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Monocarboxylate transporters: new players in body weight regulation

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Abstract

Over the last two decades, several genes have been identified that appear to play a role in the regulation of energy homeostasis and body weight. For a small subset of them, a reduction or an absence of expression confers a resistance to the development of obesity. Recently, a knockin mouse for a member of the monocarboxylate transporter family, MCT1, was demonstrated to exhibit a typical phenotype of resistance to diet-induced obesity and a protection from its associated metabolic perturbations. Such findings point out at monocarboxylate transporters as putatively new therapeutic targets in the context of obesity. Here we will review what is known about monocarboxylate transporters and their possible metabolic roles in different organs and tissues. Based on the description of the phenotype of the MCT1 knockin mouse, we will also provide some insights about their putative roles in weight gain regulation.

Structural and functional characteristics of monocarboxylate transporter isoforms

Monocarboxylate transporters belong to the SLC16A family of solute carriers that contains 14 members based on sequence homology^{1,2}. However, only 4 of them have been demonstrated by functional characterization to be true monocarboxylate transporters³⁻⁶. They are identified as MCT1 (SLC16A1), MCT2 (SLC16A7), MCT3 (SLC16A8) and MCT4 (SLC16A3). Based on the structural studies performed on MCT1, it has been proposed that these four monocarboxylate transporters have 12 transmembrane domains with both intracellular N- and C- terminals¹. They were also shown to require chaperone glycoproteins to be properly inserted in the plasma membrane. A protein named basigin (also known as CD147) was shown to be the partner protein of either MCT1, MCT3 or MCT4^{7,8}. In contrast, embigin (also known as gp-70) was found to be necessary for proper MCT2 insertion and function^{7,9}.

All four monocarboxylate transporters are proton-dependent facilitative carriers¹⁰. They exhibit different selectivity and affinity for their substrates (see table I). MCT1 has the broadest selectivity and can transport several natural short-chain fatty acids such as acetate, butyrate, propionate, lactate or pyruvate. It also transports the ketone bodies acetoacetate and β -hydroxybutyrate. MCT2 has a much higher affinity for pyruvate although it also transports lactate and ketone bodies. MCT4 was shown to transport lactate and ketone bodies but to have a very low affinity for pyruvate. Informations are more restricted concerning MCT3 but it is clearly a lactate transporter. Overall, if we consider lactate as substrate, the highest affinity is exhibited by MCT2. In contrast, MCT4 has the lowest affinity for lactate but a very high transport capacity. These kinetic characteristics are in accordance with a major role for MCT4 in lactate efflux from glycolytic tissues while MCT2 should be implicated in monocarboxylate uptake within cells which use these substrates either as oxidative fuels or for biosynthesis purposes. MCT1 (and to a lower extent MCT3 as this isoform has a very limited tissue distribution) seems to be used for both efflux and influx of monocarboxylates.

The expression of each monocarboxylate transporter varies among the different tissues and organs (see table I). MCT1 has the largest distribution among all the monocarboxylate transporters and is considered ubiquitous. Thus, it is prominently (although not exclusively)

expressed in brain, muscle, heart, liver, kidney, intestine, white adipose tissue, red blood cells, testis or placenta. At the cellular level, it can be found in several and/or distinct cell types within the same organ or tissue. For example in brain, it is found in astrocytes, endothelial cells, oligodendrocytes, ependymocytes, activated microglial cells and in at least some hypothalamic neurons. In striated muscle, it is abundant in oxidative (red, slow twitch) fibers but not in glycolytic (white, fast twitch) fibers. One cell type where it is conspicuously absent is the β cell of the pancreas. It has been shown that MCT1 expression in this cell type is under strict repression and a mutation in the promoter of MCT1 leads to a specific disease in humans that causes inappropriate insulin secretion triggered by blood lactate during exercise bouts¹¹. MCT2 has a more restricted distribution than MCT1. Indeed, it has been found to be present in brain, kidney, liver and testis. Moreover, it was found to be the main monocarboxylate transporter in neurons throughout the brain¹². In testis, it is present on the tail of elongating spermatids¹³. MCT3 is expressed in only one cell type in the body, the retinal pigmented epithelium¹⁴. Finally, MCT4 is found in brain, muscle and white blood cells. While in brain it is found exclusively on astrocytes^{15, 16}, in muscle it is expressed only by glycolytic fibers¹⁷.

Energetic roles of monocarboxylate transporters in different tissues

Despite the fact that substantial progress has been made in recent years on the description and characterization of monocarboxylate transporters (for review, see^{1, 10}), their specific involvement in energy homeostasis (together with the use of monocarboxylates as energy substrates) remains incompletely understood. An increasing number of studies have provided evidence demonstrating or at least suggesting an important role for monocarboxylates, and consequently for their transporters, in various organs and tissues. Moreover, several studies have documented specific regulations for each major monocarboxylate transporter in different tissues and cell types. Regulation of expression at both transcriptional and translational levels has been described, as well as modifications in subcellular distribution. In order to eventually understand the possible roles played by these transporters in the overall body energy homeostasis, it is important to review what is known in a few key organs and tissues in which they have been studied.

