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Benefits of natural dietary *trans* fatty acids towards inflammation, obesity and type 2 diabetes: defining the n-7 *trans* fatty acid family☆

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Abstract – Natural *trans* fatty acids are *trans* fatty acids that naturally occur in ruminant-derived foods: milk (derived from cow, ewe, goat), dairy products (yoghurt, cheese) and ruminant meat (beef, lamb). Because natural *trans* fatty acids are part of the *trans* fatty acid family, they have been compared for decades to their industrial counterparts on a cardiovascular outcome's basis. At current dietary intakes, it is now well recognized that natural *trans* fatty acids are neutral towards cardiovascular health. Still, the negative connotation remains. It is usually taken for granted in the scientific community that natural *trans* fatty acids have no known physiological function and therefore no particular nutritional interest. This prevailing view has totally hidden several studies, which pointed out unsuspected benefits of natural *trans* fatty acids on inflammation, type 2 diabetes and obesity. Some supplementation studies dealt with pure *trans*-vaccenic acid (*trans*-C18:1 n-7) and pure rumenic acid (*cis*-9, *trans*-11 C18:2), but remained somewhat aside as they were carried out on rodents. However, recent epidemiological data reached considerable impact, highlighting a protective effect of *trans*-palmitoleic acid (*trans*-C16:1 n-7) towards the risk of type 2 diabetes. Bearing in mind that natural *trans* fatty acids do not just consist of rumenic acid, this review is the opportunity to sum up scientific knowledge about each of these three fatty acids. We shall therefore, review their occurrence in foods, and their physiological impacts. An overlooked aspect of natural *trans* fatty acids is that they are metabolically connected. The second aim of this review is to underline these metabolic connections. In fact, combining physiological impacts and metabolic pathways unravel shared mechanisms of action of *trans*-palmitoleic, *trans*-vaccenic and rumenic acids, that might be explained by their common n-7 *trans* double bond.

Keywords: dairy products / metabolism / ruminant meat / *trans*-palmitoleic acid / *trans*-vaccenic acid / rumenic acid

Résumé – Bénéfices physiologiques des acides gras *trans* naturels alimentaires sur l'inflammation, l'obésité et le diabète de type 2 : définition de la famille des acides gras n-7 *trans*. Les « acides gras *trans* naturels » sont des acides gras *trans* que l'on trouve naturellement dans les aliments issus des mammifères ruminants : le lait (de vache, brebis, chèvre), les produits laitiers (yaourt, fromage) et la viande (bœuf, agneau). Comme ils appartiennent à la famille des acides gras *trans*, les *trans* naturels ont été comparés pendant des décennies à leurs homologues industriels, sur fond de risques cardiovasculaires. Il est désormais bien démontré qu'aux apports nutritionnels actuels, les acides gras *trans* naturels sont neutres sur la santé cardiovasculaire. Cependant, une connotation négative subsiste. La communauté scientifique considère encore bien souvent que les acides gras *trans* naturels ne sont associés à aucune fonction physiologique bien décrite et que leur intérêt nutritionnel est donc inexistant. Cette perception s'oppose aux résultats de

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plusieurs études démontrant des bénéfices physiologiques insoupçonnés des acides gras *trans* naturels sur l'inflammation, le diabète de type 2 et l'obésité. Ces résultats ont d'abord été obtenus par des études nutritionnelles de supplémentation en acide ruménique (C18:2 *cis*-9, *trans*-11) ou en acide *trans*-vaccénique (C18:1 n-7 *trans*) purs sur le modèle rongeur. Ces résultats ont aussi été complétés par de nombreuses données épidémiologiques récentes, qui associent les plus forts taux circulants d'acide *trans*-palmitoléique (C16:1 n-7 *trans*), marqueur de consommation de produits alimentaires issus de ruminants, à un moindre risque de diabète de type 2. Il s'agit ici de synthétiser les connaissances scientifiques obtenues sur ces trois acides gras *trans* naturels alimentaires, l'acide ruménique, l'acide *trans*-vaccénique et l'acide *trans*-palmitoléique. Dans cette revue, nous détaillerons donc d'abord leur présence quantitative dans les aliments, ainsi que leurs impacts physiologiques démontrés. Nous soulignerons ensuite les liens métaboliques existants entre ces trois acides gras. En combinant les connaissances sur les impacts nutritionnels et les données métaboliques, il apparaît que les mécanismes similaires d'action de ces trois acides gras pourraient être expliqués par leur double liaison n-7 *trans* commune.

