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Original article

Whole body glucose turnover in growing and non-productive adult ruminants: meta-analysis and review

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Abstract — The objectives of the present paper were to review and quantitatively determine the influence of the nutritional factors on whole body glucose turnover in growing and adult non-productive ruminants. A meta-analysis approach was used. The dietary grain: forage ratio significantly increased the slope of the relationship between glucose turnover and metabolisable energy intake. This effect was probably associated with the inclusion of maize rather than any other grain source in the diet. The analysis pointed out the possible differences in response between growing and adult non-productive animals, and suggested that the performance level of the animals (and their glucose requirements) could contribute to regulating whole body glucose turnover. This aspect would warrant further investigation.

whole-body glucose turnover / meta-analysis / ovines / bovines

1. INTRODUCTION

It has long been recognised that glucose is an important nutrient for ruminants, even if little glucose is directly absorbed per se from the digestive tract. Whole-body glucose utilisation rates in ruminants are similar to those in monogastrics [1]. In ruminants, glucose is metabolised for 50–55, 20–30, 0–15 and 10% within the muscles, the portal-drained viscera, the liver and the brain, respectively [2]. It is used for ATP synthesis via oxydation, it is a carbon precursor for glycogen, glycerol and intramuscular fatty acid synthesis [3]. It is metabolised via the pentose phosphate pathway for the synthesis of reducing equivalents involved in fatty acid synthesis. A high proportion of glucose is also converted into other metabolites such as L-lactate and amino acids [2, 4]. In the ruminant, glucose is synthesised de novo by 85% in the liver [2] from a range of precursors: mainly propionate, L-lactate, gluconeogenic amino acids, and glycerol which each contribute respectively to 50–70, 10–20, 10–30 and 5% to hepatic gluconeogenesis [5]. Direct glucose absorption from the gut is limited to diets rich in starch, poorly degradable in the rumen [6].

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In ruminants, glucose turnover increases with a number of factors such as energy intake and supply of gluconeogenic substrates to the liver as reviewed, for example by Stangassinger and Giesecke [4], Brockman [2] and Danfaer et al. [7]. Data obtained in lactating ruminants also show that the glucose requirements of the animals and their hormonal status have a clear impact on glucose turnover [7–9]. No literature review specifically focused on growing ruminants, which present lower and a smaller range of nutritional requirements than lactating ones, exists. Besides, considering the assumed link between glucose metabolism and meat quality [3], and when attempting to manipulate glucose metabolism, knowledge of the quantitative and relative impact of the different factors of variation on whole body glucose turnover is required.

Consequently, the objectives of the present paper were to review and appraise quantitatively the main factors which influence whole body glucose turnover in growing ruminants. The quantitative review of the literature was based on a meta-analysis approach. A difficulty arose from the fact that published data on growing ruminants are relatively scarce. Other sets of data had to be considered. Because a greater similarity exists between the planes of feeding applied to growing animals and those applied to adult non-producing ruminants rather than to lactating animals, it was decided to quantitatively review work conducted both on growing and adult non-producing ruminants

2. MATERIALS AND METHODS

2.1. Data base elaboration

The data set used here deals with whole body glucose turnover in growing and adult non-producing ruminants. A set of 39 papers published between 1965 and 2000 [10–48] was selected to build the data base. It included 91 observations. For each observation, the quantitative results of glucose turnover, quantitative variables (body weight [BW], metabolisable energy intake [MEI]) and qualitative variables (type of diet, animal species, growth stage, type of tracer, site of labelling) were collected.

2.2. Statistical analyses

Because of a general unbalance in the data, the relationships between the different criteria were studied two by two after constituting sub-data sets that were considered as being balanced for the factors of interest. Relationships were established by linear regression. Statistica version 5.5 (1984–2000; Statsoft, Tulsa, OK) was used for all statistical analyses.

