM ingested[150]. The addition of 0·5 % Cys or Met to the 1 % APAP diet or 1 % Met in drinking water restored growth but the addition of 1 % sodium sulfate to drinking water was ineffective[150]. In addition to the lowering effect of APAP on GSH in the liver, where detoxification occurs, APAP treatment decreases liver Cys concentration, plasma free cyst(e)ine (i.e. free cysteine plus free cystine) concentration, as well as intestine and muscle GSH contents[102,147,149]. Based on the inter-organ relationships involved in GSH metabolism, mechanisms responsible for the low muscular content in GSH could result from the expected low export of GSH from the liver, the low availability of Cys for the muscle, or even from a significant export of GSH from the muscle. Whatever the mechanism, all these variations support the idea that chronic APAP can generate a lack of Cys/GSH at the whole-body level in conditions that could be encountered in humans.

Literature concerning the effect of chronic APAP on Cys and GSH in humans is rather scarce, apart from toxicology-related studies. Nevertheless, the direct link between APAP metabolism and alterations in hepatic SAA metabolic rates was made in 1987 by Lauterburg & Mitchell[151]. Their work showed that single administrations of therapeutic doses of APAP triggered an elevation of Cys and GSH turnover in men. These results suggest a higher Cys need even at a therapeutic dosage to ensure APAP metabolism. More recently, a study conducted in young adults showed that a therapeutic dose of APAP induced an oxidation of plasma GSH when the diet was deficient in SAA[152].

Ageing is known to disturb GSH homeostasis; accordingly, the hepatic GSH pool has been found to be lower in old than in young and adult mice[153]. More interestingly, after a single APAP administration the GSH hepatic pool strongly decreased at 4 h and was restored by only 41 % in old mice at 24 h; whereas adult and young mice showed better recovery of 66 and 94 %, respectively[153]. The elderly could be also more vulnerable to APAP-induced disorders in Cys/GSH homeostasis due to the pre-existence of the pro-oxidant Cys and GSH redox status and the low GSH pool described above. In this context, our study with home-dwelling elderly individuals taking 3 g/d APAP for 2 weeks revealed that chronic APAP led to an increase of protein consumption from 0·93 g/kg per d before treatment to 1·06 g/kg per d at the end of the 2-week experimental period[106]. The corresponding increase in SAA ingested was equivalent to half of the sulfur excreted in urinary APAP conjugates. These results supported an elevation of SAA requirement in the elderly treated with APAP. This study also revealed that metabolic disorders occurred such as an enhanced oxidation of sulfur-containing compounds. Moreover, ageing tended to amplify the depletion of blood GSH and modified the pattern of urinary APAP conjugates in favour of an increased loss of Cys in postoperative patients under intravenous APAP treatment (1 g every 6 h)[154].

Altogether, it appears that therapeutic APAP treatment could generate perturbation of SAA and GSH metabolism leading to lower Cys availability for physiological functions. In the first part of the present review, we summarised the importance of an adequate AA supply to muscle to ensure protein homeostasis especially in the elderly. It is well known that if only one IAA is limiting or its metabolic need is increased (for example, Cys in sepsis or acute inflammation), this leads to decreased protein synthesis especially in muscle[18]. Consequently, the high prevalence of APAP treatment in the elderly could generate a risk for a frequent inadequate Cys supply to muscle and chronic treatment with APAP could be a risk factor for sarcopenia (Fig. 3).

Effects of long-term paracetamol treatment on skeletal muscle

The link between chronic APAP treatment and muscle status has been investigated in animals and human subjects (Table 2). In animals, Wu *et al.* studied very old rats (33 months) treated daily with APAP for 6 months[155–157]. These studies showed an improvement in glycaemic status and the protein muscle signalling pathway due to an antioxidant effect of APAP. These positive effects were recorded with the very low dose administrated, 30 mg/kg per d, whereas the minimal dose requested

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Table 1. Summary of studies examining the effects of paracetamol (acetaminophen; APAP) treatment related to sulfur amino acid (SAA) or glutathione (GSH) metabolism