Mots clés : acide *trans*-palmitoléique / acide *trans*-vaccénique / acide ruménique / produits laitiers / métabolisme / viandes de ruminants

1 What are natural *trans* fatty acids?

Natural *trans* fatty acids are specific fatty acids with at least one *trans* double bond. They are naturally occurring in ruminant-derived foods (milk and ruminant meat). Natural *trans* fatty acids typically arise from bacterial activity during the ruminal biohydrogenation of dietary linoleic acid (*cis*-9, *cis*-12 C18:2, LA) and α-linolenic acid (*cis*-9, *cis*-12, *cis*-15 C18:3, ALA). Since Eukaryotes are unable to synthesize fatty acids with *trans* double bonds, natural *trans* fatty acids are therefore quantitatively minor and unusual fatty acids, but still biological fatty acids.

Being mainly derived from C18 fatty acids, natural *trans* fatty acids mainly consist of C18 fatty acids as well. The most famous one is rumenic acid (*cis*-9, *trans*-11 C18:2, RMA), which is derived partly from dietary LA ruminal biohydrogenation. Another important natural *trans* fatty acid is *trans*-vaccenic acid (*trans*-C18:1 n-7, TVA) which arises both from dietary LA and ALA and can be synthesized from RMA. Finally, *trans*-palmitoleic (*trans*-C16:1 n-7, TPA) might stem from the retro-conversion of TVA that occur in the key tissues (*e.g.*, muscle, liver and mammary gland) of ruminant species.

2 *Trans*-palmitoleic acid (TPA)

Trans-palmitoleic acid (TPA) is a hexadecenoic acid having a *trans* double bond located in the 9th position (Δ-nomenclature, *trans*-9 C16:1) or in the n-7th position (Ω-nomenclature, *trans*-C16:1 n-7) (Fig. 1A). Thus, TPA is a *trans*-monounsaturated fatty acid, and a *trans* fatty acid according to several reglementary definitions (CODEX, 1985; FDA, 2003; EFSA, 2004; AFSSA, 2005). One may also find in the literature TPA denoted as "palmitelaidic acid", with reference to elaidic acid (*trans*-9 C18:1; two-carbons longer than TPA). However, because elaidic acid is not a natural *trans* fatty acid (Wolff *et al.*, 2000), this term appears inadequate.

The minor but reproducible presence of TPA in dairy products is well-documented. Destaillats *et al.* reported a mean TPA content of 0.05, 0.04 and 0.08% of total fatty acids in milk of cow, ewe and goat respectively (Destaillats *et al.*, 2000). In line with these quantitative data, epidemiological studies found dairy product consumption to be positively correlated to circulating levels of TPA in humans (Sun *et al.*, 2007; Micha *et al.*, 2010; de Oliveira Otto *et al.*, 2013; Da Silva *et al.*, 2014; Nestel *et al.*, 2014; Yakoob *et al.*, 2016; Pranger *et al.*, 2019). Despite doubts about the presence of TPA in partially hydrogenated oils (Santaren *et al.*, 2014), our research group recently demonstrated that dairy products and ruminant meat are the unique contributors of TPA intake in France, relying on accurate analytical data (Guillocheau *et al.*, 2018). In other words, circulating TPA in humans can be considered as a biomarker of ruminant fat consumption at least in countries where partially hydrogenated oils are not used anymore.