3. RESULTS AND DISCUSSION

3.1. Description of the data set

The partition of the collected published data is presented in Figure 1. The available data concerned ovines (83.5%) and bovines (16.5%). The growth stage was subdivided into two groups: growing (20%) and adult (80%) animals. The growth stage was either mentioned in some papers or identified from the age of the animals. In this data base, BW proved not to be a good indicator of the growth stage of the animals, particularly in ovines. The collected information included the ingredient composition of the diet, with the dietary proportion of forage and grain, as well as the MEI. When non specified in the publications, MEI was estimated from the national tables of feed composition. Half of the data (52%) corresponded to diets which contained at least 70% of forage and in which lucerne hay was the predominant forage used (55%). Conversely, only 16% of the data corresponded to diets with at least 60% grain; two thirds of those diets contained maize. Glucose turnover

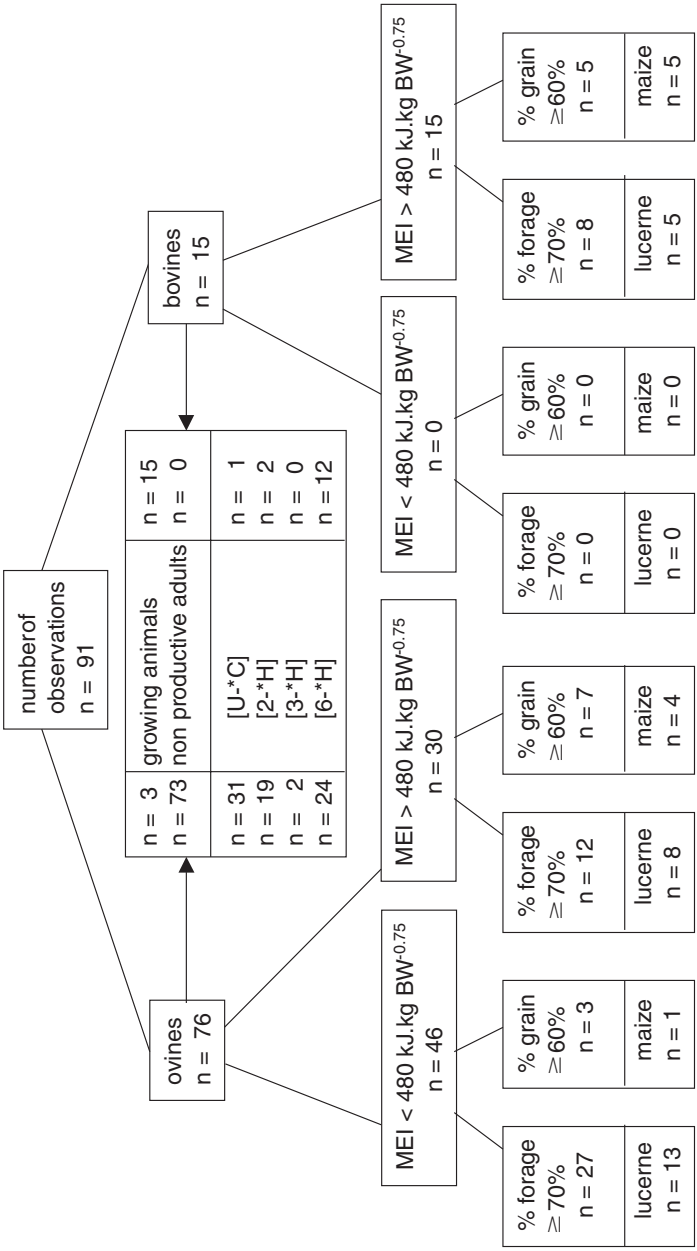

Figure 1. Partition of the collected published data on whole body glucose turnover in growing and adult non-productive ruminants.

was measured using either [2-*H]-, [3-*H]- or [6-*H]-glucose or using [U-*C]-glucose (23, 2, 40, 35%, respectively). No other labelling was used. Labelled molecules were either infused continuously in steady state conditions (60%) or injected as a single dose (40%).