Brain

A cell-specific distribution of the three major monocarboxylate transporters has been found in the central nervous system. The fact that the high affinity transporter MCT2 is the predominant neuronal monocarboxylate transporter while MCT1 and MCT4 are rather found on glial cells has been used as an indication of a potential lactate shuttling mechanism between these different cell types. Indeed, several evidence indicate that astrocytes, which express the low affinity, high capacity monocarboxylate transporter MCT4 associated with highly glycolytic cells, provide lactate to neurons in an activity-dependent manner. Such a mechanism, called the Astrocyte-Neuron Lactate Shuttle, would sustain neuronal energy needs during periods of high activity^{18, 19}. Interestingly, a similar mechanism has been proposed to take place between oligodendrocytes (which express MCT1) and axons²⁰.

Specific regulations in the expression of these transporters in each cell type have started to be uncovered. Thus, it has been shown that a series of neuroactive substances including noradrenaline, brain-derived neurotrophic factor (BDNF), Insulin-like growth factor-1 (IGF-1) and insulin cause a translationally-dependent upregulation of MCT2 expression in neurons²¹⁻²⁵. In addition, it was shown that MCT2 is distributed between a cytoplasmic, vesicular pool and a plasma membrane pool²⁶. Such a subcellular localization of MCT2 in neurons can be modified. Thus, while stimulation with glutamate and glycine or TNF were shown to enhance the accumulation of MCT2 at the plasma membrane, exposure to AMPA or insulin was shown to reduce the cell surface expression²⁷. In astrocytes, it was observed that both nitric oxide and oxygen tension can regulate in a transcriptional manner the expression of MCT4²⁸⁻³⁰. These data suggest that MCT expression in different brain cell types are subject to regulation by various signals, which could affect brain energy homeostasis, as well as cognitive functions. Indeed, it was shown that interfering with cerebral monocarboxylate transporter expression can impair learning and memory formation³¹. Moreover, alterations in MCT expression could contribute to the etiology of various neurodegenerative diseases including amyotrophic lateral sclerosis²⁰ and multiple sclerosis³².

The brain is central in the maintenance and regulation of body energy homeostasis. Apart from their direct role in brain energetics, monocarboxylate transporters could also be involved in various key processes for body energy homeostasis including fuel sensing. Indeed, all three isoforms normally expressed in the brain have been shown to be overexpressed during high fat diet induced obesity and chronic hyperglycemia^{33, 34}. This regulation underlines a specific sensitivity to the metabolic status, and a potential role for monocarboxylates and their carriers in the control of metabolism. In accordance with this point of view, the key metabolic hormone insulin was shown to stimulate the expression of the specific neuronal MCT2 isoform in cultured neurons²³. Such a result suggests an important role of the MCTs and their substrates in the metabolic actions of insulin. Insulin is one of the most important endocrine signals involved in energy homeostasis regulation. Supporting the possibility of an interaction between monocarboxylates and insulin, Park et al. have described a beneficial role of ketone bodies in type 2 diabetes. Indeed, they showed that hypothalamic infusion of ketone bodies improved leptin and insulin sensitivity of the brain in diabetic rats. Moreover, this action led to a decreased body weight and modified glucose metabolism³⁵.

All these studies demonstrate that variations in the peripheral metabolic status can alter the expression level of the MCTs in the brain, suggesting that cerebral monocarboxylate supply is altered as well. Several studies have explored the putative involvement of these monocarboxylates in the control of body energy homeostasis via a central effect. Among these, lactate is probably the most studied. Lactate was shown to play a role in the activation of the well-known glucose-sensitive neurons of the hypothalamus³⁶. Using an electrophysiological approach, it has shown that lactate reversed the inhibitory effect of a decreased glucose concentration on glucose-excited neurons. However, lactate increased the activity of the glucose-inhibited neurons (the opposite effect than with glucose)³⁶. Moreover,

as indicated by the same group, these opposite effects of lactate on glucose-inhibited and glucose-excited neurons suggest an involvement of lactate in hypoglycemia regulation³⁷. As proposed in the Astrocyte Neuron Lactate Shuttle (ANLS) model¹⁸, a predominant glycolytic metabolism in astrocyte seems to play a key role in cerebral energy homeostasis regulation via monocarboxylate supply to neurons. Accordingly, the end product of glycolysis pyruvate has been demonstrated to be key in the brain control of glucose production³⁸. In this study, lactate produced by astrocytes was suggested to be taken up by neurons and converted into pyruvate which in turn enters into oxidative neuronal metabolism. Finally, such pyruvate metabolism activates neuronal populations that leads to a decreased glucose production in peripheral organs³⁸. In parallel, several studies have demonstrated that central exposure to lactate suppresses food intake and stimulates pancreatic insulin secretion, suggesting its involvement in the sensing of increased energy supply³⁹⁻⁴¹. Lactate signaling involves neuronal responses, and most likely involves at least in part glucose metabolism in astrocytes, producing such lactate which is then transferred to neurons. In accordance with this hypothesis, recent results demonstrate that astroglial connexins are required for hypothalamic glucose sensing, suggesting that astrocyte glucose metabolism is needed for centrally mediated glucose-induced insulin secretion as well as food intake suppression⁴².

