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Encephalization – An Evolutionary Predisposition to Diabetes:
A "Large Brain Hypothesis" explaining the mechanism of Diabetes.

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ABSTRACT: *Primates have proportionately three times larger brain as compared to that of other mammals of comparable size and humans, in turn, have three times larger brain as compared to that of all other primates of similar size. So we need to meet higher energy demands because brain is energetically expensive. This has a significant impact on our dietary patterns in addition to shaping of our body composition. Here we propose that our dietary patterns to meet our higher energy demands have been ultimately set by the instinct of higher energy intake and our larger brains have a stress effect on our metabolic organs (organs involved in energy metabolism like gut, liver, pancreas etc.). We discuss these two points from evolutionary (Evolutionary instinct) and physiological (Metabolic stress) point of view and argue that these two points explain the manifestation of diabetes primarily as a human disease and enhance our understanding of its mechanism.*

Keywords: Diabetes, Dietary changes, Encephalization, Evolution, Metabolic stress

I. INTRODUCTION

True autoimmune diabetes occurs in only humans [1] and type 2 diabetes occurs in humans in far higher proportions than all other animals; although streptozotocin and total pancreatectomy induced chronic hyperglycemic and hypoinsulinemic animal models have been established [2, 3]. Therefore, the evolutionary aspects of human nutrition have received considerable attention[4-11] leading to the deliberation that humans are vastly different from evolutionary and physiological point of view from all other primates primarily because of much larger brain size and bipedal locomotion. These differences have extensive impacts on our nutritional requirements [4, 12, 13]. Owing to larger brains and bipedal locomotion, a spectrum of evolutionary processes have come to operate on humans which include energy intake controlled by brain (setting threshold on higher levels), energy allocation to other organs controlled by brain, under-muscled and over-fat body, reduction in gut and metabolic organ size, narrowing of birth canal and premature brain development at birth. All these processes have lead to distinctive energy biochemistry and physiology in humans and consequently diseases primarily found in humans (including diabetes). Here we hypothesize two postulates in order to explain diabetes, primarily a human disease, in the light of increased brain size, higher energy demands, evolutionary climatic shift with diet and other compensatory changes, bipedal locomotion with narrowing of birth canal and premature brain at human childbirth etc. Our hypothesis (with its two postulates) explains all these aspects and portrays diabetes as a natural predisposition in humans as against all other primates. We discuss the above aspects one by one and observe that every process ultimately comes to conclude at (or support) one of our two postulates viz. higher energy intake instinct and metabolic organ stress. The arguments go in synergy with Fig.1 which reveals the panoramic view of this paper. This hypothesis explains why true autoimmune diabetes is found in *H. sapiens* only and also suggests that animal models for diabetes type 1 may not represent the true etiopathological picture of this disorder in humans.

II. HYPOTHESIS

The hypothesis is aimed at understanding diabetes, primarily a human disease, with regards to evolution and distinctive features of humans against other primates. We achieve this objective by putting forth two postulates. We call the first postulate "The evolutionary instinct" and the second postulate "Metabolic stress". Following are the statements of the postulates:

1. **Evolutionary instinct:** Evolution has shaped humans to consume higher than required energy intake.

2. **Metabolic stress:** Higher energy allocation to brain in humans and reduced size of other organs has caused a consistent state of stress in energy metabolizing organs of the body.

The evolutionary instinct of over feeding exposes human body to a consistently higher concentration of energy nutrients (like glucose) which leads to energy storage as fats (predisposition to obesity) and relatively higher amounts of insulin (for glucose uptake) and leptin (for fat storage). When in excess (contrary to their normal function) these two hormones prompt the brain for increased appetite (signaling the brain about unavailability of ready energy). Insulin informs the brain about utilization of glucose by peripheral tissues while leptin signals about the conversion of ready energy substrates into fat. Also the arcuate brain develops resistance to excess amounts of insulin and leptin, rendering their appetite suppressing activity ineffective, thereby amplifying the food intake. This proportionately greater energy intake predisposes *H. sapiens* to diabetes. The higher energy availability in the body and evolutionarily reduced size of gut and energy metabolizing organs (gut, liver, pancreas etc.) causes a metabolic stress due to work overload on these organs. This condition of stress predisposes humans to metabolic diseases like diabetes.