General unbalances therefore exist in this data set, with animal species being confounded with growth stage (mostly adult ovines versus growing bovines), low planes of feeding being confounded with ovine data, and grain rich diets being partly confounded with maize based diets.

3.2. Methodological aspects

The measurement of whole body glucose turnover requires the utilisation of tracers. In all studies dealing with glucose turnover in ruminants, except those of [36, 37] who used [U-^{13}C]-glucose, and those of [34, 35, 49–51] who used [^{2}H]-glucose, radioactive isotopes ([U-^{14}C]-glucose and [^{3}H]-glucose) were used to measure the glucose turnover.

Sixty per cent of the glucose turnover results included in this data set were obtained in steady state conditions with continuous infusion of tracers and were based on plateau-specific radioactivity or enrichment values. In these conditions, the net rate of glucose production equals the net rate of glucose removal and a variety of equivalent terminologies have been used, such as "glucose turnover", "irreversible loss rate", "entry rate", "utilisation rate" [47, 52]. Nevertheless, the significance of the glucose turnover varies with the nature of the labelling. The use of [U-C*]glucose allows to determine the apparent glucose turnover. It generally underestimates glucose turnover because of recycling of the glucose carbon [53] and a subsequent overestimation of the enrichment or specific activity. The labelled carbon recycles either physically because of delays in the distribution of glucose in the extracellular space [54] or chemically following the metabolism of glucose and the reincorporation of the label into the resulting metabolites, in particular pyruvate, L-lactate, alanine, CO_2, glycerol or glycogen [15, 32, 53, 54] On the contrary, labelled [*H]-glucose yields values which depend on the position of the label on the glucose molecule. This subject has been reviewed elsewhere (e.g. 65) and will not be detailed here. Briefly, a loss of *H from the 2-position of glucose will mainly occur during the glucose-6-phosphate / fructose-1,6-bisphosphate reaction, while *H on the 6-position will be lost during the synthesis of glucose in the pyruvate carboxylase and fumarase reactions [48, 53, 55]. Thus, the difference between glucose turnover measured simultaneously by [2-*H] and [U-*C] will estimate the recycling of glucose-C, while the difference between [6-*H] and [U-*C] will estimate chemical recycling mainly via lactate and pyruvate. The tracer of choice for the study of glucose turnover per se is the irreversible [6-^{3}H] glucose [52]. The simultaneous use of [2-*H] and [U-*C] showed differences in glucose turnover of the order of 13–14% in sheep [48, 56]. On the contrary, glucose turnover values were similar whether using [U-^{14}C] or [6-^{3}H] labelled glucose [15, 48]. Indeed, in fed ruminants, recycling via lactate and pyruvate is low [15].

In 40% of the reviewed publications, single injections of [U-^{14}C] or [2-^{3}H] glucose were used to measure respectively the irreversible glucose loss rate or glucose entry rate, in non steady state conditions. In these conditions, the irreversible glucose loss rate is the rate at which glucose leaves the sampled compartment never to return to that compartment, while the glucose entry rate is the rate of entry of glucose into the sampled compartment [56]. A combination of data from publications which compared different types of tracers [27, 28, 43] showed that on average glucose entry rates are 40% higher than the irreversible glucose loss rates.

Because of these methodological specificities, care was taken when combining

published data. The rule which was followed in the subsequent analyses of data, was to pool glucose turnover data only when balanced sub-sets of data could be obtained for each type of labelling and/or when the type of labelled glucose did not statistically affect the relationships between glucose turnover and the factors of interest. Similarly, the irreversible glucose loss rate and glucose entry rate values obtained in unsteady conditions were used only when balanced sub-sets of data could be obtained for the factors of interest. Subsequently, the general terminology of "glucose turnover" was used.