First author (year)	Experimental model	APAP administration	Duration	Feeding	Selected key finding
Reicks (1988)[147]	Mice, adult	0·3, 0·6 or 1 % of the diet	4 weeks	Recorded three times per week, *ad libitum v.* PF	0·6 and 1 % APAP diets decreased weight, hepatic GSH and Cys (measured only with 0·6 % APAP diet). 1 % Met diet (twice the RDA) prevented APAP-induced decreases in body weight; and hepatic Cys and GSH
Reicks (1989)[149]	Mice, growing and adult	0·3 to 0·8 % of the diet	2 weeks	Recorded three times per week	APAP inhibited growth, decreased food efficiency and hepatic GSH and Cys. 1 % Met (twice the RDA) diet prevented these effects
Chen (1990)[153]	Mice, growing (3 months), adult (12 months) and old (31 months)	375 mg/kg, i.p.	Single injection	Not recorded	Strong depletion of hepatic GSH occurred 4 h after APAP administration. After 24 h, GSH recovered to only 41 % of in old mice *v.* 66 % in adults and 94 % in growing mice
McLean (1989)[150]	Rats (growing)	1 % of the diet	3 weeks	Not recorded	APAP inhibited growth rate. Addition of 0·5 % Met or Cys to the APAP diet restored growth
Kondo (2012)[148]	Rats (7 weeks)	Oral administration: 0, 300 or 500 mg/kg	99 d	Recorded on days 14, 35, 56, 78 and 98. Food restricted (4 h per d) *v. ad libitum*	APAP at 500 mg/kg decreased hepatic GSH in restricted rats APAP treatments increased hepatic GSH in *ad libitum* rats
Mast (2014)[102]	Rats, adult (4 months)	0·5 or 1 % of the diet	17 d	Recorded daily	No major effect with 0·5 % APAP diet 1 % APAP diet transiently decreased food intake. It decreased GSH content in liver, small intestine and muscle and decreased plasma concentration in free cyst(e)ine
Mast (2013)[160]	Rats, old (24 months)	1 % of the diet	Three cures of 2 weeks spaced by 2 weeks of washout	Recorded daily, control PF	APAP decreased food intake. Compared with PF rats, APAP decreased GSH content in liver and muscle, and GSH concentration in plasma and decreased plasma concentration in free cyst(e)ine
Lauterburg (1987)[151]	Humans, adult	50 to 1200 mg (one dose)	Single administration	Not recorded	600 or 1200 mg of APAP stimulated the turnover of Cys pool available for GSH synthesis most probably due to increased GSH turnover
Mannery (2010)[152]	Humans, adult	15 mg/kg *v.* placebo	Two doses (experimental day)	Equilibration diet (3 d) then 100 or 0 % SAA RDA diets (2 d), APAP treatment two meals (1 d)	With 100 % RDA for SAA, APAP resulted in a more oxidised plasma Cys/CySS pool *v.* placebo. APAP with 0 % SAA did not cause further oxidation beyond APAP or 0 % SAA alone. Only APAP with 0 % SAA resulted in more oxidised plasma GSH/GSSG pool
Pickering (2011)[154]	Elderly patients (65 years)	4 g/d (one dose every 6 h)	4 d post-surgery	No meal on day 1, then progressive light re-alimentation	Time-dependent decrease in blood GSH tended to be higher in >65 years than <65 years. 4 d-loss of Cys equivalent was higher in >65 years than <65 years
Pujos-Guillot (2012)[106]	Humans, elderly (>69 years)	3 g/d (three doses daily)	14 d	Reported for the 2 d before treatment and the last 4 d	APAP increased dietary protein from 0·93 to 1·06 g/kg per d. Whole-body protein stores were apparently preserved. Metabolic disorders occurred as enhanced oxidation of sulfur-containing urinary compounds was observed

PF, pair-fed; Cys, cysteine; Met, methionine; i.p., intraperitoneal; CySS, cystine; GSSG, glutathione disulfide.

