International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Prevalence of Obesity in Human Males Mediated by Aryl-hydrocarbon Receptor (AhR)

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Abstract: ***Obesity is a significant risk factor for type II diabetes and cardiovascular diseases. It is a growing worldwide problem. Recent studies and experiments showed that a highly activated AhR (aryl hydrocarbon receptor) might disrupt fat metabolism and contribute to white fat deposition in cells, which leads to obesity. The mechanism of action of AhR is dependent on the agonists and antagonists. AhR. The study was mini-survey conducted upon 110 Indian males by use of questionnaires and secondary data . We found that people consuming AhR agonists like Kynurenine (endogenous ligand) are more prone to overweight or obesity, as compared to the people who consumed more AhR antagonists like Epigallocatechin gallate (EGCG) Epigallocatechin (EGC), Glucosinolate, Flavonoids, and Resveratrol in their regular diet. Thus, we concluded that AhR is a significant factor for obesity in humans (male). Since holistic research on the Indian diet is unavailable, conclusions from our survey can be of great use for further studies on treating obesity and understanding the effects of AhR on fat metabolism. Objective: Our motive is to test our hypothesis by surveying the general population (Indian males) on their diet and to check the effect of agonist and antagonist in their diet. Hypothesis: If the value of agonists is more in the diet that will lead to activation of AhR and contribute to obesity whereas an abundant amount of antagonists in the diet leads to the deactivation of AhR and prevention of obesity***

Keywords: Obesity, agonist, antagonist, aryl-hydrocarbon receptor

1. Introduction

Obesity is an alarming global problem, yet, less is known about its causes and effective treatment. One of the accepted reasons for the worldwide rise in obesity and associated problems is the increased global consumption of the high-fat, high-carbohydrate, high-salt, and low-fiber western diet. Obesity is the contributor to inflammation, diabetes, and metabolic syndrome, cardiovascular disease, and cancer. Recent studies show AhR's (aryl hydrocarbon receptor) role in causing obesity because of its significant role in fat metabolism. The AhR is a transcription factor that regulates gene expression of various genes for example (FOXO1 and MIR-155). It was initially thought to function as a sensor of xenobiotic chemicals and regulator of enzymes such as cytochrome P450s. Exogenous AhR ligands are of two types, viz., of synthetic ligand and natural ligand. The present study scrutinized the natural ligands only.

Natural Ligand

Generally, the ligands of AhR are present in food, naturally occurring sources of the ligand are diet. The ligands can be agonists or antagonists depending upon their effects on AhR. The diet includes secondary metabolites like flavonoids, carotenoids (apo-8´carotenal, canthaxanthin,), and astaxanthin berberine, that de-activate the AhRsignaling pathway. Whereas, AhR agonists like tryptophan metabolites stimulate the AhR. However, a majority of these chemicals appear to be relatively weak AhR ligands. Some fruits, vegetables, herbs, and tea also have AhR ligands (flavonoids), which are used for protection against cancer.

Polyphenols

Flavonoids are a widely studied class of polyphenols, divided into the following classes: flavones, flavonols, flavanones, isoflavones, and catechins. Flavones and flavonols are commonly found in vegetables, fruits, tea and red wine. Citrus fruits are a rich source of flavanones, isoflavones are found in beans, and catechins in tea.

AhR Isoflavones (daidzein and resveratrol), flavanone (naringenin) and flavone (baicalein) can activate AhR. Whereas, flavone (apigenin), flavonol (quercetin) and antraquinone (emodin) had a notable inhibitory effect on the in-vitro activation of AhR induced by TCDD Green tea contains polyphenolic compound flavonol, better known as catechins. The important catechins are epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC)., EGCG and EGC were the most potent antagonists among others. Recent studies show that the EGCG does not bind to the AhR at its binding site instead it binds to the HSP90. This binding results in nuclear localization of AhR so that it becomes unable to bind with DNA. EGCG binds to the binding site of HSP90 and changes its conformation and decreases the association of ARNT (AhR Nuclear Translocator) with ligand-activated AHR.

