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Physiological and Metabolic Controls in the Brain

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Abstract: **Astrocytes create lactate and activate glycolysis and glycogen metabolism, which are necessary for neuronal metabolic processes in the brain. Glycogen's role in keeping neurons firing is undeniable, although to what extent this occurs is still hotly discussed. how much of the glycogen-derived energy is utilized by the astrocytes, and where it is for use by neurons; lactate is the form, it takes. The central nervous system of an insect consists of a brain and a ventral nerve cord that runs the length of the thorax and several abdominal segments. One of the effects of hypoglycemia is a slower rate of glucose metabolism in the brain.**

Alzheimer's disease is characterized by several anomalies in the brain, although early-stage dementia is not characterized by a significant decrease in the brain's oxygen metabolism. In this article, we'll go through the key brain areas.

Keywords: **Glucose-sensing. Hypothalamus. Brain. claudin; tight junctions; brain metabolism, and the blood-brain barrier.**

1. INTRODUCTION

For centuries, scientists have recognized the brain's exceptionally high energy requirements (Magistretti & Allaman, 2013). However, understanding how energy metabolism in the brain is connected to neuronal signaling events, neural excitability, and ultimately behavioral outcomes is crucial. and mental traits are still quite thin (Raichle, 2010). Commonly referred to as "the blood-brain barrier," this set of systems defines and regulates the adult brain's internal environment. However, these entities do not have a single identity in terms of their anatomy, physiology, or functions.

The brain's energy metabolism is intricate due to the many ways in which substances can be broken down into usable energy and the processes through which cells absorb and use that energy substrate (Kasischke, 2012; Hall, Klein-Flugge, Howarth, & Attwell, 2012, Magistretti, 2006; Volkenhoff et al., 2015; Vishwasrao, Fisher, Zipfel, & Webb, 2004; Lutas & Yellen, 2013).

Astrocytes are brain cells responsible for lactate production, activation of glycolysis, and contribution to neuronal glycogen and gluconeogenesis metabolism. Glycogen has an undeniable role in keeping neurons active in the brain, however, it is still hotly contested whether all the energy released from glycogen is used by the astrocytes themselves or instead sent to the neurons in the form of lactate (Secher, N.H 2005). Hormone replacement therapy in postmenopausal women was associated with less belly fat, less insulin resistance, and fewer cases of newly diagnosed diabetes, according to a meta-analysis of 107 separate trials (Flegal, K.M., 2010).

Insulin-induced hypoglycemia provided proof that glucose is the adult brain's sole permissible fuel source. As plasma glucose levels dropped or as the duration of hypoglycemia increased, the cognitive condition of hypoglycemic subjects progressively altered from moderate sensory abnormalities to lethargy, stupor, and coma. Rapidly reversing the behavioral

effects of low glucose levels, glucose administration was superior to other studied chemicals (including glycerol, ethanol, lactate, pyruvate, glyceraldehyde, fumarate, acetate, -hydroxybutyrate, and galactose), except for mannose and maltose. Not only are lactate and beta-hydroxybutyrate crucial fuels for the mammalian brain throughout the suckling period, but neither can repair the consequences of hypoglycemia. After weaning, however, monocarboxylic acid transporters in the brain's vasculature drop dramatically, and -hydroxybutyrate dehydrogenase activity drops to considerably lower adult levels (Cremer JE. 1981, 1082, 1983).

In this review, we first examine the structure of the insect central nervous system (CNS), noting important similarities to the CNS of vertebrates, to lay the groundwork for future research of brain energetics in insect model systems. We then discuss how insects' central nervous systems use and store energy substrates since certain energetic precursors have been linked to modulating key brain metabolic processes in mammals. Then, we move on to what is generally understood about the neural energetics of higher-level phenotypes like behavior, covering topics such as the significance of neural mitochondrial regulation, the metabolic link between neurons and glia, and the importance of glial metabolism for normal brain function.