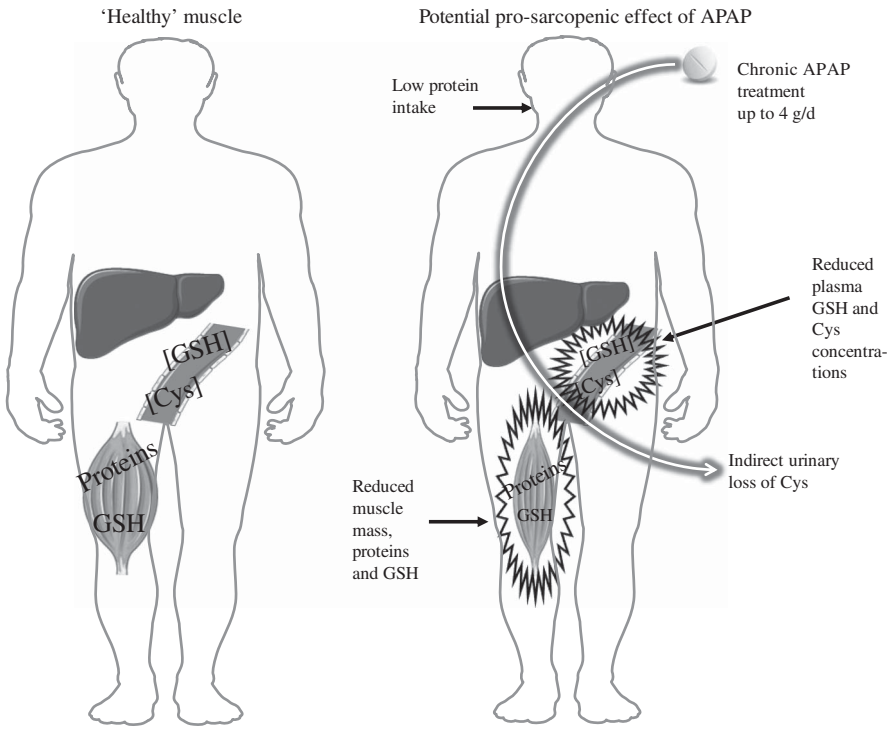

Fig. 3. Proposed mechanism for the potential pro-sarcopenic effect of chronic/repeated cures with paracetamol (acetaminophen; APAP) in older adults with low protein intake. GSH, glutathione; Cys, cysteine; [GSH], glutathione concentration; [Cys], cysteine concentration.

for analgesic effect in rats is 200 mg/kg per d[158,159]. So, at very low dose, APAP could have a beneficial effect on muscle but this amount is far below the chronic APAP prescription for its analgesic effect in humans.

We recently reported that consumption, for 14 d, of a 1% APAP diet by adult rats leading to a daily dose equivalent to the maximum therapeutic posology for humans, decreased muscle mass[102] (Table 2). APAP-induced loss of muscle mass occurred while (i) the sulfation of APAP was saturated and the GSH-dependent detoxification pathway was highly activated and (ii) plasma Cys concentration and GSH contents in liver and muscle were lowered. These results demonstrated for the first time that chronic therapeutic APAP treatment could contribute to muscle mass loss linked to a decreased Cys bioavailability even with an adequate-protein diet. We re-conducted the treatment with aged rats (24 months) submitted to repeated cures with APAP lasting 14 d and spaced by 14 d of washout to mimic treatment of chronic pain. Long-term consumption of a 1% APAP diet in old rats created a net loss of muscle mass associated with decreased muscle protein synthesis[160]. This loss of muscle mass and protein synthesis occurred simultaneously with the generalised decrease of GSH stores and plasma free cyst(e)ine but an elevation of liver protein synthesis. That suggests an inter-organ competition for the use of Cys under APAP treatment in favour of the liver and at the expense of muscle.