3.3. Level of intake and glucose turnover

The increase in glucose turnover with the plane of feeding is of little debate in ruminants, although only a restricted number of experiments strictly tested this effect. Significant linear relationships were shown between glucose turnover and digestible energy intake (expressed on a metabolic body weight basis in growing lambs [57], MEI (in fat or lean sheep [32]), or net energy intake (in steers, [39]). Significant increases in glucose turnover were also shown with increasing liveweight gains in growing lambs and cattle [57, 58]. Because the effects of intake level are unanimously considered as being highly determinant for glucose turnover, the influence of other factors was subsequently examined by testing whether these factors modified the relations between glucose turnover and intake level. This approach limited the risks of biases associated with possible remaining unbalances in the sub-data set.

3.4. Modes of expression of glucose turnover in growing bovines and adult ovines

Because of the unbalance among available data with (1) a greater proportion of ovine data than of bovine ones, (2) some confounding between animal species and growth stage, it was important to test whether ovine and bovine data could be pooled. In order to test the validity of combining data, different modes of data expression were compared. All data were expressed on a BW^{α} basis ($0 \leq \alpha \leq 1$) and different α coefficients were used (0, 0.66, 0.75, and 1) with the objective of identifying the α value which would prevent any discrimination between ovines and bovines. In a first step, distinct relations were obtained for ovines and bovines.

The first sub-set of data considered corresponded to turnover values measured in steady conditions, in adult ovines fed diets composed of a minimum of 50% forage. This was the largest sub-set of homogeneous data (n = 22). Linear regressions between turnover and MEI were calculated, using the different modes of expression (Fig. 2). The proportion of the explained variance was the highest when $\alpha = 0$, probably because of the large range of MEI considered. When $\alpha = 0.66$, 0.75 or 1, the linear regressions explained 58–60% of the total variance, with no differences between the different values of α. When the residual standard deviations were reconverted into similar units, no differences were seen whether α equalled 0.66, 0.75 or 1. When grain based diets were considered, in the same conditions as previously mentioned, the same conclusions were obtained (data not shown).

In a stepwise manner, data from growing ovines (n = 2) or growing bovines (n = 5) were included in the preceding data set. The residual standard deviation increased highly significantly (by at least 60%) whatever the mode of expression (data not shown).

We subsequently tested whether linear relationships between glucose turnover and MEI differed between adult non-productive ovines and growing bovines. Distinct linear relationships were calculated for adult ovines and growing bovines, all being fed forage based diets (Fig. 3). Because of the

