Down the drain – Brown adipose tissue as a metabolic sink

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The high metabolic demand of uncoupled respiration in activated brown adipose tissue gives it unique capabilities in combating obesity and metabolic disease. The rich supply of fuels needed to sustain thermogenesis in brown adipocytes requires substantial uptake of glucose and lipids from the blood stream, creating a metabolic sink in the tissue. In this way, excess metabolites are efficiently disposed of by using the high energy turn-over in brown adipose tissue as a metabolic drainage system to counteract metabolic dysfunctions such as dyslipidemia and hyperglycemia.

Increasing body weight is often closely followed by other metabolic disruptions such as abdominal fat accumulation, high blood pressure and increased glucose and triglyceride levels in the blood. The clustering of these related conditions greatly increases the risk of developing cardiovascular disease and type 2 diabetes. Finding new ways to combat not only obesity, but also alleviating the underlying metabolic dysfunction is of great importance. The unique ability of brown adipose tissue (BAT) to uncouple mitochondrial respiration from ATP production creates a futile cycle where energy is wasted at the expense of heat production.

From an obesity perspective this specialized function of BAT holds the potential to increase (resting) energy expenditure providing a much-needed burning of calories to normalize the weight balance. However, the therapeutic promise of BAT activity is not limited to its effect on energy expenditure, but also its ability to counteract dyslipidemia and hyperglycemia by sequestering metabolites from the circulation (Figure 1). On unit weight basis the nutrient consuming properties of BAT are unmatched by any other tissue, at least in mice [1]. From human studies it seems, that at least BAT glucose utilization is of systemic relevance, underlining its potential use as a metabolic sink for circulating metabolites.

Fueling thermogenesis – substrate uptake in BAT

The thermogenic process in BAT requires a rich supply of substrates. Ox-

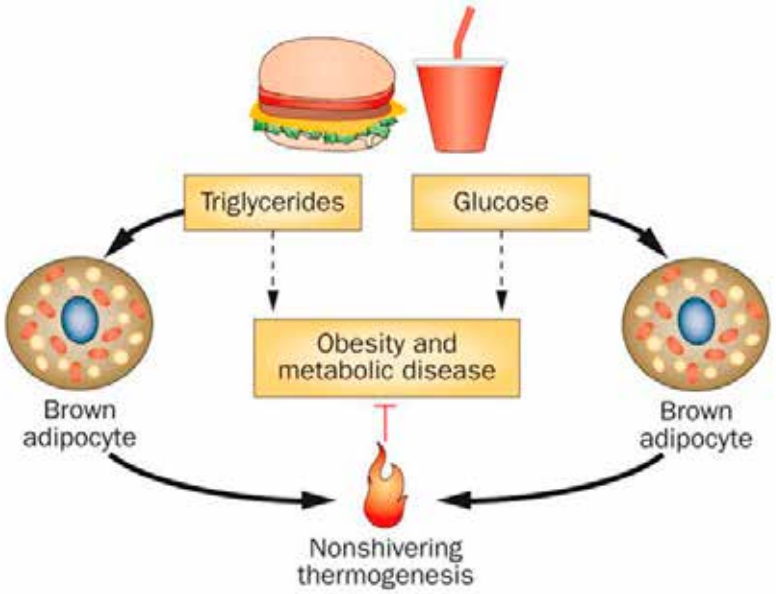

Figure 1: *Brown adipocytes can serve as a sink for harmful metabolites. Increased intake of triglycerides and glucose leads to obesity and metabolic disease. Uptake and combustion of these nutrients in brown adipocytes protect against metabolic disease and obesity by clearing excess metabolites from the circulation. Figure adapted from [1].*