These two postulates explain diabetes both from physiological as well as evolutionary point of view and provide better understanding of the disease and may in near future pave ways for the development of management strategies for diabetes and metabolic syndrome.

III. EXPLANATION

Encephalization (large brain: body mass ratio): It is now well understood that our bipedal locomotion and disproportionately large brain size make us different from other primates and have strong implications on our nutritional needs [4, 13, 14]. Encephalization is the most important feature that distinguishes us from other primates having great impacts on human nutritional biology because energy requirements of nervous tissue (including brain) are approximately 16 times that of skeletal muscles [15, 16]. This indicates that large brain size is energetically extremely expensive. In addition to this; in adult humans 20% to 25% resting metabolic rate (RMR) is constituted by brain as against 8% to 10% in other primate species [10]. Humans, for this reason, have to allocate a much greater budget of energy to feed their brains, that consequently affects our dietary patterns and energy needs.

Primate brain is thrice as big as compared to other mammals of comparable size and human brain is three times bigger than that of other primates of similar size [17]. This means that humans have nine times greater proportions of brain tissue than other non-primate mammals.

As a consequence of high energy needs, humans arguably consume food that is rich in energy. It is important to note that in order to meet the needs of higher energy to the brain; we consume much better quality diets in comparison to all other primates. Additionally, the staple food of all human communities, geographies, and ethnicities around the world is substantially denser in energy than that of all other primates [18, 19]. Most primates have large gut size (particularly colon which allows fermentation of plant fiber) for fibrous low quality diet but humans in comparison have radically smaller gut size [4, 20, 21]. The human gut size reduction is an adaptation for high quality and easily digestible diet meaning that encephalization would have demanded high quality diet and reduced gut size [20, 22, 23]. The size of brain in genus *Homo* has tripled (or more) in the past 4 million years. It has gone from 400 cm^3 in australopithecines to 1300-1400 cm^3 in humans [24]. This manifest increase in brain size was highest in human lineage at about 2.0 to 1.7 million years ago (mya), the time when human ancestors learned the use of fire to cook food for increasing diet quality and when presumably considerable reduction in gut size might have taken place. This process was more prominent in *Homo erectus* in which the brain size increased noticeably on higher pace as against australopithecines [10].

Bipedal locomotion and encephalization appeared almost simultaneously in evolution suggesting some evolutionary affiliation between the two. It presumably occurred because our ancestors 4 mya had to look for alternative forms of food in drastically changing climates of African savanna. They needed free hands to break nuts and tubers and also handle tools for hunting in the next 2-3 million years.

Climatic shift in African savanna: Human ancestors lived in African savanna some 4 mya [17]. It is the time when the climate of this region was rapidly changing with environment turning extremely dry [25, 26]. This resulted in a decline in forest area and an increase in open woodlands and grasslands [26-29]. Such climatic shift in the homeland of our ancestors would have resulted in great impact on food distribution patterns posing special challenges to our hominin ancestors. A key milestone was crossed at that time because animal food

became more abundant and consequently was the food of choice [30, 31]. This is because savannas have a very low net primary energy productivity as against woodlands (4050 kcal/m^2/yr in former and 7200 kcal/m^2/yr in latter) but the herbivore productivity in savannas is three times (10.2 kcal/m^2/yr) as compared to woodlands (3.6 kcal/m^2/yr) [13].

In addition to improvements in dietary quality by changing climates (a blessing in disguise), African savanna animal food repertoire provided higher proportions of fatty acids that might have been indispensible for hominin brain enlargement [32]. This notion is further supported by the fact that development of mammalian brain needs two long chain polyunsaturated fatty acids viz. Arachidonic acid (AA) and Docosahexaenoic acid (DHA) [32, 33]. Ready availability of these fatty acids might have accelerated the rapid brain evolution process which would not have been possible otherwise as AA and DHA are rarely synthesized by mammals. Additionally, humans lack the enzymes capable of introducing double bonds in fatty acids beyond carbon 9 and 10. Moreover, the tubers and nuts found in African savanna contained moderate amounts of AA and DHA [32].