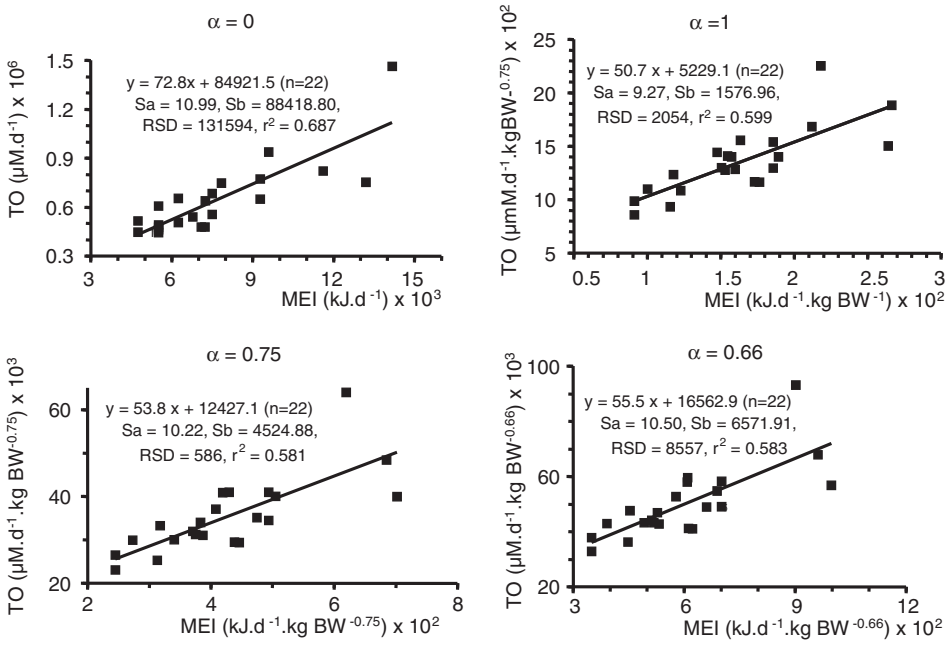

Figure 2. Linear regressions between whole body glucose turnover (TO, $\mu M \cdot d^{-1} \cdot kg\ BW^{-\alpha}$) and metabolisable energy intake (MEI, $kJ \cdot d^{-1} \cdot kg\ BW^{-\alpha}$) in adult ovines fed forage based diets. Different values of α were used (0, 0.66, 0.75, 1). [10, 12-15, 19, 23, 24, 26, 30, 31, 33, 42, 47, 78, 66].

limited number of bovine data, the corresponding regression was associated to a large residual variation. Nevertheless the response of glucose turnover to a range of MEI between 245 and 702 (ovines), and 560 and 877 (bovines) $kJ \cdot d^{-1} \cdot kg\ BW^{-0.75}$ was significantly more pronounced in growing ruminants than in adult animals (Fig. 3). This was coherent with the results from Kempton and Leng [57] showing that glucose turnover was partly associated to the growth rate. Data were also adjusted according to the different α exponents of BW (Fig. 3). In all cases, data on growing bovines differed from those of adult ovine ones. The case of growing ovines could not be clarified due to a lack of sufficient data. Huntington et al. [22, 59] conducted similar experiments both on growing ovines and growing bovines, but a comparison of the results was not conclusive.

Subsequently, ovine and bovine data were not pooled, and considering the present results plus the international conventions [60], all data were expressed on a body-weight basis using the exponent α = 0.75.

3.5. Nature of the diet and glucose turnover

Glucose turnover was often reported to be higher with mixed or grain-based concentrate diets than with forage based diets (for example [22, 39]). This increase, however, was often biased by a simultaneous higher energy intake [19, 22–24, 27, 48].