In addition to situations of increased energetic supply such as hyperglycemia or obesity, hypoglycemia was also described as a condition that involves monocarboxylates as alternative energetic substrates for the brain. Thus, studies have demonstrated that hypoglycemia is associated with increased brain MCT expression in order to favor the use of these alternative energetic substrates. Moreover, this overexpression is associated with increased monocarboxylate uptake (mainly lactate and acetate) during hypoglycemic events in type 1 diabetic subjects^{43, 44}. Furthermore, brain regions sensitive to hypoglycemia, e.g. the dorsal vagal complex, contain a neuronal population called A2 neurons that express genes encoding metabolic transducers. These neurons are sensitive to insulin-induced hypoglycemia which also decreases MCT2 levels, in parallel to increase glucose transporter and glucokinase expression. Finally, lactate infusion in this brain area reversed the insulin-induced hypoglycemia-mediated reduction of MCT2 expression and increase of GLUT3 expression⁴⁵. Such results have been observed in both hypothalamus and dorsal vagal complex, two regions implicated in glucose and energy homeostasis regulation⁴⁶⁻⁴⁸. Furthermore, inhibition of monocarboxylate transporters in these specific brain metabolic-sensitive regions is associated with a defect of energy deficiency counter-regulatory responses^{49, 50}. Finally, a study has demonstrated that blockade of monocarboxylate transporters in the dorsal vagal complex resulted in dose-dependent increases in glycemia, demonstrating the importance of monocarboxylate transport at least in glucose homeostasis⁵¹.

Quite interestingly, a mechanism related to ANLS is suggested to be involved in the activation of hypothalamic glucose responsive (GR) neurons. Indeed, using adenoviral-driven expression of recombinant targeted luciferases and bioluminescence imaging, Ainscow et al. demonstrated that GR neurons are not sensitive to increased glucose concentrations. In contrast, hypothalamic glial cells responded to glucose with an increased intracellular ATP concentration. In addition, these cells also responded to increased lactate concentrations and

the same cells were also associated with a high level of MCT1 transporter expression. Altogether, these results suggest that stimulation of hypothalamic neurons by glucose may be potentiated *in vivo* by the release of lactate from glial cells⁵². Moreover, other studies on NPY and POMC hypothalamic neurons showed that maternal obesity is associated with a loss of the NPY neuron response to hyperglycemia. Also, the authors described in the hypothalamus a lower glucose uptake and lactate release. Finally, glucose exposure induced a decrease of GLUT1 and MCTs levels, as well as of lactate dehydrogenase B (LDHB), NPY and POMC levels in offsprings exposed to maternal obesity. In the same study, the authors have also examined the same markers in postnatal HFD models and described a decreased lactate release associated with a decreased neuronal MCT2 isoform, but increased POMC mRNA levels in response to a glucose challenge. In both case (maternal obesity or postnatal HFD), lactate transport and MCTs levels are associated with a deregulated POMC or NPY neuronal response, thus leading to altered energy homeostasis⁵³. This study is in accordance with others and contributes to highlight the main role of lactate and monocarboxylate transporters in brain control of energy homeostasis. Along the same lines, Cortes-Campo et al. recently demonstrated the presence of the MCT2 isoform in the hypothalamus in 90% of orexigenic AgRP neurons and in 60% of anorexigenic POMC neurons. They also showed its role in lactate uptake by hypothalamic neurons suggesting that these neurons control food intake by detecting lactate changes which reflect glucose levels⁵⁴. Finally, a recent work showed that fatty acid-induced food intake inhibition seems to depend on astrocytic metabolism. Thus, fatty acid metabolism in astrocytes induced an increased ketone bodies production correlated with a decreased food intake as the inhibition of ketogenesis reverse the fatty acid effect⁵⁵. Accordingly, a ketogenic diet-induced weight loss is associated with alteration of circulating hormones and nutrients involved in appetite control. Among these, insulin, leptin and glucose levels decreased as well as non-esterified fatty acid levels. All of them are commonly implicated in energy homeostasis regulation⁵⁶. In addition, König et al. have demonstrated that fasting (a well-known state in which ketonemia increases) activates PPAR α which in turn increases liver, kidney and small intestine MCT1 mRNA levels⁵⁷. As PPAR α is involved in obesity, this result is in accordance with previous work from our group showing an increased expression of MCTs in brain during high fat diet-induced obesity³⁴. Recent studies have shown that ketone bodies influence AgRP orexigenic neuropeptide expression in cultured cells and *in vivo* in a type 1 diabetes model^{58, 59}. Thus, brain ketone bodies could be in some circumstances, an orexigenic signal.