Thrifty and selfish genetics: With the climatic shift and food resource redistribution in African savanna 4 mya, food stability must have been jeopardized in hominin lineages. Initiation of an evolutionary process for high energy food intake in greater proportions (thrift) and greater craving for higher energy foods (selfishness) in our ancestors living then would have set into play. With time, the hominin lineages, unto modern humans, developed a consistent sense of craving for high-calorie food fulfilling the objectives of evolutionary wisdom as abundant food was unavailable now. This established a genetic property in *H. sapiens* now referred to as thrifty gene hypothesis [34] which lends a strong support to our proposal. Food scarcity in the past and redistribution of food pattern in changing climates must have set the instinct for higher food intake and storage and that is where we derive our first postulate "Evolutionary instinct" from. Even in the modern times, we live with these thrifty and selfish genes but our food quality and availability has sharply increased leading to extremely high energy intake and storage and, therefore, much higher propensity to diabetes.

Dietary changes: Emergence of genus *Homo* was accompanied by changes in foraging patterns. Stable carbon isotope studies reveal that australopithecines were subject to diet patterns varying with seasons and their diet included plants as well as animals [37-37]. However, paleontological studies suggest that genus *Homo* had far higher proportions of animal food in their diet [31, 38-40]. Decreased tooth size and reduced masticatory complex in genus *Homo* as against australopithecines lends support to this notion [24].

Homo erectus (our ancestor 1.8 mya) witnessed many changes accompanying changes in diet which include dramatic increase in brain size, development of humanlike limb pattern with erect posture and improvements in foraging behavior [41-44]. All these changes happened because of the drastic climatic changes in the then home of human ancestors [25, 26]. Owing to these changes animal food became the diet of choice as discussed above under the heading "climatic changes in African savanna" [30, 31]. Animals as a source of food required higher intelligence for hunting and foraging, development of hunting tools and strategies. *H. erectus* seems to have achieved considerable success in this endeavor. As a consequence, meat became a more proportionate part of the diet consumed by *H. erectus* [17]. *H. erectus* also developed carcasses [31] thereby bringing the bliss of food stability and consequently the ability to meet the higher energy demands of rapidly increasing brain size.

Consumption of animal food provided higher proportions of some key fatty acids indispensible for encephalization [32]. In addition to that, members of the genus *Homo* learned the use and control of fire, in so doing, discovering the process of cooking [45] to improve the quality of their diet. Cooking (gelatinization) of tubers found in African savanna softens them and improves their bioavailability [46] as against the raw food [47, 48]. Gelatinization also aided digestion [49] improving the availability of easily digestible energy rich food which supplied much needed energy to support the rapidly increasing brain size. Studies have shown that this marked increase in bioavailability due to cooking emerged at 0.25-0.20 mya. This must have supported the high energy budget needed for encephalization and given brain an upper hand in energy allocation due to its evolutionary demands. Supporting our "Evolutionary instinct" postulate, this would have had great impacts in shaping our instinct for higher food intake.

Here it can be concluded that following the climatic shift in African savanna, diet changes improved in human ancestors rather than worsening (4-1.8 mya). This happened in two ways (a) improvement in dietary quality with addition of animal food and improvement in bioavailability due to cooking [10, 32] and (b) diet stability brought about by behavioral changes (foraging and gregarious hunting) as a consequence of increased brain size and intellectual abilities [40, 50, 51]. It appears that an increase of brain size and intelligence was