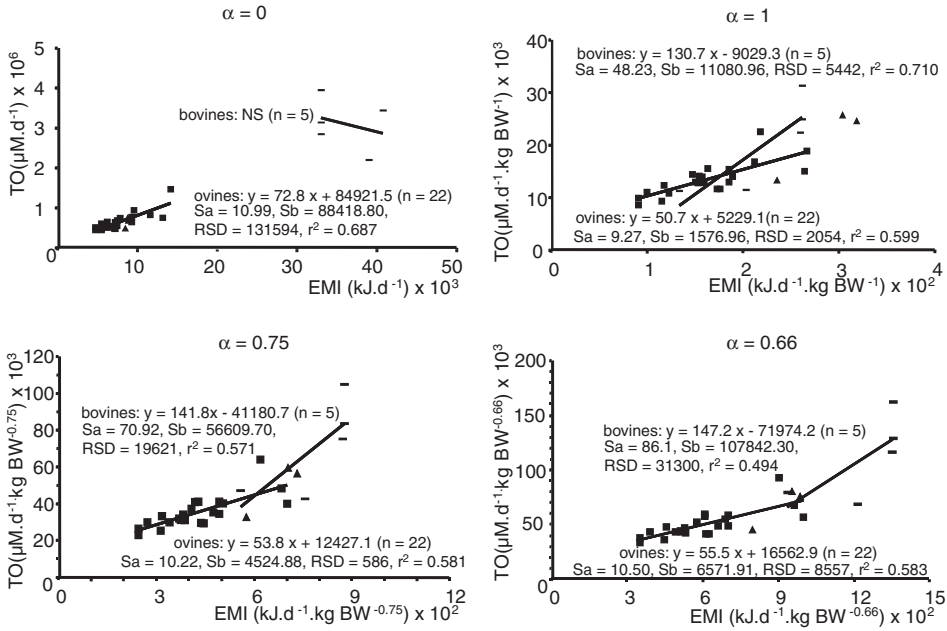

Figure 3. Linear regressions between whole body glucose turnover (TO, $\mu M \cdot d^{-1} \cdot kg\ BW^{-\alpha}$) and metabolisable energy intake (MEI, $kJ \cdot d^{-1} \cdot kg\ BW^{-\alpha}$) in adult ovines (■) and growing bovines (–) fed forage based diets. Different values of α were used (0, 0.66, 0.75, 1). Data in growing ovines (▲) were also plotted. [10,12-15, 19, 20, 22-24, 26, 30, 31, 33, 40–42, 45–48, 66, 69].

When intakes were kept isoenergetic, the glucose turnover measured was often similar for forage and concentrate based diets in growing bovines [20, 21, 39] and in ovines [42, 57, 61]. Only a few studies showed a significant effect of diet composition on glucose turnover. The first convincing evidence was given by Evans and Buchanan-Smith [18] who showed in sheep a 27% increase in glucose turnover with a high maize diet at maintenance and a 56% increase at twice maintenance. In growing steers fed at similar MEI, Seal et al. [40] reported a 26% increase in glucose turnover with a maize-forage diet (50/50) compared to a forage diet.

To get a more general view of this issue, all data collected in adult ovines were pooled. The responses of glucose turnover to MEI (ranging between 240 and 1060 $kJ \cdot kg\ BW^{-0.75}$) were significantly increased by including grains in the diets (Fig. 4). More precisely, the influence of the dietary forage: grain ratio on glucose turnover measured intra-publications (in ovines and bovines) with isoenergetic intakes and in steady conditions is depicted in Figure 5. All the studies which showed a positive effect of grain on glucose turnover used maize as the grain source. Consequently, this suggests that at isoenergetic intakes (between 0.5 and 2.2 times maintenance), the influence of the dietary forage: grain ratio on glucose turnover is mainly due to the inclusion of maize in the diet.

The dietary protein level may also influence the dynamics of glucose metabolism as shown in lactating cows [62]. Unfortunately, the available set of literature data collected for the present meta-analysis in growing and

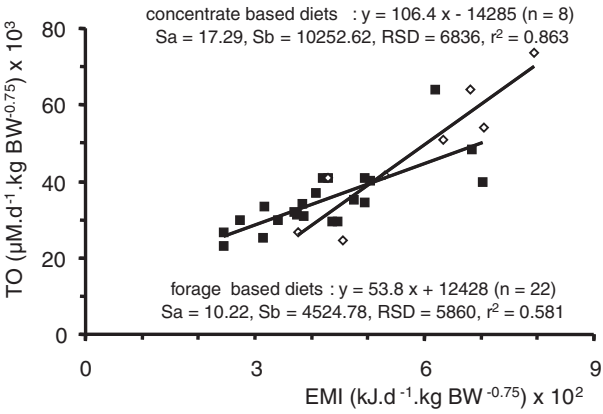

Figure 4. Linear regressions between whole-body glucose turnover (TO, $\mu M \cdot d^{-1} \cdot kg\ BW^{-0.75}$) and metabolisable energy intake (MEI, $kJ \cdot d^{-1} \cdot kg\ BW^{-\alpha}$) in adult ovines fed forage based diets (■) or grain based diets (◇).