Tryptophan Metabolites

The aromaticity of the tryptophan structure has led to the idea that its metabolites could be the AhR agonists. Indeed, it was confirmed that tryptamine acetic acid (TAA), as well as other endogenous ligands, acts as weak AhR activators as compared to TCDD. Tryptophan is 70um in plasma, it acts as an activator, and stimulates AhR transformation, DNA binding and induces expression of an AhR-dependent

reporter gene in the cells.The UV radiation of tryptophan produces new compounds that have a high affinity for AhR and have greater potency to induce Cyp1a1.6-formylindolo [3,2-b] carbazole (FICZ) and 6,12-diformylindolo [3,2-b]carbazole are two high affinity AhR ligands. The exposure of human skin to UV-b was shown to induce Cyp1a1 and Cyp1a2 mRNAs and proteins. UV irradiation translocated the AhR into the nucleus and induced Cyp1a1 gene expression.2-(1-H-Indole-3-Carbonyl)-Thiazole-4-Carboxylic Acid Methyl Ester (Ite) also an AhR agonist ligand.

2. Literature Survey

The aryl hydrocarbon receptor is a ligand-dependent transcription factor that can be activated by a structurally diverse range of synthetic and natural chemicals. AhR can mediate the toxic and biological effects of environmental contaminants such as 2,3,7,8-tetrachlorodibenzo p-dioxin (TCDD). Extracts of 22 dietary herbal supplements and 21 food products were screened for AhR agonists. Although some food extracts (corn, Jalapeno pepper, Green bell paper, Apple, Brussels, Sprout, and Potato) were relatively potent activators of AhR DNA binding. Overall, these results demonstrate that dietary products which are consumed by humans can be a major source of naturally occurring AhR ligands. (2).

Ahr may disturb fat metabolism and contribute to obesity. The AhR is a nuclear/transcription factor that is best known for responding to environmental toxicant exposures to induce a battery of xenobiotic metabolizing genes. The AhR is also activated by dietary components and there is evidence which links the activated AhR to major diseases like obesity. Several studies examined the relationship between the AhR and fat metabolism using a model system to identify a possible role for the AhR is obesity. The model had two groups of male mice that differ at AhR affinities. Group 1 with high AhR affinity and Group 2 with low AhR affinity. The two groups were fed with different diets, low fat regular chow for group 1 and high fat western chow for group 2. After 28 weeks the mouse on high fat diet with high affinity AhR had a greater body mass (obese), as compared to low affinity AhR group. (6).

The physiologic functions of AhR has expanded with recent studies demonstrating its role in immune regulation, organogenesis, mucosal barrier function and the cell cycle. These functions are likely dependent upon ligand mediated activation of the receptor. High affinity ligands of AhR have been classifically defined as xenobiotics, such as polychlorinated biphenyls and dioxins. Identification of endogenous AhR ligands is the key to exploring the physiologic functions of this enigmatic receptor. Targeting metabolic pathways of tryptophan and indole can lead to a myriad of AhR ligands. Many of these ligands exhibit species specific preferential binding to AhR. The discovery of species specific tryptophan metabolites as AhR ligands may provide an insight concerning the location ofactivation in an organism, like at the site of inflammation or within the intestinal tract (12)