Most of the available data regarding the promising health effects of TPA comes from prospective epidemiological studies dealing with the risk of type 2 diabetes. In the CHS cohort, Mozaffarian *et al.* found a significantly reduced risk of type 2 diabetes in the highest quintile of circulating TPA (Mozaffarian *et al.*, 2010). Consistently, an inverse relationship was found between circulating levels of TPA and type 2 diabetes risk in the MESA cohort (Mozaffarian *et al.*, 2013). In both HPFS and NHS cohorts, high circulating levels of TPA were again associated with significantly lowered type 2 diabetes risk (Yakoob *et al.*, 2016). In addition of these prospective studies, two meta-analyses found a significantly reduced risk of type 2 diabetes with the extreme quintiles of circulating TPA (de Souza *et al.*, 2015; Imamura *et al.*, 2018). In addition, some of these epidemiological studies measured circulating metabolic parameters. Importantly, both the CHS and the MESA cohorts pointed out significantly reduced levels of fasting insulinemia across quintiles of circulating TPA, contributing to a better insulin-sensitivity as measured by the HOMA-IR index (Mozaffarian *et al.*, 2010, 2013). These two prospective studies suggest a favourable impact on circulating insulinemia at the very early stages of metabolic dysfunctions, thus preventing from the settlement of the latter. One may suppose insulin secretion and/or insulin clearance to be targeted by dietary TPA.

Several studies carried out on cell models investigated the physiological impacts of TPA. In endothelial (HUVEC) and hepatic (HepG2) cells, TPA reduced TNF-α induced inflammatory expression (Da Silva *et al.*, 2017). Another interesting study highlighted improved pancreatic β-cell function (INS1 cells) following incubation with TPA, by means of higher PPAR-γ expression (Kraft *et al.*, 2015). This latter finding closely parallels the epidemiological studies that assumed an improved β-cell function associated with high levels of circulating TPA.

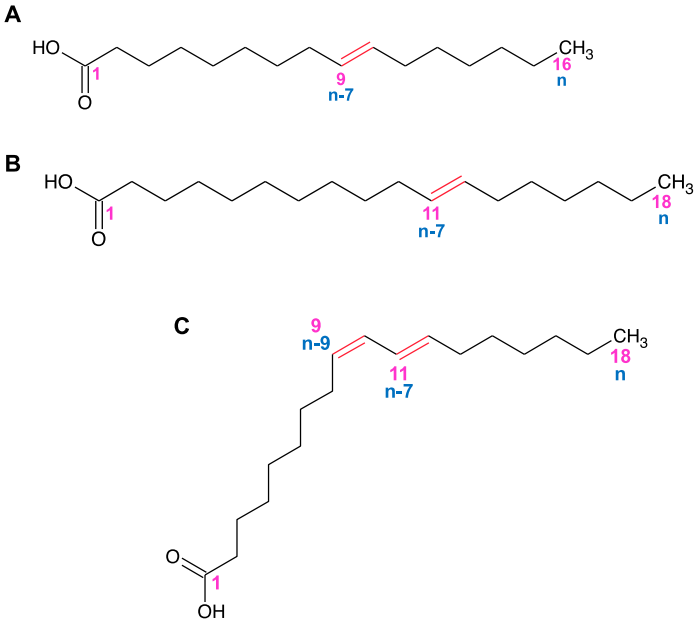

Fig. 1. Structure of (A) *trans*-palmitoleic acid, (B) *trans*-vaccenic acid and (C) rumenic acid. The location of the double bond relies on either the Δ-nomenclature (pink), or the Ω-nomenclature (blue).

Of note, a TPA-supplementation study carried on ApoE$^{-/-}$ male mice was recently published (Cimen *et al.*, 2019). Given the chosen rodent model, this study dealt more about atherosclerosis rather than type 2 diabetes, but still deserves some attention. Indeed, TPA was found to be neutral as regards to the progression of atherosclerosis. Besides, TPA did not impact the ratio between total cholesterol and HDL-cholesterol in plasma, suggesting a neutral effect of TPA on biomarkers of cardiovascular diseases.

So far, to the best of our knowledge, there is no published supplementation study involving TPA to confirm a favourable impact towards insulin sensitivity and pancreatic β-cell function. This is due to the very low availability of pure TPA in enough amounts, at least to carry out a supplementation study on rodent models. However, it should be underlined that the treatment of insulin-resistance by TPA was patented in 2014 by Dariush Mozaffarian and his research group (Patent No. Patent US 8,889,739 B2, 2014), testifying of the probable interesting health benefits of TPA.