We emphasize insect examples throughout that mirror the major findings from mammals, such as evidence for a glial-neuronal metabolic coupling system in insects that is substantially like mammals. At last, we talk about the phenomena of brain aerobic glycolysis, which has been observed in several settings in mammals and is now thought to play a role in the behavior of honeybees. Aerobic glycolysis is a rare example of a brain metabolic phenotype that considers the metabolic dynamics of both glia and neurons. We explore the many roles of metabolic pathways in normal brain function beyond ATP production, and we review the incidence of aerobic glycolysis and its functional consequences. Finally, we discuss some of the obstacles and possibilities of using insect model systems to investigate the metabolic underpinnings of behavior.

2. METABOLISM-DEPENDENT

2.1. The detection of oxygen

Most cells rely on aerobic respiration to convert their metabolic resources into ATP. Alveolar ventilation, gas diffusion between alveoli and the pulmonary blood, and the transport of oxygen and carbon dioxide to and from all tissues in the body are all crucial to the supply of oxygen and the removal of carbon dioxide in air-breathing animals. Carotid bifurcation and aortic arch oxygen chemoreceptors are responsible for monitoring arterial blood's partial pressure of oxygen (PO2) (in some species). Most people believe that the carotid body's chemosensitivity glomus cells are the only oxygen sensors in mammals' respiratory systems. The hypoxic stimulation of carotid bodies triggers a chemoreflex, which in turn stimulates the brainstem's respiratory and sympathetic circuits (Guyenet, P. G. 2006).

Higher creatures like mammals must keep their blood and tissue oxygen and carbon dioxide levels within the physiological range. This is largely facilitated by efficient gas exchange mechanisms, which draw atmospheric oxygen into circulation via the lungs and exhale metabolic waste products such as carbon dioxide. Bioenergetic crisis and oxidative stress, respectively, can occur if oxygen levels in the body are too low (hypoxia) or too high (hyperoxia), and both can cause cell, tissue, and organism death. Additionally, similar pathogenic abnormalities in the cellular acid-base balance can occur if CO2 levels drop too low (hypocapnia) or increase too high (hypercapnia), both of which can have serious clinical implications. Therefore, the evolution of the ability to detect and respond to settings where endogenous levels of O2 and CO2 change, and to adapt via quick effector mechanisms to preserve homeostasis, has been an important development in the history of life on Earth (Davenport, Brewer, Chambers, & Goldschmidt, 1947).

When the body is functioning normally, the amounts of oxygen and carbon dioxide in the blood do not change much from resting to exerting oneself. Central and periphery chemo-sensing processes work together to keep things as they are. Co2 chemoreception is more sensitive than O2 chemoreception, which is interesting. The usual circulating level of Pco2 is 45 mmHg, therefore an increase of just 10 mmHg causes a significant shift in ventilation. Basal breathing, on the other hand, is significantly altered at a Po2 reduction of 20-40 mmHg below physiological levels. When the arterial blood pressure (Po2) in the carotid body drops from 80 to 100 mmHg to 60 mmHg, the sensitivity of the peripheral chemoreceptors to oxygen increases considerably (Wilson DF, 2005). The hypoxic ventilatory response also recovers in experimental animals whose carotid bodies have been surgically denervated or removed, suggesting that the brain may also contain functional

respiratory oxygen sensors (Davenport, Brewer, Chambers, & Goldschmidt, 1947; Miller & Tenney, 1975; Olson, Vidruk, & Dempsey, 1985; see also Gourine & Funk, 2017 for a review).

Recent research findings (Angelova et al., 2015) suggested that astrocytes may act as physiological sensors of brain oxygenation. Decreases in inspired O2 (from 21% to 15% or 10%) were observed to elicit strong increases in astroglia Ca utilizing two-photon imaging of cortical astrocytes in anesthetized and mechanically ventilated rats (Angelova et al., 2015). The hypoxia sensor was found to be in the mitochondria, and in vitro investigations confirmed that oxygen sensitivity is a characteristic shared by astrocytes throughout the brain. Parallel evaluation of mitochondrial Observations of changes in membrane potential (Dwm) and Ca in cultured astrocytes revealed that low PO2 significantly decreases Dwm and increases Ca. An effect that comes before elevations in Ca. Mitochondrial reactive oxygen species (ROS) generation increased under these conditions, alongside the inhibition of mitochondrial respiration.