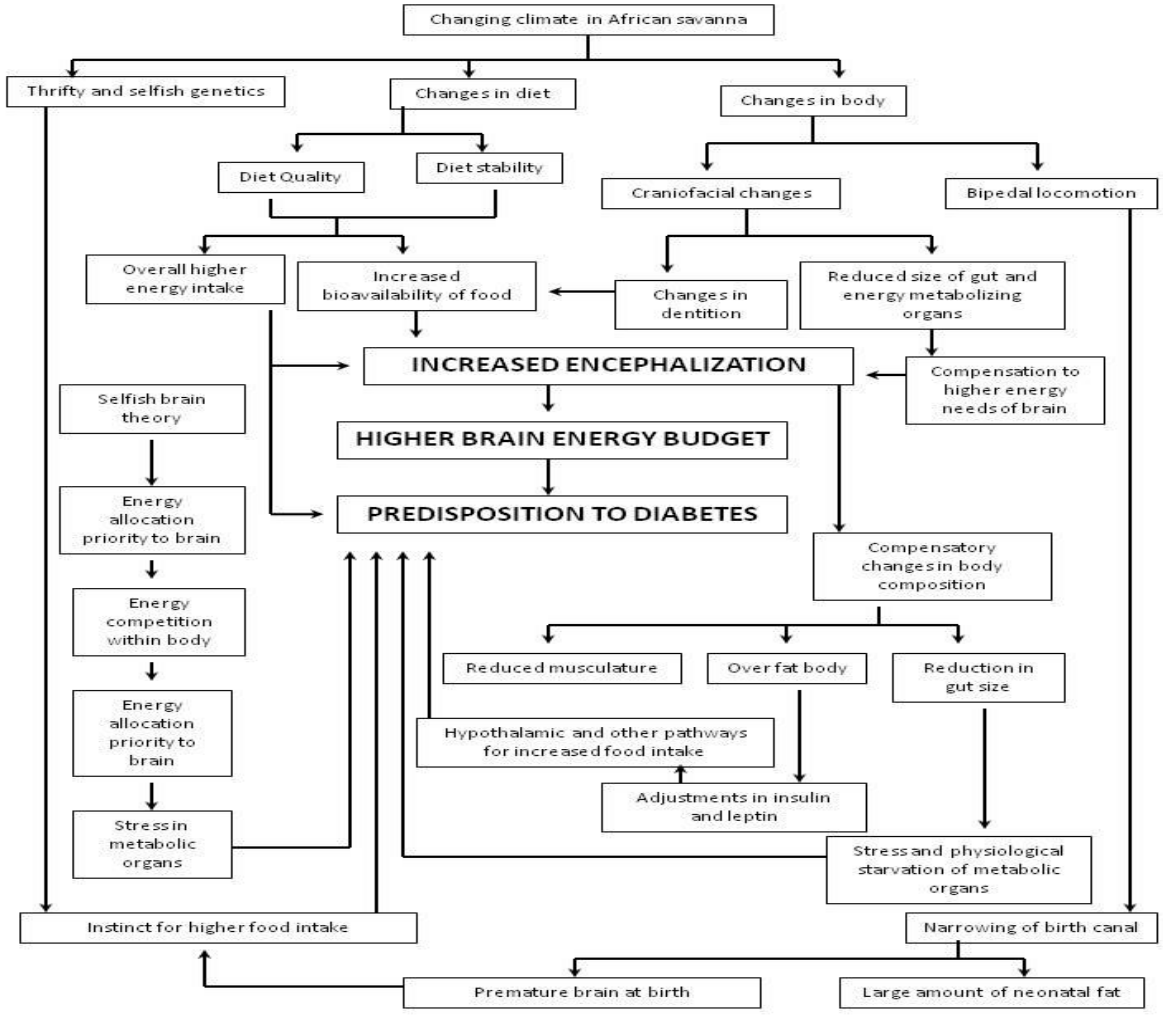

Fig. 1: Showing various evolutionary and physiological mechanisms and their long term effects on human body with panoramic view on the mechanism of diabetes in *Homo sapiens*. Food intake regulation and energy distribution within the body is also illustrated.

necessary for survival 4-1.8 mya and it might have been necessary to forge the instinct of higher food intake (our first postulate) and craving for energy rich diet to support the dramatic increments in brain size.

Changes in body composition: Among the many changes that occurred due to climatic shift in African Savanna, encephalization, reduction in gut (and metabolic organs viz. liver and pancreas), size and development of bipedal locomotion were the most important. Reduction in gut size was primarily a compensatory mechanism to spare energy for larger brain (gut being composed of energy expensive tissue). Bipedal locomotion was a consequence of changes in food patterns like use of upper limbs for hunting, free hands for breaking tubers, bringing carcass to home base etc.

The extremely large brain size in human evolution has a metabolic toll over other parts of the body because bigger brain is energetically extremely expensive [52]. Due to this, increased brain size in evolution has developed in harmony with compensatory mechanisms of changes in body composition including reduction in gut and metabolic organ size. In consequence, it precipitates a physiological stress in these organs- a premise for our second postulate of metabolic stress, decrease in muscularity and other energy expensive tissues and increase in adiposity (a predisposition to obesity).

According to selfish brain theory, humans allocate a much greater amount of energy to brain than any primate of comparable size [53] putting a rider of size reduction in other energy expensive tissues. A little extrapolation of this theory leads to a natural conclusion which becomes the basis for our second postulate (the metabolic stress postulate). Reduction in the size of energy expensive tissues coupled with higher energy metabolism demands has tendencies to stress out the organs. This stress presumably increases propensity of humans towards diabetes.