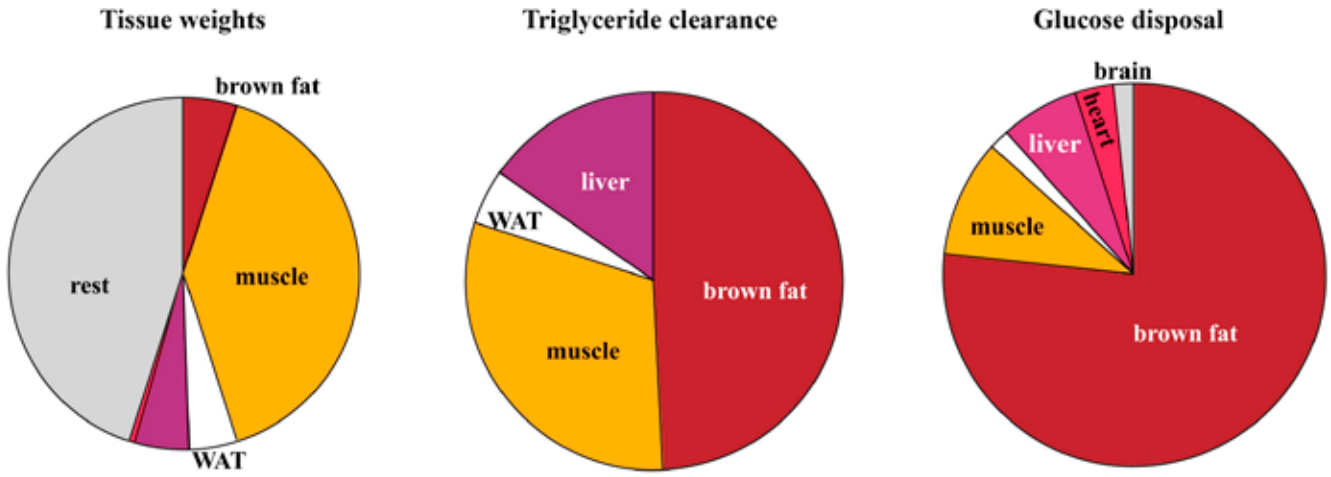

Figure 2: *Brown adipose tissue substrate uptake. Left panel: relative amounts of different tissues in normal ("lean") mice. Middle panel: proportions of ingested triglyceride taken up by different tissues following feeding with a fatty meal. Right panel: proportion of ingested glucose taken up by different tissue in obese mice exposed to cold. Figure modified from [7], based on data presented in [2].*

idative phosphorylation of fuels such as sugar and lipids in the mitochondria extracts high-energy electrons that are transported by the electron transport chain (ETC) to their ultimate destination, molecular oxygen, which is reduced to water in the last step of the chain. The ETC uses this flow of electrons to establish an electrochemical proton gradient across the inner mitochondrial membrane. Re-entering of protons to the mitochondrial matrix is usually coupled to ATP synthesis, but in activated BAT uncoupling protein 1 (UCP1) allows for protons to leak across the inner mitochondrial membrane, bypassing ATP production and dissipating the stored energy as heat. Hence, during thermogenesis fuel oxidation is uncoupled from ADP phosphorylation, resulting in an energy-consuming futile proton cycle.

Initially the brown adipocytes can utilize its internal stores of lipids, but to sustain the high energy demands, substrates from outside the tissue are needed. Cold-activated brown adipocytes therefore take up large quantities of lipids and glucose from the bloodstream to use for immediate combustion, or to store in lipid droplets or glycogen for later use.

In cold-exposed mice it has been shown that following a fatty meal, nearly 50% of the ingested triglycerides ended up in BAT, underlining the magnitude of BAT's lipid clearing capabilities (Figure 2) [2]. Following cold exposure, the triglycerides are efficiently channeled into BAT by upregulation of specific transporters and enzymes that boost triglyceride availability and uptake. Importantly, it was shown that under pathophysiological conditions thermogenic activation could correct hyperlipidemia and improve the deleterious effects of obesity in mice [2]. Initial reports show that activated human BAT utilizes its internally stored lipids but also take up fatty acids from the circulation, but its contribution to systemic clearance is comparatively small.

Glucose clearance by BAT

Glucose uptake in BAT is at basal conditions comparable to the uptake in highly glycolytic tissues such as brain and kidneys and after cold exposure glucose uptake is even further increased. In fact, cold-activated BAT has the highest glucose uptake of any tissue in mice (Figure 2) [2]. BAT's avid uptake of glucose is actually what led to its rediscovery in adult humans 10 years ago, since human brown fat was first noticed by radiologist as symmetrical areas with high glucose uptake in PET scans of cancer patients.

Later it was shown that cold exposure of could increase glucose uptake in human BAT even further, and that this cold-induced BAT activity positively impacts whole-body glucose homeostasis and insulin sensitivity. Even in subjects initially classified as BAT negative (based on baseline scans) cooling can induce glucose uptake in BAT, although to a lesser extent than in BAT positive subjects.