Mitochondrial uncoupler (FCCP), Mito-antioxidant (MitoQ), and ROS scavenger all significantly decreased or eliminated hypoxia-induced reactive oxygen species (ROS) generation and Ca responses in astrocytes (a-tocopherol). In astrocytes, hypoxia causes inhibition of mitochondrial respiration, increased production of free radicals, lipid peroxidation, activation of phospholipase C, and recruitment of Ca21 from IP3-sensitive intracellular stores; this all points to a hypoxia-sensitive signaling pathway that can be tested pharmacologically (Angelova et al., 2015).

Physiologically, astroglia regulation of presynaptic brainstem neurons becomes evident in the presence of central hypoxia. It is well established that reductions in local tissue PO2 or cytotoxic hypoxia trigger significant stimulation in these sympathoexcitatory neurons, which then leads to systemic increases in a central sympathetic drive (Sun & Reis, 1994; D'Agostino, Mazza, & Neubauer, 2009; Marina et al., 2015). It appears that ATP and lactate generated by adjacent astrocytes modulate the susceptibility of C1 pre-sympathetic neurons to hypoxia. It was revealed that blocking metabotropic ATP receptors or inhibiting glycogenolysis significantly reduced the hypoxia-induced activation of C1 neurons (Marina et al., 2015). To continue, the presence of the ATP-degrading enzyme apyrase greatly lowered the excitement of C1 neurons in response to optogenetic activation of astrocytes (Marina et al., 2013).

In conclusion, there is evidence that brain tissue PO2 is the primary metabolic component that dictates the direction of cerebral arteriole response (constriction at high PO2 and dilatation at physiological/low PO2) that follows astroglia Ca increases (Gordon, Choi, Rungta, Ellis-Davies, & MacVicar, 2008). The mechanism of direct oxygen sensing by astrocytes (Angelova et al., 2015) may be important for the regulation of cerebral microcirculation in conditions of increased local oxygen demand or regional brain tissue hypoxia, as astrocytes can alter cerebral blood flow by releasing vasoactive substances in response to changes in oxygen levels (Attwell et al., 2010; Mishra et al., 2016; Bazargani & Attwell, 2016). While this theory awaits experimental scrutiny, the available data strongly suggest that brainstem astrocytes stimulate the networks of the respiratory and pre-sympathetic neurons and contribute to the development of the ventilatory and cardiovascular responses that ensure appropriate oxygenation and delivery of the arterial blood.

2.2. The detection of glucose

When blood sugar drops, the vesicular glutamate transporter 2 (vGLUT2)-expressing neuronal populations in the ventral hypothalamus become more active, secreting glutamate and noradrenaline (Shiraishi T 1991). It's conceivable that neurons in the gastrointestinal tract regulate sympathetic and hormonal activity in response to the hyperglycemic and hyperinsulinemia circumstances of a patient with a protective mechanism against high blood sugar (Tong Q, 2007).

Energy-rich and necessary for numerous metabolic activities, glucose is a vital nutrient. Within the first two hours after eating, blood glucose levels can rise to as high as 140 mg dl21, which is significantly higher than the fasting range of 70–100 mg dl21 throughout the course of 24 hours. Maintaining a blood glucose level within a normal range and meeting the metabolic needs of all body tissues, including the brain, need a complex network of neuronal and hormonal regulatory mechanisms. Patients with diabetes who are using insulin or sulphonylureas are at a higher risk of experiencing acute hypoglycemia. Significant harm to neuronal function, including brain damage and even death, can result from hypoglycemia (Frier, 2014).

However, the brain isn't the only organ that might suffer from persistently high plasma glucose levels. So, homeostasis is maintained by coordinating hormonal (insulin and glucagon secretion), autonomic (liver glucose generation), and behavioral (feeding initiation and termination) mechanisms; this makes physiological glucose sensing extremely crucial.

There's some data suggesting astrocytes in the brainstem can act as glucose sensors in the central nervous system. Mice genetically depleted of the GLUT2 glucose transporter were unable to secrete more glucagon in response to systemic hypoglycemia (Marty et al., 2005).