Altogether, these results strongly suggest that monocarboxylates are involved in brain control of food intake. Thus, MCTs and their level of expression in various cell types might be key players of centrally controlled body energy homeostasis regulation.

Muscle

Peripheral organs or tissues involved in the control of energy homeostasis are also known to present a metabolic sensitivity to monocarboxylates. Muscles are certainly a predominant source as well as users of monocarboxylates. Indeed, some forms of exercise are well known to induce an increase of glycolytic activity in certain muscle fiber types causing a large release of lactate. This lactate can in turn be recycled in part within the muscle itself,

since surrounding oxidative muscle fibers will use it as an additional oxidative energy substrate⁶⁰. In such case, lactate metabolism involves distinct MCT isoforms differentially expressed on muscle fibers¹⁷. However, still few studies have investigated the role of muscle monocarboxylate transporters in the maintenance of the body energy homeostasis balance. Muscle is implicated in glucose homeostasis and in insulin resistance. An interesting study has looked at the possible link between lactate transport and the known beneficial effects of food restriction⁶¹. Indeed, food restriction is known to increase insulin sensitivity but the mechanisms are not fully understood. However, in this study the authors provided evidence that food restriction reduces muscle lactate content as well as glycogen content. Such reduced intracellular lactate is accompanied by an increased lactatemia. Altogether, the authors described an increased lactate transport capacity in the muscle even without altered MCT1 or MCT4 expression⁶¹. Such results suggesting a beneficial role of lactate production during obesity or diabetes at least in part explains the improved insulin sensitivity observed during food restriction. Moreover, it has been reported that maternal obesity is associated in offsprings with increased body weight, insulin and lactate concentrations, and reduced GLUT4 as well as increased MCT1 levels in muscle⁶². Moreover, these dams from obese mothers are more sensitive to obesity development. So, the increased lactate and MCT1 levels suggesting an increased lactate transport might be in part associated with the metabolic disease sensitization. On the opposite, obese subjects which present an increased MCT4 protein level in muscle compared to lean subjects exhibited decreased MCT4 levels down to the lean control level when submitted to a weight loss⁶³. Concerning MCT1, this study did not describe any change in muscle expression after weight loss. However, it has been described that this isoform is preferentially found in oxidative fibers. Moreover, several studies described modifications in MCT1 expression levels during obesity depending on changes in oxidative parameters and adipose tissue content⁶⁴⁻⁶⁶. In skeletal muscle, two monocarboxylate transporters have been mainly described: MCT1 and MCT4, and both are involved in pH and lactate regulation. Moreover, exercise has been shown to modify the expression level of these two isoforms in sarcolemmal membranes suggesting an adaptation as a function of the energetic needs. Finally, MCT1 and MCT4 are differentially regulated by exercise. MCT1 exhibited greater increases in expression than MCT4 after acute exercise, but both are increased to similar extent during chronic exercise. Such regulations seem to be correlated to modifications in energy needs, and alterations in MCTs levels are considered as an important adaptation to increased energy demands demonstrating their sensitivity to energy requirements in muscle⁶⁷. Interestingly, Huber et al. also demonstrated an increase in expression of MCTs in muscles of offsprings after an intra-uterine growth restriction and moderate daily exercise⁶⁸. They described changes in muscle structure and metabolic function in part due to increased MCTs levels. This increased MCTs expression allowed to prevent exercise-induced lactate accumulation in the offsprings. Thus muscle contractility is facilitated and allows the newborn to better support exercise and prevent obesity development⁶⁸. Moreover, in the insulin-resistant Zucker rat model, a decreased lactate influx in skeletal muscles was accompanied by a decreased expression of the transporters MCT1 and MCT4. In addition, the authors also showed a redistribution of the LDH isozymes which is fiber specific. The localization of LDH5 was found to be related to MCT1 only in obese animals, which came as a surprise since LDH5 is more related to glycolysis than oxidative

metabolism⁶⁹. Finally, as an inverse correlation exists between plasma lactate and insulin sensitivity⁷⁰, these results suggest a role in lactate transport and muscle metabolism that can be linked to insulin sensitivity. Interestingly, ketone bodies are also described to inhibit insulin-induced glucose uptake in oxidative muscles but not in glycolytic ones by inhibiting insulin signaling⁷¹. Such a result suggests that ketone bodies could also alter muscle energy homeostasis.