Clinical studies tested the effect of repeated APAP administration on muscle in combination with physical exercise[161–166] (Table 2). They were carried out because APAP is a cyclo-oxygenase inhibitor[167] that could make an impact on prostaglandins, potential mediators of the muscle protein synthesis response to exercise[168]. The first study was performed after a high-intensity eccentric exercise in young adults receiving 4 g/d APAP, the first dose taken at the start of the exercise[161,162]. At 24 h post-exercise, results showed an increased muscle fractional synthesis rate associated with increased prostaglandins. APAP attenuated the positive effects of exercise, but had no effect on muscle soreness over the following 9 d[161,162]. The second study, in older individuals, consisted of three sessions of exercise per week for 12 weeks associated with 4 g/d of APAP[163,164]. Results showed a potentiation of muscle volume and force gain with APAP in exercised muscles, without any effect in non-exercised muscles. This effect seemed to be more pronounced in type I muscle fibres[166]. The beneficial effect of long-term treatment with APAP on the exercised muscle was contradictory with the first study but could be explained by differences in the protocol design. Notably, all meals were standardised all through the first study, whereas only the evening meal before the biopsy was standardised in the second study. It is well known that protein intake is in large part responsible for protein muscle metabolism and in a previous study we showed that chronic APAP treatment in the elderly led to a spontaneous increase of dietary protein intake[106]. Thus, it is unknown whether the beneficial effect observed in exercised muscle was only attributable to the combined effect of exercise and APAP or also to a change in dietary protein intake. In the third study, APAP was administered at a lower dose (1 g/d) and only on days of exercise (3 to 5 d/week) for 16 weeks[165]. APAP did not affect the exercise-induced increase in fat-free mass, or physical performance for

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Table 2. Summary of studies examining the effects of paracetamol (acetaminophen; APAP) treatment related to muscle mass and metabolism

First author (year)	Experimental model	APAP treatment	Duration	Other intervention	Feeding	Selected key finding
Wu (2009)[155]	Rats, very old (33 months)	30 mg/kg, drinking water	6 months	–	Not recorded, *ad libitum*	APAP attenuated age-associated elevation in blood glucose, muscle Glut4 protein and decreased superoxide level and oxidatively modified proteins
Wu (2009)[156]	Rats, very old (33 months)	30 mg/kg, drinking water	6 months	–	Not recorded, *ad libitum*	APAP attenuated age-related Akt dysfunction, muscle fibre cross-sectional area decrease and myocyte apoptosis increase
Wu (2010)[157]	Rats, very old (33 months)	30 mg/kg, drinking water	6 months	–	Not recorded, *ad libitum*	APAP ameliorated age-related impairments in Akt/mTOR signalling and phosphorylation of $eIF2_{\alpha}$ (regulators of protein synthesis)
Mast (2014)[102]	Rats, adult (4 months)	0·5 or 1 % of the diet	17 d	–	Recorded daily	No effect on muscle with 0·5 % APAP diet 1 % APAP diet decreased N balance, whole body, small intestine and muscle protein contents
Carroll (2015)[169]	Rats (10 weeks old)	200 mg/kg, oral administration once per d	8 weeks	Exercise 5 d per week, 60 min per d	Not recorded, *ad libitum*	APAP blunted exercise-induced increase in skeletal muscle collagen. Skeletal muscle of APAP-treated had lower collagen cross-linking. Skeletal muscle water content was not altered by APAP
Mast (2013)[160]	Rats, old (24 months)	1 % of the diet	Three cures of 2 weeks spaced by 2 weeks of washout	–	Recorded daily, control pair-fed	Compared with pair-fed rats, APAP decreased muscle mass, protein content (trend) and absolute rate of protein synthesis
Trappe (2001)[161]	Humans, adult	4 g/d (three doses)	Day of exercise. A single dose the day after	A bout of high-intensity eccentric exercise	Not recorded	APAP blocked the increase in muscle $PGF_{2\alpha}$ and PGE_2 proteins
Trappe (2002)[162]	Humans, adult	4 g/d (three doses) from day 7 to day 16	9 d	A bout of high-intensity eccentric exercise on day 7	Standardised meals providing 1·2 g protein/kg per d from day 1 to day 16	APAP (1 d) blocked the increase in muscle protein synthesis 24 h after the high-intensity eccentric exercise without affecting whole protein breakdown. No effect of APAP on muscle soreness over the 9 post-exercise days
Trappe (2011)[163]	Humans, elderly (64 years)	4 g/d (three doses)	12 weeks	Progressive resistance training, 3 d/week	Not recorded, last meal before biopsy was standardised	APAP promoted exercise-induced muscle volume and strength increase but muscle protein and water content were unchanged. These effects occurred only in the exercised muscle
Trappe (2013)[164]	Humans, elderly (64 years)	4 g/d (three doses)	12 weeks	Progressive resistance training, 3 d/week	Not recorded, last meal before biopsy was standardised	APAP blunted exercise-induced increase in mRNA levels of IL-6, IL-10 and MuRF-1. Interstitial level of 3-methylhistidine (myofibrillar proteolysis marker) was not affected by exercise or APAP
Jankowski (2013)[165]	Humans, > 50 years (mean 64 years)	1 g/d (one dose) every day of exercise	16 weeks	Progressive resistance training 3 to 5 d/week	Not recorded	APAP had no effect on fat-free mass and upper- and lower-body muscle strength responses to training, with the exception of knee flexion strength, which was increased
Trappe (2016)[166]	Humans, elderly (64 years)	4 g/d (three doses)	12 weeks	Progressive resistance training, 3 d/week	Not recorded, last meal before biopsy was standardised	APAP increased type I fibre size in exercised muscle but did not change capillary density