Selective re-expression of GLUT2 in brainstem glial cells, but not in neurons, restored the ability to release glucagon in response to hypoglycemia (Marty et al., 2005).

A previous study found that the activation of hypothalamic and brainstem neurons in response to hypoglycemia was inhibited when astroglial glutamate metabolism was disrupted with the glutamine synthetase inhibitor methionine sulfoximine (Young, Baker, & Montes, 2000).

These results add to the growing body of evidence that metabolic coupling and signaling between astrocytes and neurons are necessary for the brain to recognize hypoglycemia. Supporting this notion, studies have demonstrated that astrocytes regulate (through lactate release) the activity of hypothalamic orexin neurons that increase alertness, food intake, and hepatic glucose synthesis (Parsons & Hirasawa, 2010).

While astrocytes are glucose-sensitive, the cellular and molecular mechanisms underpinning this trait are yet unknown. New evidence suggests that astroglia insulin signaling regulates hypothalamic glucose sensing and systemic glucose metabolism, as reported by Garcia-Caceres et al. (2016).

By eliminating insulin receptors in hypothalamic astrocytes, the scientists showed, glucose-induced activation of pro-opioid and melanocortin neurons was blunted, and physiological responses to shifts in glucose availability were hampered. Mice deficient in astroglia insulin receptors had lower levels of glucose and insulin in their cerebrospinal fluid after systemic glucose injection. The scientists concluded that insulin's action on hypothalamic astrocytes regulates brain glucose sensing and, by extension, systemic glucose metabolism. Astroglia insulin receptors were also found to have a significant impact on modifying glucose transport across the blood-brain barrier, as indicated by findings provided by (Garcia-Caceres et al. 2016).

2.3. The detection of carbon dioxide and pH

To maintain metabolic equilibrium, waste materials must be flushed out efficiently. The amount of carbon dioxide exhaled is directly related to both metabolic activity and the substrates used for energy production. Alveolar ventilation removes most of the CO2 produced by the body at rest (12 mmol kg21 h21) with expired air. The rate at which CO2 is produced is directly proportional to the partial pressure of CO2 (PCO2) in the arterial blood, while the rate at which CO2 is eliminated by the respiratory system is inversely proportional. When hydrogen ions are produced as a result of increased CO2 production or impaired CO2 elimination (respiratory acidosis), the state must be immediately addressed by adaptive alterations in the ventilatory and cardiovascular activities to enable adequate CO2 removal.

Specialized pH-sensitive neurons in the brainstem are thought to keep tabs on fluctuations in arterial and brain PCO2/ PH. (Loeschcke, 1982).

The retrotrapezoid nucleus (RTN), which is located close to the ventral surface of the brainstem, contains pH-sensitive neurons, and current models of central respiratory CO2 chemosensitivity (the mechanism that adjusts breathing by changes in brainstem parenchymal PCO2/pH) center on this region (Guyenet, & Mulkey, 2010).

Experimental investigations have shown that the loss of RTN neurons, either permanently or acutely (Dubreuil et al., 2008; Guyenet et al., 2009; Guyenet & Mulkey, 2010; Marina et al., 2010; Ramanantsoa et al., 2011), eliminates or greatly lowers ventilatory CO2 sensitivity. The current prevailing view is that RTN neurons play the key role in developing the ventilatory response to CO2, although other notable groups of brainstem neurons, such as 5-HT neurons of the raphe nuclei, are intrinsically chemosensitivity (Teran, Massey, & Richerson, 2014) and contribute to this process (Ray et al., 2011, Guyenet et al., 2016).

Evidence suggests, however, that the pH sensitivity of RTN neurons is mostly mediated by responses elicited in nearby astrocytes in response to chemosensory inputs (Gourine et al., 2010). Subjects were sedated and subjected to mechanically controlled experiments. In a study using ventilated rats, Gouriné et al. (2010) found that astrocytes in the RTN region of the brainstem respond to drops in pH by exhibiting strong elevations in intracellular [Ca]. This stimulates RTN neurons (Gourine et al., 2010) and other respiratory neurons that represent other functional divisions of the ventral respiratory column (Gourine et al., 2003) via Ca-dependent vesicular release of ATP (Gourine et al., 2010; Kasymov et al., 2013).