3 *Trans*-vaccenic acid (TVA)

Trans-vaccenic acid (TVA) is an octadecenoic acid having a *trans* double bond located in the 11th position (Δ-nomenclature, *trans*-11 C18:1) or in the n-7th position (Ω-nomenclature, *trans*-C18:1 n-7) (Fig. 1B). Therefore, TVA is a *trans*-monounsaturated fatty acid and a *trans* fatty acid (CODEX, 1985; EFSA, 2004; FDA, 2003; AFSSA, 2005), just like TPA. Formally speaking, *vaccenic acid* refers to what we call here *trans vaccenic acid*. To avoid any confusion with the *cis* isomer (*cis*-11 C18:1, or *cis*-C18:1 n-7) which is sometimes called *vaccenic acid* as well, we shall use here the term *trans vaccenic acid* (TVA).

Consistent accurate data reported the presence of TVA in dairy products available in supermarkets. TVA content in such products is comprised between 1.5 and 4% of total fatty acids (Precht and Molkentin, 1996, 2000b; Kuhnt *et al.*, 2011). Ruminant meat also contains TVA which accounts for between 1 and 3% of total fatty acids (Aldai *et al.*, 2009, 2010; Bravo-Lamas *et al.*, 2016). Even if TVA is often found in partially hydrogenated oils (Precht and Molkentin, 2000a; Wolff *et al.*, 2000), our research group recently provided formal evidence of the exclusive contribution of ruminant-derived foods to TVA intakes in France (Guillocheau *et al.*, 2018). Just like circulating TPA, circulating TVA in humans can, therefore, be considered as a biomarker of ruminant fat intake at least in countries where partially hydrogenated oils are not used anymore.

Like TPA, there is a strong lack of commercial availability of pure TVA. Fortunately, the main difference is that self-chemical synthesis and purification of TVA are already described (Duffy *et al.*, 2006; Mouloungui and Candy, 2009; Gebauer *et al.*, 2011), making TVA-supplementation studies feasible. Most of these studies were carried out on rodent models. In JCR-LA:cp rats which are a rodent model of type 2 diabetes and dyslipidemia, a TVA-enriched diet led to significantly reduced levels of TAG (Wang *et al.*, 2008), reduced NAFLD and decreased hepatic expression of *FAS* and *ACC* (Wang *et al.*, 2008; Jacome-Sosa *et al.*, 2014). Furthermore, a significant decrease in adipose tissue weight and adipocyte size was noticed in both JCR-LA:cp (Jacome-Sosa *et al.*, 2014) and Zucker rats (Mohankumar *et al.*, 2013) fed with pure TVA. This latter impact might be due to the ability for TVA to be a natural ligand of PPAR-α and PPAR-γ (Wang *et al.*, 2012). Finally, dietary TVA exerted anti-inflammatory effects on JCR-LA:cp splenocytes (Blewett *et al.*, 2009). Taken together, these studies highlight interesting features of dietary TVA towards insulin resistance, dyslipidemia and systemic inflammation. So far, no study was carried out on healthy rodents challenged with a Western-country diet while supplemented with TVA to investigate the preventive impact of dietary TVA towards type 2 diabetes.

To our knowledge, only one clinical study investigated the effect of pure TVA on metabolic parameters related to type 2 diabetes (Gebauer *et al.*, 2011, 2015). In this study, healthy volunteers fed with pure TVA had no change as regards to glycemia, insulinemia and insulin resistance compared with the control group. These results may suggest a neutral effect of dietary TVA, but it is worth underlining that volunteers were healthy and received a normal diet.

Finally, very recent epidemiological work cross-sectionally associated circulating levels of TVA in humans with lower adiposity, diabetes risk and systemic inflammation (Pranger *et al.*, 2019). To the best of our knowledge, this is the only epidemiological study focusing on the physiological impacts of dietary TVA.