Adipose tissue

Adipose tissue is another key player in the control of body energy homeostasis. In addition, lactate production by adipose tissue is described as depending on nutritional state^{72, 73}. Moreover, it has been known for decades that a correlation exists between fat cell size and conversion of glucose into lactate. In fact, by producing lactate adipose tissue seems to provide lactate to liver as a substrate for gluconeogenesis during fasting or for glycogen synthesis after a meal. In the case of obesity, lactate production by the adipose tissue is increased. Moreover, this overproduction is also correlated with insulin resistance⁷⁴. Altogether, it appears that lactate production is important in adipose tissue metabolism. Moreover, it suggests an important role of MCTs in adipose tissue contribution to energy homeostasis. In human adipocytes, MCT1, 2 and 4 mRNAs are expressed, and in mice, MCT1 was described in both brown and white adipose tissue⁷⁵⁻⁷⁷. Of particular interest, a recent study showed that hypoxia induced an increase in MCT1 and 4 mRNA expression but decreased MCT2 mRNA expression in adipocytes finally leading to an increased production of lactate. The authors suggest that this could be an adaptive mechanism to low O₂ tension as adipose tissue expands during obesity development⁷⁶. Another group has shown a decrease of MCT1 levels in adipocytes from diabetic rats. Such a decrease in transporter expression is associated with a fall in lactate transport, thus confirming an important role of lactate transport and metabolism in adipose tissue and energy homeostasis as this lactate lifespan is a key element in glucose homeostasis⁷⁸. In parallel, it was demonstrated that a ketone ester feeding induced hyperketonemia activates heat production in mice, in part by increasing the formation of brown adipose tissue. Interestingly, it was also demonstrated to decrease brain malonylCoA, an important determinant of appetite and described to be beneficial against obesity. Finally, ketones appear to be able to mimic the metabolic action of insulin and can be used to overcome the effects of insulin resistance⁷⁹. These actions in relation with adipose tissue roles in body energy homeostasis likely require the presence of monocarboxylate transporters.

Liver

Hepatocytes express both the MCT1 and the MCT2 isoforms. MCT1 in the liver has been shown to be a key player in lipid and glucose homeostasis, as it has been demonstrated that agonists of PPAR α (which mediates the adaptive response to fasting and upregulates MCT1) such as oxidized fat and linoleic acid increase the level of MCT1 expression in the liver of both rodents and pigs. Moreover, the authors described an upregulation of CD147 which is required for the translocation and transport of MCT1 to the plasma membrane^{8, 80}. These results indicate that MCT1 is involved in the adaptation to the fasting state. In addition,

researchers have shown parallel changes in glucagon and insulin sensitivity associated with increased MCT1 and decreased MCT2 levels in liver in undernutrition conditions. Such modifications could be interpreted as an adaptation to food restriction, allowing cells to maintain a normal activity by the use of alternative substrates such as ketone bodies whose concentration increases in such conditions⁸¹. Moreover, liver is one of the main sites of neoglucogenesis, an important mechanism involved in response to fasting and in metabolic regulations. Such a mechanism involves in part lactate via its conversion to pyruvate, and thus lactate uptake via monocarboxylate transporters on hepatocytes would be critical to sustain such a process. Moreover, ketone bodies have also been described to prevent the nuclear localization of ChREBP, the glucose responsive transcription factor involved in lipid synthesis in liver, thus inhibiting fat synthesis in liver. This demonstrates a role of ketone bodies in energy homeostasis regulation⁸². Thus, monocarboxylate transporters might be important elements regulating the involvement of the liver in the regulation of body energy homeostasis.

Intestine

In the intestine, the role of MCT1 has been mostly associated with the absorption of short-chain fatty acids (SCFAs). SCFAs were shown to induce an upregulation of MCT1 expression and function⁸³⁻⁸⁵. In fact, SCFAs seem to modulate the localization of MCT1 on the apical membrane facilitating the transport of SCFAs themselves⁸⁶. The intestinal localization and abundance of MCT1 expression has been well described, notably in pigs⁸⁷. This study revealed a higher expression in the large intestine than in the small intestine. In addition, if MCT1 is localized in immune cells and lamina propria in the small intestine, this transporter is mainly found on epithelial cells in the colon⁸⁷. However, even if some recent papers have described the presence and regulation of MCT1 in the intestine of various species including man⁸⁸⁻⁹², little is known about its specific involvement in nutrient absorption for instance. Nevertheless, some studies suggest that butyrate which is transported in the colon by MCT1 serves as a substrate for de novo lipogenesis, and that SCFAs downregulate genes involved in cholesterol synthesis, suggesting a role of the intestinal MCT1 in lipid metabolism^{93, 94}. Moreover, obesity is associated with an increase in colon permeability to lipopolysaccharide (LPS). This process seems to be sensitive to acetoacetate, a ketone body transported by MCT1. In fact, LPS permeability of the colon seems to be due to lipid peroxidation. Thus, addition of antioxidants like vitamin E inhibits this permeability. Finally, as acetoacetate inhibits high peroxide production, a succinate dependent mechanism, they can act as an antioxidant and thus, prevent LPS permeability (see review of Alexandre⁹⁵). Thus, intestinal MCT1 is likely to be an important factor in different physiological and pathophysiological situations affecting energy metabolism.