The exact amount of glucose, that activated BAT can clear from the blood stream in humans still remains to be determined, but a conservative estimate is somewhere between 3-9 grams of glucose per day depending on BAT volume and activation degree. In a study with lean patients, glucose uptake per gram tissue in BAT was shown to be equal to that of skeletal muscle, and exceed that of insulin-stimulated skeletal muscle when the subjects were cold-exposed [3].

Underscoring the important role of glucose metabolism many genes involved in glucose uptake and catabolism are upregulated in BAT after cold exposure, and the activity of several key glycolytic enzymes is also increased in cold acclimated rodents. The glucose consumed by activated BAT can be channeled into different catabolic pathways, it might be used directly as a fuel through glycolytic breakdown to pyruvate or be turned into triglyceride to replenish intracellular lipids stores [4].

Recent studies showed unaltered glucose uptake in UCP1 knockout (thermogenically defect) mice. This observation means that even though most of the time, glucose uptake coincides with thermogenesis, it is not a direct consequence hereof. In line with glucose uptake, noradrenaline induced increase in BAT blood flow is also independent of UCP1. Suggesting these processes might not be functionally connected but rather stimulated in parallel by cold-exposure.

The clever thing about utilizing BAT as a glucose sink for treatment of diabetes is that cold-induced glucose uptake is insulin-independent, making this

approach viable even in subjects with insulin-resistance. Proof-of-principle studies in mice have actually shown that increasing BAT mass by transplantation can improve glucose tolerance and insulin sensitivity in models of obesity and type I diabetes. Together this makes BAT a desirable target for anti-diabetic treatment.

Sequestering of signaling metabolites in BAT

Lipids and glucose are the classic metabolites associated with uptake in brown adipocytes, but brown adipocytes also take up other metabolites. This is of particular interest because multiple metabolites have been shown to not only function as energy sources and anabolic substrates, but also as intra- and extracellular signaling molecules [5].

Recently, we identified that cold-activated BAT can accumulate substantial amounts of the Krebs cycle metabolite succinate [6]. We showed that activated BAT actively take up succinate from the circulation, a hitherto undescribed phenomenon, which also provides an integrating paradigm for the longstanding observation of variable and substantial concentrations of succinate in the blood stream. The source tissue for succinate is still undetermined, but at least under cold conditions BAT acts as a specific sink for circulating succinate.

The uptake and accumulation of a metabolite like succinate is interesting for multiple reasons. First, we observed that succinate in itself was an activator of thermogenesis in brown adipocytes, and that just adding succinate to the drinking water of mice could increase their energy expenditure and counteract diet-induced obesity. Hence, our findings suggest that dietary interventions that involve acute elevation of systemic succinate levels may protect against metabolic disease, but only for individuals with a sufficient endowment of thermogenic adipose tissue.

Furthermore, it has been suggested that chronically elevated succinate can promote an inflammatory response. Therefore, our findings imply that a major anti-inflammatory mechanism of BAT activity may involve sequestration of circulating succinate to antagonize systemic inflammation. Since the metabolic disruptions coinciding with obesity are also associated with a chronic low-grade inflammation, using BAT to sequester potential pro-inflammatory metabolites, like succinate, could be of substantial interest. The discovery that a single mitochondrial metabolite is a molecular driver of adipocyte thermogenesis opens many interesting avenues of investigation into the selective uptake of metabolites not only in BAT, but also other metabolically active tissues.

Perspectives

Exposure to environmental cold effectively drives BAT activation and improves metabolic profiles in both mice and humans. Curiously, it seems that BAT has a unique ability to sequester multiple different metabolites from the circulation, many of which when present in excess amounts have deleterious effects on health. The sink and drain effect, where activated BAT not only takes up these metabolites, but also has an efficient way of disposing of them via uncoupled respiration is quite unique. To take advantage of this effect we need to establish efficient ways of boosting BAT activity, and preferably find alternative ways of activating metabolite uptake besides just letting mice and people freeze. Being able to control the flow of metabolites in the blood stream could pose huge advantages to treating obesity, diabetes, heart disease, inflammation, fatty liver disease, and many others.

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signals regulate plasticity? And are there fundamental functional differences between the brown and brown-like thermogenic program, or do brown-like adipocytes represent shades of brown? Resolving these fundamental questions will require a combination of the use of intelligent lineage-tracing mouse models, single cell sequencing and advanced molecular studies.

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