4 Rumenic acid (RMA)

Rumenic acid (RMA) is an octadecadienoic acid having one *trans* double bond located in the 11th position (Δ-nomenclature), or n-7th position like TPA and TVA

(Ω-nomenclature). In addition, RMA has a *cis* double bond located in the 9th position (Δ-nomenclature), or n-9th position (Ω-nomenclature). Thus, RMA (*cis*-9, *trans*-11 C18:2 using the Δ-nomenclature) has a conjugated-double bond system (Fig. 1C) and belongs to the well-known conjugated-linoleic acid (CLA) family. Whether RMA is a *trans* fatty acid is a much-debated issue: while the EFSA and the ANSES consider RMA as a CLA and as a *trans* fatty acid (EFSA, 2004; AFSSA, 2005), the FDA and the Codex Alimentarius (CODEX, 1985; FDA, 2003) consider RMA as a CLA and not as a *trans* fatty acid. Such a distinction between CLA isomers and *trans* fatty acids is based on the widespread idea that all CLA isomers should exert health benefits, contrary to *trans* fatty acids (*e.g.*, TPA and TVA). In this review, we shall agree with the EFSA and the ANSES considering RMA as a *trans* fatty acid naturally occurring in ruminant-derived foods.

Like for TPA and TVA, the presence of RMA in dairy products available at retail is well-documented. RMA accounted for approx. 0.5% of the total fatty acids in Canadian dairy products (Sehat *et al.*, 1998; Mendis *et al.*, 2008). Higher variability is encountered in ruminant meat. In Canadian beef, RMA levels were between 0.26 and 0.41% of total fatty acids (Aldai *et al.*, 2009, 2010), while Spanish lamb samples displayed an RMA content up to 0.7% of total fatty acids (Bravo-Lamas *et al.*, 2016). Thus, RMA is a fatty acid specific to ruminant fat.

To the best of our knowledge, there are no epidemiological studies focusing on physiological effects of RMA. As regards to supplementation studies, the situation is the same as for TPA and TVA, that is a lack of availability of pure RMA in elevated amounts despite some protocols describing how to get enough amounts of pure RMA (Duffy *et al.*, 2006). It is worth underlining how crucial the purity issue is in the case of RMA. Indeed, numerous randomized control trials were performed using CLA supplements that actually consist of a mix of CLA isomers, as reviewed by Tremblay and Rudkowska (2017). In particular, the *trans*-10, *cis*-12 C18:2 fatty acid (*i.e.*, a CLA isomer) is usually encountered in these dietary supplements. However, all CLA isomers are not equivalent to human health, particularly when it comes to diabetes and NAFLD (Clément *et al.*, 2002; Roche *et al.*, 2002). Thus, all these clinical studies are not suitable for assessing the physiological impacts of dietary RMA and thus shall not be reviewed here.

Just like TVA, most supplementation studies involving pure RMA were carried out on rodents. Roche *et al.* found a significant decrease in SREBP-1c expression in the liver of *Ob/Ob* mice fed pure RMA, followed by a significant decrease in circulating NEFA and TAG (Roche *et al.*, 2002). In strong agreement with these findings, dietary RMA prevented NAFLD in Wistar rats fed a high-fat diet (Gaita *et al.*, 2014). It was proposed that such effects of dietary RMA might be mediated by favourable inflammatory impacts in white adipose tissue of *Ob/Ob* mice (Moloney *et al.*, 2007). In fact, it was very soon proposed that dietary RMA acted as a ligand of PPAR-α and PPAR-γ (Moya-Camarena *et al.*, 1999). Such mechanism is consistent with the improvement of type 2 diabetes and NAFLD in studies involving rodents. In strong agreement with this hypothesis, other studies carried out on cell models (Yang and Cook, 2003; Jaudszus *et al.*, 2005; Reynolds *et al.*, 2008; Loscher *et al.*, 2014), rodents (Jaudszus *et al.*, 2008) and humans (Turpeinen *et al.*, 2008) also pointed out anti-inflammatory impacts of dietary RMA that may involve PPAR-γ. Overall, interesting health benefits of dietary RMA are highlighted towards systemic inflammation, NAFLD and dyslipidemia.

The only clinical study that investigated the physiological impacts of dietary TVA also focused on dietary RMA. Relying on another group fed with pure RMA, Gebauer *et al.* did not show any effect of dietary RMA on glycemia, insulinemia and insulin-resistance (Gebauer *et al.*, 2011, 2015). Again, it should be quoted that the study was carried out on healthy volunteers fed a normal diet.