Cruciferous vegetables and citrus fruits are reported to possess beneficial properties but also have been shown to contain natural AhR agonist (NAhRAs). Binding to the AhR is widely assumed to activated the main pathway by which dioxin, like 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) extent their toxicity. To establish if activation of the AhR pathway by NAhRAs and dioxin like substances result in similar cellular responses. Cells were exposed to indolo (3,2-b) carbozole, an acid reaction product from cruciferous vegetables, and to extracts of citrus pulp and grapefruit juice. Gene expression profiles induced by these NAhRAs were compared to those of the xenobiotics AHR agonists TCDD and benzo (a) pyrene. Over 20 genes were found more than 1.5 times up-or down-regulated by TCDD, and the expression of most of these genes was modulated in the same direction and to a similar extent by B(a)P and the NAhRAs. Results were confirmed by RT-PCR and many of these genes may be involved in dioxin-related toxin effects. In conclusion, this in vitro induced by NAhRAs, TCDD, B(a)P at the transcription level in a human intestinal cell line(13). Thirty-nine food extracts including vegetables, fruits, herbs and tea were initially screened in vitro. First examined the application of both bioassay 13 methods using green tea extracts and epigallocatechin gallate, reported antagonists of the AhR, since the result could reveal an inhibitory effect versus the control in both assays. Food extracts were then tested. Among the herbs, extracts of sage, among the vegetables, green leafy ones such as spinach, and among the fruit, citrus showed inhibitory effects on AHR activation by TCDD, although some tested samples did not show parallel behavior in both assays. Sage had a remarkable inhibitory effect and its effects were does dependent. The result suggests that these assays might be applicable to the preliminary screening of antagonists activity against the AHR. Moreover, based on these results, the potential benefit of factors that function as dietary ligands of the AHR and are present in several foodstuffs is indicated(15).

The aryl hydrocarbon receptor receives much attention for its role in the toxicity of dioxins and dioxin like- PCBs. However, also many other compounds have been reported to bind and activate the AHR, of which natural food components are of interest from a human health prospective. Using the protopical AHR-agonists TCDD as standard, estimated that the daily intake of NAhRAs may be considerably higher than the reported intake of dioxins and dioxin-like PCBs. Potatoes, cruciferous vegetable, bread, french fries, hamburgers and grapefruit juice contained most NAhRAs. Food preparation and acid treatment can show a significant effect on the AHR activation.

3. Materials and Methodology

A questionnaire was prepared after a thorough literature review of AhR agonist and antagonist. The selected antagonist and agonist for the survey are given in the table below (Table no.1) and (Table no.2)

Table 1: AHR Agonist in Obesity

S. No.	Agonist	Source
1.	Kynurenine	meat, poultry, eggs, almonds, oats, dried dates

Table 2: AHR Antagonist in Obesity

Sr.no.	*Antagonist*	*Source*
1.	Epigallocatechingallate (EGCG) and Epigallocatechin (EGC)	Green tea
2.	Glucosinolate	Broccoli, Cauliflower and Black mustard seed
3.	Flavonoids	Citrous food and dark chocolate
4.	Resveratrol	Red wine

Standard BMI charts were used for categorizing the persons under survey into underweight, normal, overweight, and obese. The inclusion and exclusion criteria for the survey are in table no. 3.

Table 3: Inclusion and exclusion criteria

S. no.	Parameter	Inclusion	Exclusion
1.	Gender	Males	Females
2.	Age	19 yrs. – 30 yrs.	Below 19 yrs. and Above 30 yrs.
3.	Diseased person	All except the excluded	diabetes, thyroid, or genetic diseases

The survey was conducted on 110 humans (male) of age group between 19 to 30 years. The participants suffering from or having a family history of diabetes, thyroid, or any other genetic disorder were considered as unideal. Based on exclusion and inclusion criteria (table no.3) a total of 110 persons under survey were differentiated as 89 ideal and 21 unideal. The BMI of each ideal person was compared with the standard BMI chart according to which they were segregated as underweight, normal, overweight, and obese. From 89 ideal persons, we got 16-underweight, 56-normal, 14-overweight and 3-obese.

A points system was established to get results from the survey. One point was assigned for each consumed agonist and antagonist which was multiplied by the number of days (in a week) it was consumed by the participants. For each category, a high and low consumption of agonist and antagonist were segregated, and graphs were plotted accordingly.