Certain membrane transporters are essential for the detection of PCO2/[H1] elevations and the [Ca] responses in brainstem astrocytes (Turovsky et al., 2016). Na1 entrance was observed to precede CO2-induced acidification (respiratory acidosis-induced Ca] responses in astrocytes, to be attenuated by blocking the Na1/HCO2 3 cotransport (NBC) or the Na1/Ca exchange (NCX), and to be eliminated when extracellular Na1 was not present.

Brainstem astrocytes from NBCe1-deficient animals showed dramatically diminished acidification-induced Ca responses (Turovsky et al., 2016). Thus, functional pH-sensitivity of brainstem astrocytes appears to be underpinned by combined NBC and NCX activity, leading to increases in intracellular [Ca].

CO2/pH sensitivity appears to be a unique feature of specialized astrocytes which populate the brainstem areas at and near its ventral surface (Gourine et al., 2010; Kasymov et al., 2013; Turovsky et al., 2016), in contrast, to direct oxygen sensing, which is ubiquitously shared by astrocytes residing in different CNS regions (Angelova et al., 2015).

This was shown in a comparative investigation where it was shown that only astrocytes in the brainstem responded to changes in PH. (Kasymov et al., 2013). Analysis of transcriptome data showed that NBCe1 expression in brainstem astrocytes was significantly higher than in cortical astrocytes (Turovsky et al., 2016).

KCNJ10 (Turovsky et al., 2016) is a gene that encodes the KIR4.1 subunit of inwardly rectifying the K1 channel, and its expression was shown to be considerably greater in brainstem astrocytes. Astrocyte-specific selective deletion of KIR4.1 in mice has been shown to reduce CO2 chemosensitivity in the respiratory system (Hawkins et al., 2014).

3. COMPLEX MOLECULAR ARCHITECTURE OF BRAIN BARRIER JUNCTIONS

3.1. The Blood–Brain Barrier

The BBB is a selective permeability barrier that prevents neurotoxic substances from crossing from the bloodstream into the brain. Despite Ehrlich's 1885 discovery, it wasn't until a succession of studies in the 1920s that the blood-brain barrier was given its current name (Abbott, N.J. 1992).

Gautier, Goldman, Stern, and Lewandowsky. As a group, they were able to demonstrate through their research on the brains of vertebrates that tracers and poisons like trypan blue dye couldn't cross the blood-brain barrier (Bauer, H.C, 2014).

put into a mouse's brain stayed in the brain, but the same dye injected elsewhere in the mouse's body diffused throughout the body. Except for the brain, the entire body was tainted by the brain. Because of its low permeability, this barrier is a trait acquired by evolution in vertebrates, crucial to regulating central nervous system function (Begley, D.J.; Brightman, 2003).

There are no energy reserves in the brain like there are in other organs, therefore regular brain function necessitates continuous nutrient delivery via the bloodstream. Control over the brain's microvasculature is essential for the transport of vital nutrients while shielding the brain from potentially harmful alterations in its internal chemical equilibrium, to the development of severe disease disorders (Daneman, R., Prat, A., 2015).

The BBB depends on a particular physical barrier called tight junctions (TJs) located on the tops of endothelial cells. These adhesion connections between cells serve as regulators of passive diffusion of molecules in the paracellular pathway and ions to the cerebral cortex. High electrical resistance (>1000-3000 cm2) (Butt, A.M.; Jones, 1990, Abbott, N.J.; 2010) is created across the BBB when TJs are formed there. Cell polarization is another consequence of TJ presence. where the endothelia are compartmentalized into an apical layer and a basolateral layer. The asymmetrical endothelium-specific expression of transporters and receptor proteins in the cell membrane can regulate transcellular permeability. membrane's apical face the membrane's forward-most face. Pathologies of diseases can damage TJs, causing dysfunction. to the breakdown of barrier selectivity in both transcellular and paracellular routes (Pardridge, 2005).

While the BBB plays an important role in the nervous system, its selective permeability makes it difficult to transfer drugs to the brain. When medications are unable to cross the BBB, they cannot be used to effectively treat neurodegenerative illnesses like Alzheimer's and Parkinson's. (Pardridge, W.M., 2012).