5 Metabolic pathways: bridging the gap between TPA, TVA and RMA, and derivatives

TPA, TVA and RMA all arise from ruminal biohydrogenation of dietary fatty acids. Some metabolic connections between these fatty acids are already described in ruminants but remain somewhat overlooked when it comes to human nutrition. Despite not being able to synthesize *trans* fatty acids, humans are however able to metabolize dietary natural *trans* fatty acids by reactions of elongation, β-oxidation and desaturation (Fig. 2).

To the best of our knowledge, only our research group deeply investigated the metabolism of TPA in fresh cultured rat hepatocytes, relying on [1-^{13}C]-TPA (Guillocheau *et al.*, unpublished results). On the one hand, an unlabeled *trans* C14:1 compound was detected, presumably the *trans*-7 C14:1 testifying of the ability of TPA to undergo peroxisomal β-oxidation (Fig. 2). On the other hand, ^{13}C-labelled TVA was detected, undoubtedly arising from an elongation step. Importantly, we did not detect any *trans* C16:2 compound that would highlight a desaturation step involving TPA. Thus, TPA can only undergo elongation and peroxisomal/mitochondrial β-oxidation reactions.

Perhaps the main reaction that dietary TVA undergoes is its Δ9-desaturation yielding RMA (Fig. 2), a well-described step in both rodents (Santora *et al.*, 2000; Gruffat *et al.*, 2005; Kraft *et al.*, 2006) and humans (Turpeinen *et al.*, 2002; Kuhnt *et al.*, 2006; Mosley *et al.*, 2006). Our research group also demonstrated the Δ13-desaturation of TVA to obtain a conjugated *trans*-11, *cis*-13 C18:2 fatty acid (Rioux *et al.*, 2013; Garcia *et al.*, 2017, 2018). Besides, TVA may be converted to the *trans*-13 C20:1 thanks to an elongation step (Rioux *et al.*, 2013). Last but not least, our research group recently gave formal evidence of the peroxisomal β-oxidation of dietary TVA yielding TPA (Guillocheau *et al.*, 2019).

As great attention was paid to CLAs isomers – including RMA – in the past decades, the metabolism of RMA in humans was extensively investigated. It is here the opportunity to remind what kind of fatty acids can arise from RMA in humans (Fig. 2). Because RMA has a conjugated double bond system, all the fatty acids that metabolically arise from it will have such a system as well. The main characterized pathway in rodents starting from RMA consists first in a Δ6-desaturation step (conjugated *cis*-6, *cis*-9, *trans*-11 C18:3 fatty acid), second in an elongation step (conjugated *cis*-8, *cis*-11, *trans*-13 C20:3 fatty acid), and third in a probably Δ5-desaturation step