4. Results and Discussion

Results of underweight group from survey:

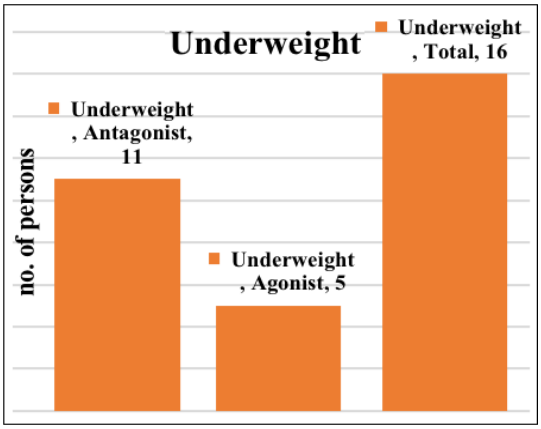

Figure 1: Antagonist consuming candidates are 68.75% and Agonist consuming candidates are 31. 25% in the underweight group in a total of 16 participants

Underweight group participants have more agonist consumers the antagonist consumer. It also implies that consuming Antagonist causes more problems of underweight, but if agonist is consumed, it can be helpful in increasing weight. Hence we can suggest from our survey that agonist is helpful for gaining weight.

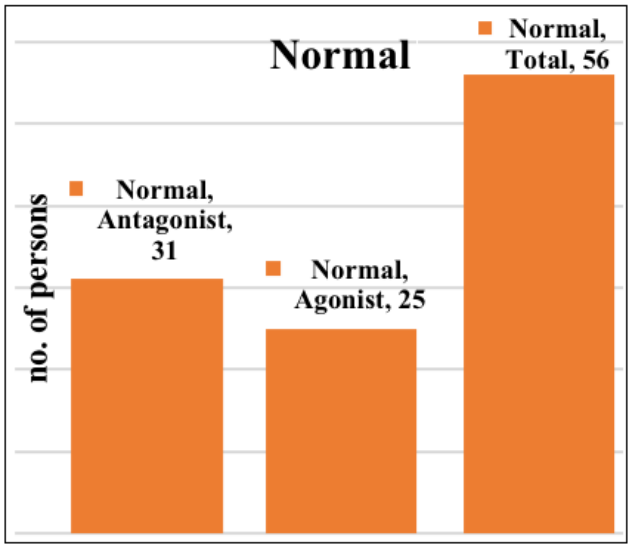

Figure 2: Normal BMI group had 55.3% participants who consumed antagonists and 44.6% consumed agonists in a total of 56 participants

The results of the survey show that people who consumed antagonist have been found to be normal than those who consume agonists. However, the difference of consumption of agonists and antagonists is less.

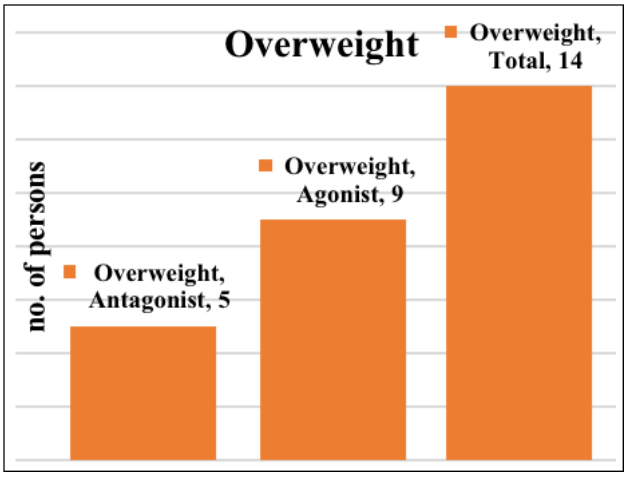

Figure 3: Overweight BMI group had 64.28% participants who consumed agonists and 35.71% consumed antagonists in a total of 14 participants

The survey shows that agonist consumers have higher tendency to become overweight as compared to the antagonist consumers . Therefore the surevy can suggest AhR and its dietary ligands affect fat metabolism in adult males.