With the emergence of bipedal locomotion, an evolutionary dilemma called the obstetric dilemma arose in the evolutionary process of *H. sapiens*. Walking upright required broadening of sacrum (with broadening of the pelvis) to maintain the erect posture providing support to visceral organs and shifting the centre of gravity to the spine [54, 55]. This was accompanied with a marked decrease in the size of birth canal. In parallel to this, there was the important trend of increase in brain size (as discussed at many places in this paper) which required a large cranium. There was, therefore, a dilemma of competing trends which was efficiently resolved by leading to premature birth of human babies. Human infants are, for this reason, born with only 25% of their brain with full capacity [56]. As a result there was a great need of forging a mechanism to lead to unhampered and fully mature brain growth in human infants immediately after birth. Two mechanisms make this possible. One mechanism is that human infants are born with proportionately very high fat content in the body (compared to all other animals including primates) [57]. This helps in two ways (a) fats are energetically less expensive and no enemies to brain energy consumption and (b) fats are readily available storage form of energy. The second mechanism is that the human genes have forged the instinct of craving for high calorie food with higher intake in order to make sure the sufficient energy becomes available for brain development following birth. This instinct for high energy diet in high proportions lends support to our first postulate. Such an instinct also exposes our bodies to very high concentration of energy nutrients even after our brain is fully developed which in consequence predisposes humans to obesity, diabetes and metabolic stress of energy managing organs.

It is important to note that higher fat proportions and higher glucose concentrations are accompanied with proportionate rise in blood leptin and insulin levels respectively [58-61]. Both insulin and leptin are signal molecules for the brain informing the brain that energy is not available in the body. This is because insulin leads to glucose uptake by muscles and other tissues and leptin mediates energy storage in terms of fat. Both are, in a way, hypoglycemic factors. So both these hormones (throughout the human life) initiate a cascade of energy stress in the brain prompting the brain to increase the energy intake in the form of food by modifying appetite. This again supports the first postulate of our hypothesis.

The selfish brain theory: The selfish brain theory also lends support to our hypothesis. It argues that the brain enjoys hegemony of metabolic energy control in the body and prioritizes energy allocation to itself first [53]. The brain is, therefore, controlling organ for the regulation of energy allocation.

Biochemically speaking, the brain receives information from peripheral organs (liver, pancreas etc.) through afferent neuronal pathways and hormones (like insulin and leptin) and then controls their function via efferent nerve pathways [62]. In order to account for its higher energy demand, the brain manifests its physiological energy selfishness by prioritizing its own ATP concentration and competing for energy with other organs. This bolsters the second postulate of our hypothesis.

Taking the argument off from selfish brain theory, the priority of energy allocation to the brain leaves other organs (muscles, gut, liver, pancreas etc.) at the mercy of brain's decisions about energy allocation which may cause a physiological starvation of these organs adding to the stress they witness due to high metabolic workload and size reduction due to evolution. This physiological starvation can, therefore, be thought as a result of high energy demand by the brain, low energy availability due to selfish brain and evolutionary size reduction in metabolic organs to allow encephalization. This is consistent with metabolic stress and this stress predisposes humans to diabetes.

IV. CONCLUSION

We, therefore, conclude that *H. sapiens* have higher energy demands owing to exceptionally larger brain among all primates; this higher energy demand was a necessary condition for encephalization in evolution. Our higher energy needs are satisfied by many mechanisms which can be reduced to essentially two postulates comprising our hypothesis. The two postulates are the instinct for higher energy intake ("Evolutionary instinct" postulate) and stress in the metabolic organ ("Metabolic stress" postulate).

As shown in Fig.1, all mechanisms of evolutionary energy management strategies and metabolic physiology boil down to these two postulates. It, therefore, makes a sense to consider these two postulates as evolutionary formulas to compensate for encephalization followed by higher energy demands. Our hypothesis provides both evolutionary and physiological understanding of diabetes and can, in principle, be applied to other disorders also (e.g. Obesity, metabolic syndrome, some psychiatric derangements like eating disorders and depression). This hypothesis also explains evolutionary, genetic and physiological picture of diabetes in relation to each other and gives a panoramic understanding of the disease. A thorough understanding of these two

postulates may pave way for understanding many aspects of diabetes and related disorders and may, in consequence, lead to their better management.

V. CONFLICT OF INTEREST

All the authors declare no conflict of interest

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