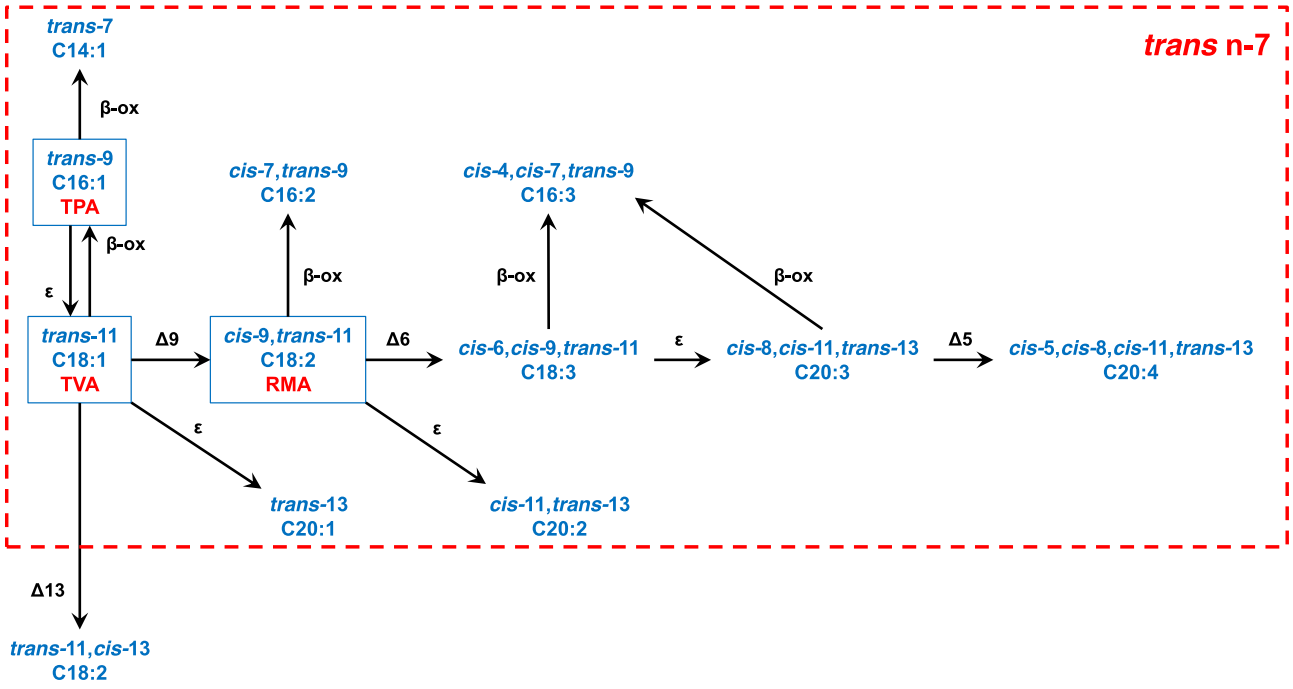

Fig. 2. Metabolic connections between *trans*-palmitoleic acid, *trans*-vaccenic acid and rumenic acid in humans. Abbreviations: RMA: rumenic acid; TPA: *trans*-palmitoleic acid; TVA: *trans*-vaccenic acid. Symbols: β-ox: peroxisomal β-oxidation; Δ: desaturation; ε: elongation.

(conjugated *cis*-5, *cis*-8, *cis*-11, *trans*-13 C20:4 fatty acid) (Sébédio *et al.*, 1997; Banni, 2002; Berdeaux *et al.*, 2002; Banni *et al.*, 2004a, b). Apart from this pathway, RMA is likely to be elongated and converted to the conjugated *cis*-11, *trans*-13 C20:2 fatty acid. Of note, several studies pointed out conjugated C16:2 and C16:3 fatty acids probably arising from peroxisomal β-oxidation of RMA and its derivatives (Sébédio *et al.*, 2001; Sergiel *et al.*, 2001; Banni, 2002; Banni *et al.*, 2004a, b). It is worth underlining that there is no study so far that investigated the physiological effects of all these fatty acids derived from RMA.

6 Are all dietary natural *trans* fatty acids bioactive?

As said above, TPA, TVA and RMA are fatty acids of interest in human nutrition as many studies about them were carried out. Given the metabolic connections that exist between the three of these dietary natural *trans* fatty acids in humans, we cannot help asking a tricky question: when consuming a ruminant-derived product, are all dietary natural *trans* fatty acids bioactive once incorporated in humans? Following the numerous randomized control trials carried out with dairy fat or natural *trans*-fatty acids enriched dairy fat, RMA has very often been considered responsible for the nutritional benefits. Presumably, this has to do with its belonging to the CLA family. It is actually impossible to conclude from all these studies which natural *trans* fatty acid is biologically active.

As regards to TPA, it should be underlined that the epidemiological link between circulating levels of TPA and lower risk of type 2 diabetes remained significant after adjustment on circulating levels of TVA (Mozaffarian *et al.*, 2010; Yakoob *et al.*, 2016). Thus, these findings strongly suggest that dietary TPA possesses physiological effects that are independent of those exerted by TVA. On the other hand, the physiological impacts of *trans*-7 C14:1 are totally unknown. Beyond, it is not known if TPA acts by itself or through metabolites other than fatty acids (*e.g.*, oxygenated mediators).

Can TVA act independently of other natural *trans* fatty acids? Putting TPA apart, according to the prevailing view TVA is only the precursor of RMA thanks to its Δ9-desaturation. In other words, TVA would exert its benefits only because it can be converted to RMA, which belongs to the CLA family. One should keep in mind that TVA was proposed as a ligand of PPAR-α and PPAR-γ, just like RMA. In strong agreement with this idea, one remarkable study demonstrated that TVA and RMA had similar but independent anti-inflammatory effects on human peripheral blood mononuclear cells; both anti-inflammatory impacts relied on the same mechanism (Jaudszus *et al.*, 2012). For the first time, TVA and RMA are suggested to share some physiological effects but behave independently of each other.