In vivo animal models allow researchers to test hypotheses in a setting that is physiologically like humans, which is crucial for the discovery of effective novel treatments. Unfortunately, in vivo investigations are less useful for medication development because of their high cost and the incomplete translation of disease pathology from animal models to people. Since this occurs so early in the development of a medicine, in vitro models are being employed to examine BBB permeability (Wolburg, H.; Lippoldt, A., 2002).

3.2. Role of Claudin-5 in the BBB

The tight junctions (TJs) between endothelial and epithelial cells are primarily mediated by members of the Claudin family of membrane proteins (González-Mariscal, 2003, Morita, K.; Furuse,1999). It is now well established that claudins are expressed in all epithelial cells, including those lining blood vessels (Furuse, M.; Hata, 2002).

There are at least 27 members of the claudin family that have been linked to functional expression in mammals. Both classic claudins (1–10, 14–17, and 19) and non-classic claudins (anything else) exist (Günzel, D.; Yu, 2013, Van Itallie, 2013, Krause, G.; Winkler, 2008).

A group of claudins (11-13, 16-18, 20-27) that have structural and genetic similarities (Buckley, A.; Turner, 2018, Wang, H.; Yang, 2015). Multiple claudin family members are expressed at TJs in most tissues. Proteomic Claudins (~20-30 kDa) assemble a TM1-4 helix bundle with two extracellular loops (ECL1-2) and a cytoplasmic loop (Suzuki, H.; Nishizawa, 2014). The side-by-side exchanges facilitated by Claudin TM and ECL domains interact in a cellular process known as cis-membrane tethering (Nitta, T.; Hata, 2003).

Multiple claudins engage in cis interactions in the membranes of expressing cells. Subsequently, Trans assembly occurs when ECL loops of different claudins engage head-on to produce the formation of a macromolecular TJ involving cells that express claudins next to each other (Krause, G.; Winkler, L.; Piehl, 2009).

4. ESTROGENS IN THE BRAIN INCREASE PHYSICAL ACTIVITY

4.1. brown adipose tissue thermogenesis

The brown adipose tissue is the primary site of adaptive thermogenesis in mammals (BAT) (Cannon, B., 2004, Silva, J.E., 2006). Large amounts of functional BAT are seen in tiny mammals that inhabit the sub-thermoneutral region (Nedergaard, J., 2007). BAT was found to have a negative correlation with human age. However, new research shows that adults can really have viable brown fat stores (Cypess, A.M., 2009, Nedergaard, J., 2014). Brown adipocytes have a high mitochondrial concentration and a high number of tiny lipid droplets that may be seen under the microscope (Futai, M., 1989).

The energy created by the mitochondria during the transfer of electrons along the respiratory chain is briefly stored as a proton gradient across the inner mitochondrial membrane (von Ballmoos, 2009). The ATP synthase then uses the energy from this proton gradient to produce ATP from ADP (Morrison, S.F., 2014). Retrograde transport of protons back into the mitochondrial matrix, bypassing ATP synthase activity and releasing energy as heat, is enabled through alternative routes that occur in the internal membrane of mitochondria in BAT and involve the uncoupling protein 1 (UCP1). The brain and the rest of the nerve system work together to control BAT (Contreras, C., 2015).

The role of the sympathetic nervous system (SNS) in triggering thermogenesis in the brown adipose tissue (BAT) is crucial (Cannon, B., 2004). When the sympathetic neurons that supply brown adipose tissue (BAT) fire more rapidly, they secrete norepinephrine (NE) at the nerve terminal, which in turn activates G-protein coupled receptors in the brown adipocytes called b-adrenergic receptors, primarily of the b3 subtype (b3-AR) (Silva, J.E., 2006). When a G protein is coupled to the b3-adrenergic receptor (AR), adenylate cyclase (AC) is activated, leading to an increase in intracellular cyclic adenosine monophosphate (cAMP), which in turn activates protein kinase A (PKA), resulting in thermogenesis and the subsequent activation of p38 mitogen-activated protein kinase (MAPK) (Nedergaard, J., 2007). High amounts of cytosolic free fatty acid (FFA) are produced as an immediate response to PKA by stimulating lipolysis (Nicholls, D.G., 1984).

Adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL; with PHSL being the active version), and monoacylglycerol lipase will sequentially hydrolyze triglycerides, leading to an increase in free fatty acids (FFAs) (MGL). Carnitine palmitoyl transferase 1a (CPT1a) transfers the FFAs-CoAs (FFAs activated to acyl CoAs by acyl-CoA synthetase) into the mitochondria, where FA oxidation triggers the synthesis of NADH and FADH, which are oxidized further down the electron transport chain (Whittle, A.J., 2011).

4.2. The 17 beta-Immediate estradiol's Impact on BAT

In the 1970s, it was discovered that 17beta-estradiol binds to both brown and white adipocytes in the interscapular region. 17beta-estradiol increased BAT lipolysis and thermogenesis, which led to increased energy expenditure in rodents (hamsters, rats, and mice) (Wade, G.N., 1978).

Importantly, these results were linked to an uptick in NE turnover that was mitigated by OVX, indicating not only direct action of 17bestradiol on BAT but also an indirect regulatory action on the central regulation of the sympathetic firing on BAT (Edens, N.K., Wade, 1983, Bartness, T.J., 1984, Schneider, J.E., Palmer,1986). Thyroid hormones (THs) similarly cause NE-induced lipolysis; therefore, the effects of this modulatory mechanism would be analogous to those of THs on UCP1 expression (Yoshida, T., Nishioka, 1987).

The direct effect of 17beta-estradiol on BAT has been shown to be attributable to changes in I adrenergic receptors (AR) and mitochondrial biogenesis-signaling factors like phosphatase and tensin homolog (PTEN), (ii) nuclear respiratory transcription factor 1 (NRF1), and (iii) likely peroxisome proliferator-activated receptor g coactivator-1a (PGC-1a) (Lopez, M., 2013).

Brown adipocytes express ERs in a sex-dependent manner, with greater ERa densities in male than female rats, as shown by numerous studies. Despite this, no definitive data on the direct effect of estrogens on BAT has been produced by phenotypic studies of ERa knockout mice. In addition, data have been made public revealing that ERa knockout mice exhibit an age-dependent rise in adiposity, namely in white fat depots, which is accompanied by hyperplasia and hypertrophy (Martinez-Sanchez, 2014).

However, no such variations were found in the BAT (in either males or females), suggesting the possibility of central effects despite impaired energy expenditure (Rodriguez, A.M., Monjo, M., Roca, 2002). However, mice fed a conventional diet and maintained at 25 degrees Celsius show no signs of obesity or metabolic changes after ERb deletion (Monjo, M., 2003). While wild-type animals housed at 25C tend to be leaner and more muscular, those fed a high-fat diet (HFD) gain weight and develop more adipose tissue (Rodriguez-Cuenca, 2007).

When treated with peripheral 17beta-estradiol, the enlarged BAT pads seen in aromatase knockout (Arko) mice shrink (Heine, P.A., 2000). Regardless of sex, mice deficient in the G protein-coupled estrogen receptor (GPER) develop a mild form of obesity characterized by decreased energy expenditure, (ii) increased BAT lipid content (suggesting a reduced thermogenic activity), and (iii) decreased expression of UCP1 and b3-AR when maintained at 23-24 degrees Celsius (Davis, K.E., Carstens, 2014).

The role of ERs in human BAT was not thoroughly studied until recently. In 2014, researchers discovered that ERa and ERb were expressed in human fetal BAT, with ERa showing somewhat greater expression (Velickovic, K., 2014). The discovery of functional BAT in adults raises the possibility that ERs have a role in regulating human brown fat activity, however, this is still debated (Nedergaard, J., 2014). Recent studies corroborate these observations by demonstrating that women have a bigger proportion of functionally active brown adipose tissue (higher F-fluorodeoxyglucose (F-FDG) absorption) than males do. Human BAT may be directly modulated by gonadal steroids like estrogens, as evidenced by the observed sexual dimorphism (Cypess, A.M., 2009).

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