Pancreas

Monocarboxylates and their transporters are also important for pancreas function, and in particular glucose-stimulated insulin secretion, a key event in maintaining glycaemia in the normal range. Indeed, the TCA cycle fueled by glucose-derived pyruvate is strongly involved in β -cell function by generating the intracellular messenger ATP, glutamate for mitochondrial

metabolism and eventually the electron transfer chain ROS production involved in insulin secretion⁹⁶⁻⁹⁹. Potentially, the transport of pyruvate (as well as lactate) could be an important element in the regulation of β -cell insulin release. Under physiological conditions, MCTs and LDHs exhibit a low expression/activity in β -cells, a situation which contribute to prevent pyruvate from leaving the cell¹⁰⁰. Interestingly, the low expression of MCTs in the plasma membrane of islet cell types seems to be an advantage for proper cell function, as overexpression of MCT activity confers insulin secretion sensitivity to lactate in islets whose insulin secretory capacity is lost¹⁰¹. Finally, congenital hyperinsulinism is also associated with an increased expression of MCT1. Such congenital hyperinsulinism is characterized by a deregulated secretion of insulin from β -cells and causes hyperinsulinemia and hypoglycemia¹⁰². Thus, a tight control over the expression of MCTs by β -cells must be exerted in order to ensure that they will maintain their critical role of glucose-dependent insulin suppliers.

The proof-of-concept: resistance to diet-induced obesity of the MCT1 knockin mouse

As highlighted above, the MCT1 isoform is found in several tissues including the brain, muscle, liver adipose tissue and the intestine, all involved in energy homeostasis regulations¹⁰³. Moreover, all these tissues are known to exhibit either high monocarboxylate utilization (e.g. lactate or pyruvate) or lactate production for instance. It is however difficult to predict what could be the overall impact of altered MCT1 expression/activity in these different tissues and organs on body energy homeostasis. In this regard, transgenic animals are extremely useful tools to provide an integrated view of the particular role of a specific protein. Recently, a knockin mouse for the *mct1* gene was produced and its phenotype was characterized⁷⁵.

The strategy used was to disrupt the *mct1* gene by replacing part of the coding sequence by the *LacZ* gene coding for the bacterial enzyme β -galactosidase placed in frame with the *mct1* promoter. This approach had the advantage of creating a reporter gene for MCT1 expression while invalidating the original gene. Expression of the reporter gene could also be used to confirm the success of the invalidation and the presence of the modified allele in a particular tissue. The first interesting information emerging from the generation of this transgenic mouse is the fact that the null mutant (homozygote carrying both mutated alleles or MCT1^{-/-}) was not viable. Indeed, it seems that the embryonic development was halted quite early on as both homozygote newborns and embryos were never observed. Although it is quite difficult at this stage to provide a precise explanation for this lethal phenotype, it points out at the importance of monocarboxylates for early development. It is important to underline the fact that MCT1 expression is high in the placenta¹⁰⁴, and the lack of its expression in this tissue might have played a critical in the embryonic development of null mutants.

In contrast to homozygotes, heterozygotes for the invalidated *mct1* allele (MCT1^{+/-}) survived and lived normally throughout adulthood. Indeed, no effect on longevity or survival rate was noted for these animals. Extensive investigations at the morphological, histological and behavioral levels did not uncover major differences nor deficits compared to wildtype animals (MCT1^{+/+}). Apart from a small but significant difference in length (MCT1^{+/-} are

shorter than MCT1^{+/+}), heterozygotes are indistinguishable from wildtype animals (see Figure 1). It is important to mention that as a consequence of the partial invalidation, MCT1 expression at both the mRNA and protein levels is variably affected from one tissue to another. In some cases it is reduced by up to 50% (e.g. brain) while in others it is marginally affected (e.g. adipose tissue or liver).

However, the most striking change took place when mice were fed a high sugar, high fat diet for several weeks. Under such conditions, wildtype C57BL/6 mice gained weight and became obese as this strain is known to be particularly sensitive to diet-induced obesity. In contrast, MCT1^{+/-} mice fed a similar high sugar, high fat diet resisted to the development of obesity, an effect observed in male⁷⁵ as well as in female mice (Figure 1). Such a phenotype could be explained by modifications of energy intake and/or energy expenditure. Indeed, it was found that MCT1^{+/-} mice exhibited a reduced food intake compared to wildtype animals, but only when exposed to a high sugar, high fat diet. As mentioned earlier, MCT1 was shown previously to be expressed by some populations of hypothalamic neurons and suggested to play a role in nutrient sensing⁵². Moreover, a mutant of the MCT1 ortholog was produced in *Drosophila* and called *Silnoon*¹⁰⁵. Interestingly, this mutant exhibited halted food intake, reinforcing the view that MCT1 expression is critical for the regulation of food intake. In addition to food intake, intestinal nutrient absorption by MCT^{+/-} mice was clearly reduced compared to MCT1^{+/+} mice as the caloric content of their stool was higher. Concerning energy expenditures, although no significant difference in physical activity could be detected between the two genotypes, MCT1^{+/-} mice had a higher basal metabolism specifically during their resting (diurnal) period, as revealed by a higher O₂ consumption and CO₂ production, but only when fed a high sugar, high fat diet. The respiratory quotient however was similar between the two genotypes, indicating that there was no shift in the use of carbohydrates and lipids.