Even if RMA was described as a ligand of PPAR-α and PPAR-γ, the many fatty acids arising from RMA through elongation, peroxisomal β-oxidation and desaturation pathways should not be forgotten (Fig. 2). To the best of our knowledge, there is so far no existing work investigating the physiological effects of this distinct family of PUFAs. Because all these fatty acids were detected whenever RMA was supplemented through diet (Piras *et al.*, 2015; Murru *et al.*, 2018), one cannot conclude that RMA is solely responsible for any noticed benefits.

7 Conclusion: defining the n-7 *trans* fatty acid family, and opening up new research hypotheses

For decades, it has been all about natural *trans* fatty acids *vs.* industrial ones as regards to the risk of cardiovascular diseases: for all these fatty acids, a negative connotation has remained. Meanwhile, CLA isomers have always been considered as beneficial fatty acids and distinguished from *trans* fatty acids, leading to a positive connotation.

In this review, we summed up the scientific knowledge about natural *trans* fatty acids which mainly consist of TPA, TVA and RMA. Because it is now recognized that current intakes of natural *trans* fatty acids are neutral towards cardiovascular outcomes, we wished to go beyond the cardiovascular level by emphasizing overlooked results dealing with inflammation, type 2 diabetes and obesity. We also highlighted that natural *trans* fatty acids share biochemical features (*i.e.*, a n-7 double bond) and physiological impacts. For the first time, results about dietary TPA, dietary TVA and dietary RMA have been put in relationship, strengthening the conclusions about physiological impacts of dietary natural *trans* fatty acids.

According to the prevailing view, RMA should be the only fatty acid exerting benefits on human health. Yet, at the present time, there is no evidence of RMA being more beneficial than TVA or TPA. From this point of view, epidemiological associations linking TPA to a lower risk of type 2 diabetes independently of both TVA and RMA is a breakthrough in the field of dietary *trans* fatty acids. For the first time, a *trans* mono-unsaturated fatty acid is associated with health benefits in humans and with a positive connotation. Such results debunk the traditional distinction between CLA isomers and *trans* fatty acids: the former would exert benefits contrary to the latter.

Rather, the location of the last double bond (starting from the first carbon) is crucial when it comes to the relation between the biochemistry of dietary fatty acids and nutritional impacts. A well-known example is the difference between n-6 and n-3 polyunsaturated fatty acids. Presumably, this holds true for dietary *trans* fatty acids as well. Fascinatingly, TPA, TVA, RMA and all its derivatives share their last *trans* double bond in the n-7th position. Both dietary TVA and RMA have been proposed as powerful ligands of PPAR-α and PPAR-γ to explain their health benefits, which are very close to those presumed for dietary TPA. We propose to define the *trans* n-7 fatty acids, corresponding to the natural *trans* fatty acids and gathering TPA, TVA, RMA and all its derivatives. We also hypothesize that all these fatty acids target PPAR-α and PPAR-γ, explaining their protective impact towards inflammation, type 2 diabetes and obesity.

Further research is needed to confirm such interesting hypothesis, including epidemiological data but especially supplementation studies. Defining the n-7 *trans* fatty acid family triggers to several scientific questions. First, even if natural *trans* fatty acids share some common features, we cannot rule out the existence of specific physiological impacts. Second, it is still unknown whether these fatty acids act directly or through lipid mediators, like n-6 and n-3 polyunsaturated fatty acids. Third, how about comparing n-7 *trans* and n-7 *cis* fatty acids? Not only was *cis*-palmitoleic acid (*cis*-C16:1 n-7) described in 2008 as a lipokine (Cao *et al.*, 2008), but Mozaffarian *et al.* also assumed that *cis*-palmitoleic and its *trans* isomer (*i.e.*, TPA) act the same way (Mozaffarian *et al.*, 2010). Finally, one should also keep in mind the ability for gut microbiota to synthesize TVA and RMA from dietary LA and ALA (Druart *et al.*, 2013), just like what happens in ruminants. Thus, *trans* fatty acids might be intermediate molecules by which gut microbiota exerts benefits on humans.

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