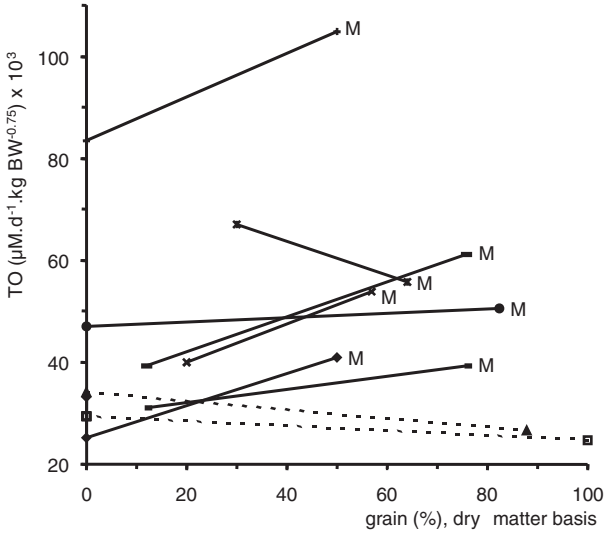

Figure 5. Intra-publication effects of the influence of the dietary proportion of grain (%) on whole-body glucose turnover (TO, $\mu M \cdot d^{-1} \cdot kg\ BW^{-0.75}$) measured at isoenergetic intakes. Diets containing maize were identified (M).

adult non-pregnant non-lactating ruminants was not sufficiently informative on the dietary protein contents to test its influence on glucose turnover. A few experimental data exist, however, which also showed a positive effect of ruminally undegradable proteins or intraduodenally infused casein in those animals on glucose turnover [63, 64]. However the responses could not be attributed to a specific effect of protein supply other than that associated with an increased supply and oxidation of gluconeogenic amino acids.

3.6. Glucose precursors and glucose turnover

To understand the significant effects of the dietary forage to grain ratio on glucose turnover, we surveyed the literature data obtained after modifications in the supply of gluconeogenic substrates, with a special

focus (1) on propionate which is produced in higher amounts in grain rich diets and (2) on glucose absorbed from bypass starch. Insufficient data were published to quantitatively analyse them, so only a qualitative review was feasible. Interestingly, when the supply of glucose precursors was increased experimentally in growing bovines or in adult sheep, glucose turnover was not systematically increased [31, 41]. No significant relationship was noted between the molar proportions or the production rate of propionate in the rumen and glucose turnover in sheep [61] or steers [21]. When measuring the pre- and postprandial variations in propionate production rate and glucose turnover, Van der Walt [65] suggested that the homeostatic control of the overall glucose metabolism was remarkably stable in light of the 2.4 fold variation in ruminal propionate production rate. Still, over longer periods of adaptation to dietary conditions, increases in glucose turnover with increasing propionate supply have been noted [41, 45, 46, 65, 66], however, the responses were never directly proportional to propionate supply. The results suggest that for feeding levels close to or above maintenance, the availability of propionic acid may not be limiting gluconeogenesis. In any case, when propionate availability rises, it is preferentially used by the liver as a precursor for additional glucose [46].

One particular case of gluconeogenic substrates is that of glucose. The previous survey of the literature specifically indicated that the inclusion of maize in the diet improves glucose turnover. With maize based diets, rich in bypass starch, absorbed glucose may contribute to glucose turnover to a variable but sometimes to a considerable extent (up to 60% [23, 27, 31]). In beef steers fed dry-rolled sorghum, it was evaluated that glucose absorption from starch intestinal digestion could account on average for a third of the glucose metabolism [6]. In these cases, the endogenous hepatic glucose production was significantly reduced but not on a 1:1 basis, such that the rise in glucose absorption was accompanied by a rise in whole body glucose turnover. Similarly, exogenous glucose supply, either via intraduodenal or intrajugular infusions, increases glucose turnover in sheep [11, 23] despite some reduction in endogenous glucose synthesis (noted by 59 only). The degree of inhibition of endogenous glucose synthesis is dose dependent with intrajugular infusions of glucose up to 0.5 $mmol \cdot min^{-1}$ [26].

