

SUMMARY

Non-Human Primates as Models for Diabetes Research: A Skeptic Outlook

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ABSTRACT

Apart from numerous parallels, human beings have different evolutionary, physiological and biochemical features when compared to non-human primates. This has particular relevance to our nutrition patterns, stress (and the relevant coping mechanisms) and energy metabolism. These differences make a case for *Homo sapiens* to be a distinct species with unusual categories of diseases for which non-human primates may not supplement as true model organisms. The comparatively larger human brain proportionate size and consequently higher energy demands, bipedal locomotion (ensuing immature brain development at birth), unique craniofacial and dental structures with increased quality, availability and bioavailability of food, distinct stress biochemistry and endocrinology with disparate adrenal and thyroid sizes to other primates predispose us to many disorders not found in other non-human primates. One of the most important of these syndromes is diabetes Type-1. Since we know that autoimmune diabetes does not occur in non-human primates we may, at the outset, think that a true physiological and biochemical model of this disease in them may have important shortcomings. This paper discusses relevant physiological differences between *Homo sapiens* and other non-human primates lending enough support to the view that non-human primates may not substantiate as diabetes models for research. This paper puts forth imperative arguments centered upon differences between humans and other non-human primates in the light of brain size, body composition, evolutionary development, stress biochemistry and energy metabolism. Finally the discussion suggests that relevant factors should be taken into consideration when studying diabetes in these animal models. JMS 2018; 21 (1):61-67

Key words: Primates, Diabetes, Metabolic syndrome, Obstetric dilemma, Insulin, Brain, Encephalization hypothesis

INTRODUCTION

Human nutrition and diabetes mellitus has always witnessed a lot of attention which seems to have substantially increased in the recent past^[1-8]. These studies have lead to the understanding that *Homo sapiens* are a distinct species from evolutionary and physiological point of view as against other Non-human primates (NHP) regardless of the similarities we have with them. These differences occur due to our much larger proportionate brain size, high energy demands, different relative sizes of metabolic organs, bipedal locomotion, different energy and stress physiology. These unique dissimilarities of humans with NHPs have shaped our nutritional requirements^[1, 9, 10]

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and consequently the etiology, pathogenesis and pathology of related disorders including diabetes. In our encephalization hypothesis, we have already discussed that comparatively larger brain and bipedal locomotion has shaped the human metabolism in a peculiar manner so as to fine-tune with compensations and adaptations (on both anatomical and physiological level) including readjustment of the metabolic organ size (like adrenal and thyroid) and their physiology^[11]. In addition to this, human beings as a species are under-muscled and over-fat with reduced gut size. These distinctive features of energy biochemistry and physiology have shaped *Homo sapiens* into disparate organisms^[11]. Due to this, humans are predisposed to diseases not found in NHPs of which diabetes is presumably the most important^[11]. The biochemical networks and physiological characteristics involved in diabetes presumably involve the differences that we have with

NHPs. For this reason NHPs cannot substantiate as animal models for diabetes research though they can be used as partial models with certain species specific considerations. This paper discusses evolutionary and physiological reasons as to why NHPs may not be suitable to serve as true animal models systems for diabetes and suggests that these differences should be taken into consideration in studies on diabetes and metabolic syndrome.

Humans have much larger brain than NHPs

Bipedal locomotion and disproportionately large brain size in humans differentiate us from other NHPs with respect to our nutritional needs.^[1,10,12,15] Energy requirements of nervous tissue (owing to action potential and neurotransmitter release and reabsorption) are approximately 16 times that of muscular tissue^[13,14] indicating that human metabolism is extremely expensive from energy point of view. In *Homo sapiens* 20 to 25 percent of the resting metabolic rate (RMR) is constituted by brain alone. This is significantly higher than that of NHPs (8 to 10 percent)^[7]. As a result we need to apportion a big chunk of energy budget to nourish our brains. This has a great impact on our diet patterns, thereby, significantly differentiating us from NHPs from metabolic point of view.

High energy demands have shaped humans to consume energy rich food and our advancements in technology have further enhanced our ability in having access to the same. We consume better quality diets in contrast to NHPs to meet the needs of higher energy of our brain^[16,17]. NHPs have proportionately much larger gut size than humans^[1,18,19] because of their relatively poor diet quality^[18,20,21]. The reduced gut size in human is an adaptation to compensate for brain size that has gone from 400 cm³ in *Australopithecines* to 1300-1400 cm³ in humans^[7,22]. Owing to these changes, glucose metabolism and insulin kinetics is likely to be substantially different in humans as compared to NHPs. The glucose physiology and diabetes mechanism in humans will, hence, be substantially different from NHPs.