Akt, protein kinase B; mTOR, mammalian target of rapamycin; $eIF2_{\alpha}$, eukaryotic initiation factor 2_{α}; MuRF-1, muscle ring finger protein.

several upper- and lower-body exercises, with the exception of knee flexion strength, which was increased. Altogether, these clinical studies were performed in healthy volunteers, whose dietary protein intakes were probably far above the value that theoretically places older individuals at risk of uncovered SAA requirement after APAP detoxification[107]. Accordingly, GSH and Cys homeostasis, which was not investigated, was probably unimpaired in these experimental conditions. We are aware of no study in patients suffering from myodystrophies or muscle disorders other than sarcopenia.

Further studies are still needed to determine whether repeated cures with APAP in the upper range of therapeutic doses in the elderly with low protein intakes could or not worsen sarcopenia (Fig. 3). Of course, this will be complicated by several confounding factors, such as (i) modification of dietary protein intake under APAP treatment, (ii) intrinsic effects of pathologies on muscle mass, (iii) modifications of physical activity that could be enhanced following the reduction of pain with APAP, and, of course, (iv) the difficulty to assess muscle mass variations over short periods of time. To overcome the latter, the determination of plasma and muscle Cys and GSH pools could be the first step to determine whether the availability of Cys for muscle decreases in older individuals under APAP treatment. If so, older individuals with suboptimal dietary protein intake could be supplemented with Cys in order to cut down the potential pro-sarcopenic effect of APAP. Indeed, in growing animals, supplementation with SAA was shown to be effective in counteracting the negative effects induced by APAP doses that are considered equivalent to the maximum therapeutic posology for humans.

Nutritional implications of paracetamol treatment

APAP detoxification requires sulfate and GSH, both originating from Cys. Cys comes from dietary proteins, and its endogenous synthesis from Met. Theoretically, SAA requirement is enlarged by APAP treatment. The extent to which APAP treatment increases SAA requirement in humans is not yet known. That extent is not expected to vary linearly with the APAP dose because the contribution of the GSH-dependent pathway largely increases when sulfate and glucuronide conjugations are exceeded. The maximum increase of SAA requirement is still to be determined in human subjects, including older individuals, under treatment with the maximum therapeutic dose of APAP (4 g/d). The 24 h indicator AA oxidation technique, based on the breakpoint of the whole-body oxidation rate of an indicator AA when the intake of the test AA increases, could be used[108]. Alternatively, GSH pools or APAP–protein adducts could be helpful indicators to determine the safe SAA requirement under the maximum dose of APAP. Indeed, plasma APAP–protein adducts are expected to be high when SAA intake is not sufficient and to progressively decrease with increasing SAA intake until a breakpoint corresponding to the requirement for minimum adverse effects of APAP. However, from an ethical point of view, such studies could probably not be realisable due to the potential toxic effect of the maximum therapeutic dose of APAP under low SAA intake. A compromise could be to set the lowest test intake of SAA at the mean established requirement. It would also be interesting to know whether the Met-sparing effect of Cys is affected by APAP treatment.