When body composition was examined, it became clear that MCT1^{+/-} mice had a reduced fat mass compared to MCT1^{+/+} mice. Further histological analysis revealed that some but not all white adipose tissues were reduced in size. For example, it was the case for the subcutaneous and perigonadal but not the inguinal adipose tissue. The main factor apparently contributing to the reduced adipose tissue mass appeared to be the size of the adipocytes, suggesting a reduced capacity to accumulate and store lipids. In parallel, a clear reduction in the size and appearance of the liver was evidenced (Figure 2). Indeed, the liver of MCT^{+/-} mice was smaller and of a dark red color compared to the bigger and pink liver of MCT1^{+/+} mice. An histological analysis confirmed that while the liver of MCT1^{+/+} mice was full of lipid droplets, a clear sign of hepatic steatosis, the liver of MCT^{+/-} mice was free of any lipid deposition. Interestingly, exposure to a high sugar, high fat diet led to an enhancement in the hepatic MCT1 expression of MCT1^{+/+} mice. This effect was blunted in the liver of MCT^{+/-} mice. Similarly, several genes involved in either lipid synthesis, transport, release, storage or oxidation, as well as transcription factors regulating the expression of these genes, have seen their enhanced hepatic expression induced by exposure to the diet to be prevented in the liver of MCT^{+/-} mice. Thus, it appears that hepatic lipid metabolism has become impervious to dietary changes in MCT^{+/-} mice.

In addition to reduced weight gain by limited increase in fat mass and protection from hepatic steatosis, MCT^{+/-} mice did not exhibit the usual glucose intolerance and insulin resistance that normally arise following exposure to high sugar, high fat diet. Moreover, both insulinemia and leptinemia remained in the normal range for MCT^{+/-} mice compared to MCT^{+/+} mice. Thus, the haploinsufficiency for the *mct1* gene has important metabolic consequences relevant for energy homeostasis. It clearly modifies the way the organism handles a diet rich in both sugars and lipids, offering some sort of protection from the deleterious aspects of such an obesogenic diet. However, the precise mechanisms by which MCT1 is involved in these different effects remain to be established.

Conclusion

Over the years, several genes have been identified which appear to play a critical role in body weight control. This is the case notably for the genes encoding the hormone leptin and its receptor. Mutations or invalidation of these genes generally lead to an obese phenotype. There exists however a small group of genes for which invalidation rather confers a resistance to the development of diet-induced obesity. Such genes encode proteins belonging to different categories including for example enzymes involved in lipid metabolism or neuropeptides. With the monocarboxylate transporter MCT1, a new category of nutrient transporters can be added to the list. However, more work is needed to clarify the exact role of MCT1 in each organ and tissue in which it is expressed to the integrated regulation of body energy homeostasis. Although some clues have emerged concerning its involvement in food uptake regulation and intestinal lipid metabolism, much remains to be done for several organs (e.g. liver, muscle or adipose tissue) and/or distinct functions (e.g. basal metabolism). Moreover, the role of the other MCT family members has not been explored yet and would certainly deserve further attention in the near future.

Considering their distribution and their suggested functions in various aspects of metabolism, it is likely that their expression both in the central nervous system and in the periphery might be influenced by nutritional manipulations including caloric restriction and refeeding. Although nothing has been published so far in this direction, it is tempting to speculate that monocarboxylate transporters might play a key role in the adaptations taking place during weight loss and upon weight regain. Further investigations of these questions would certainly benefit in the near future from the generation of transgenic mice allowing to produce tissue-specific invalidated animals for one or the other monocarboxylate transporter. With these animals in hand, it would become very interesting to explore in more details the role of monocarboxylate transporters in dieting and weight regain.