Insights from evolution

Ancestors of *Homo sapiens* are thought to have lived in African savanna 4 million years (MYA) ago^[15] when the

climate was rapidly changing^[23, 24] resulting in a decline in forests and a simultaneous increase in open woodlands and grasslands^[24-27]. Such climatic shift had an immense impact on food distribution patterns with a substantial increase in availability of animal food^[28, 29]. This is because savannas have a very low net primary energy productivity as against woodlands (4050 kcal/m²/yr in former and 7200 kcal/m²/yr in latter) but the herbivore productivity in savannas is three times (10.2 kcal/m²/yr) as compared to woodlands (3.6 kcal/m²/yr) [10].

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 indispensable for hominin brain enlargement^[30]. This notion is further supported by the argument that development of mammalian brain needs two long chain polyunsaturated fatty acids viz. Arachidonic acid (AA) and Docosahexaenoic acid (DHA)^[30, 31]. Ready availability of these fatty acids is thought to 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^[30].

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 (thrifty) and greater craving for higher energy foods (selfishness) in (the genetics/metabolism of) hominin 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 largely unavailable. This established a genetic property in *Homo sapiens* now referred to as thrifty gene hypothesis^[32]. 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 *Homo sapiens* derive their first postulate “Evolutionary instinct” from. 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.

Nutritional differences

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^[33-35]. However, paleontological studies suggest that genus *Homo* had far higher proportions of animal food in their diet^[29,36-38]. Decreased tooth size and reduced masticatory complex in genus *Homo* as against *australopithecines* lends support to this notion^[22].

Homo erectus (supposed to have lived some 1.8 MYA) witnessed many changes accompanying modifications in diet which include dramatic increase in brain size, development of humanlike limb pattern with erect posture and improvements in foraging behavior^[39-42]. All these changes occurred because of the drastic climatic changes in the then home of human ancestors^[23,24]. Owing to this change animal food became the diet of choice as discussed above under the heading “climatic changes in African savanna”^[28,29]. Animals as a source of food required higher intelligence for hunting and foraging and development of hunting tools and strategies. *H. erectus* seems to have achieved considerable success in this endeavor. As a consequence, meat saw an increase in terms of proportion in the diet consumed by *H. erectus*^[15]. *H. erectus* also fed on carcasses^[29] 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 indispensable for encephalization^[30]. In addition to that, members of the genus *Homo* learned the use and control of fire, in so doing, discovering the process of cooking^[43] to improve the quality of their diet. Cooking

(gelatinization) of tubers (found in African savanna) softens them and improves their bioavailability^[44] as against the raw food^[45,46]. Gelatinization also aided digestion^[47] 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 the “Evolutionary instinct” postulate, this would have had great impact in shaping the human instincts 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^[7,30] and (b) diet stability brought about by behavioral changes (foraging and gregarious hunting: leading to the development of language) as a consequence of increased brain size and intellectual abilities.^[38,48,49] It appears that an increase in brain size and intelligence was necessary for survival 4-1.8 MYA and it might have been necessary to forge the instinct of higher food intake (first postulate) and craving for energy rich diet to support the dramatic increments in brain size.

Distinctive 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^[50]. 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^[51] putting a burden of size reduction in other energy expensive tissues. A slight 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 *Homo 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^[52,53]. 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 (yet with a significant trade-off) by leading to premature birth of human babies. Human infants are, for this reason, born with only 25 percent of their brain with full capacity^[54]. 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 is that human infants are born with proportionately very high fat content in the body (compared to all other animals including primates)^[55]. 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 that 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 human bodies to very high concentration of energy nutrients even after our brain is fully developed. This, in consequence, predisposes humans to obesity, diabetes and metabolic stress of energy managing organs (liver and pancreas).

It is important to note that higher fat proportions and higher glucose concentration are accompanied with proportionate rise in blood leptin and insulin levels respectively^[55-60]. 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 intake by muscles and other tissues and leptin mediates energy storage in terms of fat. Both are, in a way (contrary to the general belief) **“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.

CONCLUSION

From the above discussion, it can be concluded that human energy metabolism, nutritional patterns, food quality, food availability and bioavailability, body tissue proportions and distributions, insulin kinetics, genetics, behavioral instincts are fundamentally different from the NHPs. For these reasons NHPs cannot be thought to substantiate as model systems for human diabetes. This is despite the fact that humans have immense similarities with NHPs, the differences *Homo sapiens* display with NHPs exert a far greater effect on energy metabolism and insulin kinetics which renders the similarities relatively ineffective. NHPs can, however, serve valuable models for toxicity studies. Also, we suggest that the aspects discussed in the paper may be taken into consideration when conclusions are drawn on diabetes related studies conducted on NHPs.

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