The frequency of prescriptions and self-medication uses of APAP that occur concomitantly with low protein intakes (i.e. below the mean protein requirement of 0·6 g/d) is not documented. It is also unknown whether individuals treated with high doses of APAP and having a low protein intake are aware of the risk they take regarding APAP toxicity. In addition, the potential pro-sarcopenic effect of APAP might occur insidiously due to the slow process of sarcopenia, and be undetected by physicians. We suggest that high plasma APAP–proteins could be an indicator of an APAP-induced Cys/GSH deficiency.

Meanwhile, it is prudent to recommend that clinical nutritionists consider APAP treatment, when it is chronic and at high dosage, as a potential determinant of sarcopenia, notably when liver and muscle pools of GSH are impaired. They should pay attention to the quantity and the origin of proteins in order to evaluate the SAA intake. Animal proteins contain more SAA than plant proteins[125]. If SAA intake is lower than the population-safe recommendation of 21–27 mg/kg per d, potential alternative drugs/strategies of chronic treatment with high doses of APAP should be discussed within multidisciplinary medical teams in order to evaluate benefit/risk of all the components of the care of patients, case by case.

Conclusion

APAP is the first-intention treatment of chronic pain of small to moderate intensity and is widespread in the elderly. Detoxification of APAP occurs in the liver and utilises sulfate and GSH, both of which are issued from Cys, a conditionally IAA. The detoxification-induced siphoning of Cys, which occurs under chronic treatment with APAP at the upper range of therapeutic doses, could reduce the availability of Cys for skeletal muscle. Since a lack of one IAA leads to lower protein synthesis especially in muscle, an APAP-induced decrease in Cys availability could exert a pro-sarcopenic effect. This potential negative drug–nutrient interaction deserves attention because sarcopenia is an important component of the frailty syndrome and can lead to dependency. It is of prime importance in the prevention of sarcopenia.

Preclinical and clinical studies gathered here provide evidence that APAP treatment can affect skeletal muscle. In combination with exercise, the effects of APAP could be related to either its role as a cyclo-oxygenase-inhibitor or linked to an APAP-induced shortage of Cys. Studies performed in growing animals have clearly shown that APAP treatment can impair growth rate and that supplementation with SAA was effective in restoring growth. Moreover, muscle mass decreased in adult rats and sarcopenia was worsened in old rats under an APAP treatment that activated the GSH-dependent detoxification pathway and impaired whole-body Cys and GSH homeostasis. These observations indicate that chronic treatment with a dose comparable with the maximum dose for humans increases the requirement of SAA. This is consistent with the spontaneous increase in protein ingestion observed in aged patients treated with APAP. The extent to which SAA requirement is increased is still to be determined.

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Concerning the elderly, it is suggested that SAA requirement could not be covered when chronic treatment with the maximum therapeutic dose of APAP is associated with low protein intake. None of the clinical studies performed so far with chronic administration of APAP investigated the potential pro-sarcopenic effect of chronic/repeated APAP treatment in the elderly with low protein intake. Further clinical studies are needed to clarify the effect of chronic treatment on muscle, taking into account dosage and the heterogeneity of older populations regarding health, physical activity and nutritional status. It will be worthwhile to determine whether APAP can decrease Cys availability for muscle and consequently aggravate sarcopenia in the elderly. If so, the consumption of a high-protein diet or proteins rich in SAA (for example, eggs, cereals and lactoserum) will be the logical issue to be tested in order to cut down the pro-sarcopenic effect of chronic APAP treatment. Alternatively, nutritional supplements dedicated to the elderly with low dietary protein intake could be enriched in SAA to cover the specific APAP-induced increase in Cys requirement.

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