3.7. Nutritional status of the animal and glucose turnover

For growing or adult non-producing ruminants, the driving role of dietary changes in determining whole body glucose turnover is thus questioned outside that of MEI and of the specific case of bypass starch. Lindsay [67] pointed out the general surplus of gluconeogenic precursors with regards to the actual amounts of glucose being synthesised. Other regulating factors are certainly active for a fine homeostatic tuning of metabolism. The hormonal control of glucose metabolism has been reviewed elsewhere [68] and will not be addressed here. Instead the issue will be raised as to the importance of the production level or of the nutritional status in determining glucose turnover.

Interestingly, when the two glucose turnover values published for growing ovines [22, 45] plus that of the companion paper [67] were plotted along the relationships between MEI and glucose turnover established for adult ovines and growing bovines (Fig. 3), the results obtained were situated at the intersection between those of adult ovines and those of growing bovines. Some logical discrepancy seemed to exist between those limited data since data for finishing growing lambs [45] were closer to those of adult ovines than those of younger growing lambs [22, 69] which were closer to those of growing bovines. These results suggest that the effects of growth stage on glucose turnover rate are probably as important as the

effect of animal species. Direct experimental evidence would be required on this point. This hypothesis is, however, compatible with a decreasing contribution of muscles to BW with age in bovines and ovines [70, 71], and with a higher contribution of muscles to total energy expenditure and total protein synthesis in young versus mature animals [72, 73].

In lactating or pregnant ruminants, glucose turnover is clearly affected by changes in glucose requirements [12, 74–76]. In adult sheep, glucose turnover was better correlated with energy balance than with intake level, suggesting that the nutritional status of the animal had at least as much influence as the supply of glucose precursors [32]. Ulyatt et al. [42] had been the first to stress the importance of fat and glycogen stores on whole body glucose turnover as further reviewed by Stangassinger and Giesecke [4].

Since muscles are important net utilisers of glucose [3], it may be questioned whether any modifications in muscle growth and/or composition may influence glucose requirements. This issue has not been directly addressed. Growth rates are linearly and clearly related to glucose entry rates in lambs and cattle [58]. In growing lambs fed a low protein basal diet, supplements of ruminally undegradable protein improve growth rates but at high levels of protein intake; growth rates are even further improved by supplements of glucose [57, 77]. Additionally, in moderately growing lambs, protein growth is higher with maize than with barley, wheat or sorghum based diets [78]. Thus glucose requirements increase with protein intake and growth rates, and the specificity of a "glucose" rather than of a more general "energy" requirements would be worth investigating.

Experimentally, glucose requirements may be increased by creating an artificial drain for glucose, such as with a phlorizin treatment which induces urinary glucose excretion. In sheep [9] and steers [46], injection of phlorizin significantly increases glucose turnover rate at fixed intakes. This is accompanied by a reduction in glucose oxidation and an increased efficiency of precursor use. More generally, an increase in glucose requirements has been noted to increase the efficiency of conversion of precursors into glucose [21, 64]. Interestingly, both the effects of phlorizin injection and of precursor (propionate) supplementation on glucose turnover are additive in steers fed slightly above maintenance [46].

Thus a fine balance probably exists between the availability of glucose precursors and the ability of the organism to handle the additional glucose, keeping in mind that the glucose economy in ruminants can not be dissociated from that of its precursors and subsequent metabolites [79].

4. CONCLUSIONS

The present review allowed to generalise some response laws of glucose turnover to nutritional changes. The influence of MEI on glucose turnover was quantified in adult ovines. It showed that the dietary forage: grain ratio has a significant impact on this relationship which was probably associated with the inclusion of maize rather than any other grain source in the diet. It suggested that in fed non-lactating non-gestating ruminants, the supply of gluconeogenic precursors is probably non limiting. It pointed out to possible differences in the response between growing and adult non-productive animals, and suggests that the performance level of the animals (and their glucose requirements) could contribute to regulating whole body glucose turnover in growing animals. This aspect would warrant further investigation.

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