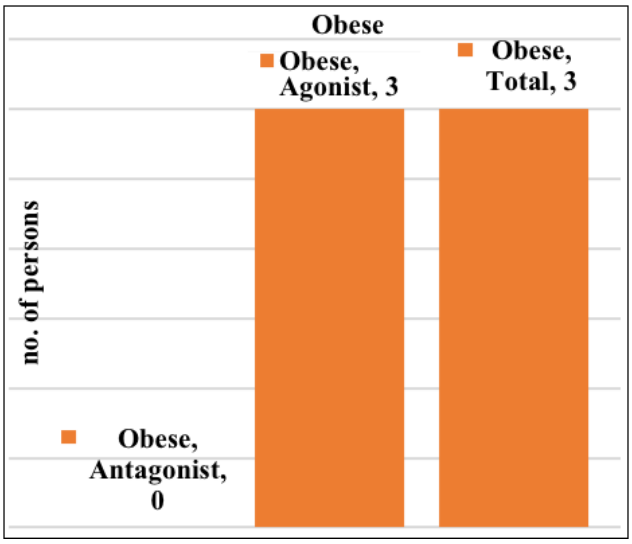

Figure 4: Obese group had 100% participants who consumed agonists in a total of 3 participants

The participants in the obesity group predominantly shared a common feature of higher agonist consumption. However, we will need more participants in the obese group for normalizing our data. Hence, the tendency of agonist consumption and its relation to obesity remains inconclusive. Although, the data from overweight group shows a positive correlation between agonist rich diet and abnormal BMI. As of now, the positive correlation can be considered as of point of reference for further studies on Obesity group.

Our hypothesis to establish a positive correlation between consumption of high dietary agonists and obesity remains inconclusive. However, the survey can act as starting line for robust clinical studies further. The influence of agonist-rich western diet on Indian males was one of the outcomes from the survey which demands another study. The correlation between overweight, normal and underweight group, with AhR ligands was putatively associative. Amongst the total of 16 underweight participants 11 consumed more antagonist and 5 consumed more agonist in their diet. Hence, the survey can suggest the more the antagonist in diet less the chances of getting obese in future if this diet is followed. Similar results were found in normal group, whereby, 31 consumed more antagonist and 25 consumed more agonist from a total of 56 participants. The overweight group had 5 participants who consumed more antagonist and 9 participantswho consumed more agonist. Hence, the correlation can become a solid evidence for further clinical interventions on metabolic and genetic aspects of fat metabolism in people.The survey also begs for a molecular analysis of AhR ligands and its interaction with AhR to understand the altercations caused by it on the fat metabolism. .

Hence, one can understand that sources of agonist of AhR in diet like consuming more of non-veg, almonds, or oats which are giving rise to an endogenous AhR agonist that is Kynurenine which is a tryptophan metabolite could play an important role in activation of AhR which may lead to overweight and obesity. Morever, the consumption of antagonists like Epigallocatechingallate (EGCG) Epigallocatechin (EGC), Glucosinolate, Flavonoids and Resveratrol may reduce altercations on fat metabolism and prevent obesity. The causes for errors in this study could be due to AhR affinities, which could vary among individulas. Also, the other parameters included in the questionnaire like exercise, occupation, nutrient supplements, cooking medium oil and fast food consumption has to be taken in consideration for errors. So also, Indian diet has a great difference as compared to the western diet, which may also be a reason for negative results.

5. Conclusion

AhR could be a putative target for developing treatments for obesity. An overall diet having agonists and antagonists in balanced amounts may prevent overweight and obesity The selected agonists of AhR in obesity that is kynurenine, which is found in meat, poultry, eggs, almonds, oats, and dried dates, were seen to mediate weight gain. Whereas, the antagonists of AhR selected for the survey, which is found in broccoli, cauliflower, black mustard seeds, green tea, red wine, citrus foods, and also dark chocolate, were observed to prevent weight gain among participants. Scanty research on human subjects on AhR and its ligands remains the main cause of lack of molecular data. Hence, the mini-survey can be of advantage for further relevant studies and better management of obesity. Furthermore, Our results could be taken in consideration for finding a therapeutic treatment for obesity, by focusing on the activity of Ahr and treatment of diabetes,

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