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Table I. The four most studied monocarboxylate transporters and their main characteristics

Name	Gene	Main substrates	Substrate affinity (K_m in mM)	Tissue distribution/cellular localization
MCT1	SLC16A1	Lactate, pyruvate, ketone bodies, acetate, butyrate, propionate	3.5 (Lactate) 1.0 (Pyruvate) 10.1 (BHB) 5.5 (AcAc)	Ubiquitous: Muscle (red fiber), heart, liver, adipose tissue (white), intestine, red blood cells, placenta, brain (astrocytes endothelial cells, oligodendrocytes, ependymocytes, activated microglia, some hypothalamic neurons), etc
MCT2	SLC16A7	Pyruvate, lactate, ketone bodies	0.08 (Pyruvate) 0.74 (Lactate) 1.2 (BHB) 0.8 (AcAc)	Brain (neurons), liver, kidney, spermatogonia
MCT3	SLC16A8	Lactate	6.0 (Lactate)	Retinal pigment epithelium
MCT4	SLC16A3	Lactate, ketone bodies	28 (Lactate) 130 (BHB) 216 (AcAc)	Muscle (white fiber), brain (astrocytes), white blood cells

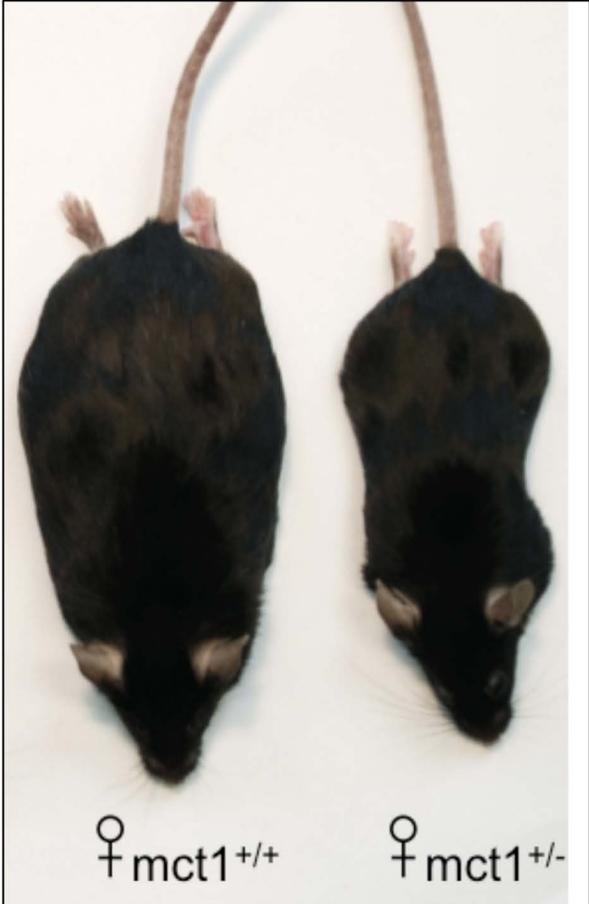
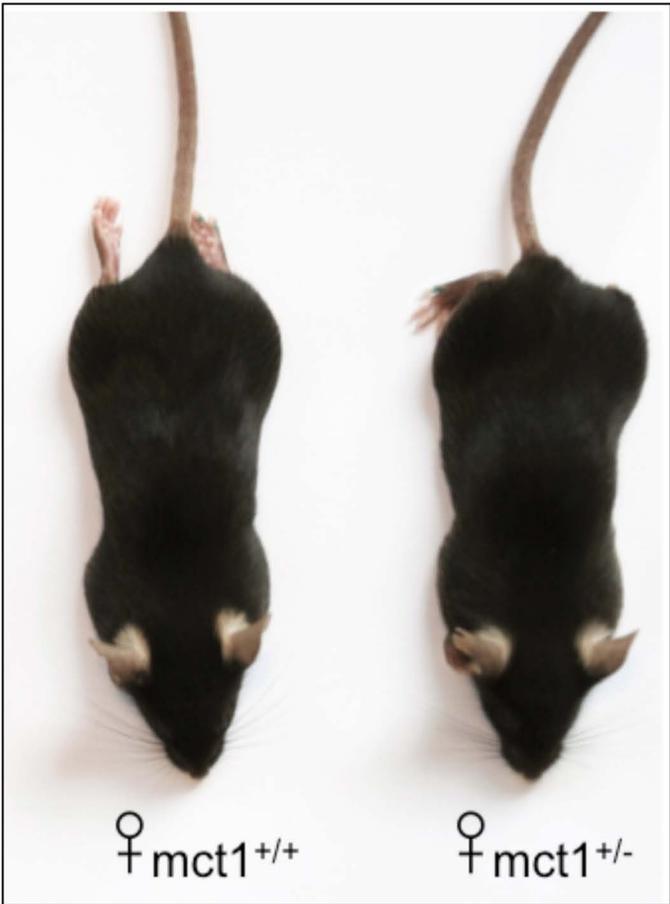
Figure legends

Figure 1. Photographs of representative MCT1^{+/+} and MCT1^{+/-} female mice fed either a normal chow diet (left panel) or a high sugar high fat diet for 12 months (right panel).

Figure 2. Photograph of the liver from a MCT1^{+/+} mouse (left panel) or a MCT1^{+/-} mouse (right panel) fed a high sugar high fat diet for 3 months. Notice the difference in size (MCT1^{+/+} >> MCT1^{+/-}) and in color (pink vs. dark red).

NORMAL CHOW DIET

HIGH SUGAR HIGH FAT DIET



MCT1^{+/+}



MCT1^{+/-}

