In silico analysis to link insulin resistance, obesity, and ageing with Alzheimer's disease

Priyanka Sarkar

Vellore Institute of Technology: VIT University

Premkumar Jayaraj

Vellore Institute of Technology: VIT University

Ketaki Patwardhan

Vellore Institute of Technology: VIT University

Samiksha Yeole

Vellore Institute of Technology: VIT University

Sourajit Das

Vellore Institute of Technology: VIT University

Yash Somaiya

Vellore Institute of Technology: VIT University

Rajagopal Desikan

Vellore Institute of Technology: VIT University

Kavitha Thirumurugan (✉ m.kavitha@vit.ac.in)

Vellore Institute of Technology: VIT University <https://orcid.org/0000-0002-4673-4099>

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Abstract

The process of ageing accompanies several metabolic diseases. With ageing, fats accumulate to increase the visceral and abdominal adiposity leading to hyperinsulinemia, insulin resistance, obesity and several other diseases. *Drosophila melanogaster* is often used to study the ageing process and its related disorders. Therefore in this study, we performed an *in silico* analysis to relate the process of ageing and insulin resistance. We analyzed data of insulin resistant *drosophila* from GEO database and compared it with the data from the literature survey. We observed that 98 genes were common in both the models, and they showed gene modulations related to metabolic pathways, fatty acid metabolism, insulin resistance, and neural receptor-ligand binding pathways. Analysis of the REACTOME database against human data revealed that TRKB signalling pathway is commonly affected. TRKB mediated BDNF pathway is a major regulator of memory loss. We further analyzed the common genes in Alzheimer's disease and compared the fly data with human data to identify the diseases related to these common genes. Then we performed a literature survey to provide protective mechanisms for TRKB signalling pathway activation, mediated through polyphenols. We treated the flies with sesamol conjugated lipoic acid derivative (a phenolic compound) at hormetic doses to evaluate its effect on the memory of flies.

Introduction

Ageing is an irreversible process of multicellular organisms and unicellular organisms. Scientific community is researching and adding hypotheses to elaborate on the cellular and molecular machinery of ageing. Recent research in this field has made it progressively clear that ageing is due to the build-up of molecular damage, which gives a unified theory of ageing. Ageing is a process that predisposes metabolic imbalances like insulin resistance and oxidative stress that ultimately lead to age-related disorders like obesity, diabetes, neurological disorders, and memory impairments (de la Monte 2017). For decades *drosophila* has been used as a model organism to study ageing and age-related diseases. *Drosophila melanogaster* belongs to the genus *drosophila* of family Drosophilidae. This *Drosophila* genus contains about 1,500 different species, and they have diversity in appearance, behaviour, and breeding habitat. *D.melanogaster* has been widely used in genetic research and is a preferred model organism in developmental biology studies (Deepa Parvathi V, Akshaya Amritha S 2009). *Drosophila* is the dominant model used to understand the development of an organism from an embryo to an adult. Many genes of *drosophila* are homologous to human genes and therefore studied to gain a better understanding of these genes in humans (Jennings 2011). Pathways like malonate–acetate, shikimic acid, and isoprenoid are involved in polyphenol production. They have proven therapeutic effects against several pathological conditions, including neurodegenerative diseases (Stewart and Stewart 2008). Sesamol mitigates memory impairment and causes neuroprotection via activation of Nrf2, NFκB and BDNF (Kumar et al. 2010; Liu et al. 2017, 2018; Ren et al. 2018).

Therefore in this study, we have tried to identify the common genes involved in ageing, insulin resistance, and neurodegenerative diseases. We have also analyzed the effect of a phenol derived synthetic compound's ability to mitigate age-related memory impairment.

Materials And Methods

Gene Expression data

We used the Gene Expression Omnibus (GEO) database to obtain *drosophila* insulin resistant obese samples and ageing samples data. We have analyzed the data set (GSE105448) for high-sugar fed male *drosophila* against normal diet-fed male *drosophila*. These samples are insulin resistant and obese. We obtained ageing fly data from a literature survey on genetic responses towards mating and ageing in *drosophila* (Zhou et al. 2014). We also used the dataset (GSE48681) for analyzing the Alzheimer's disease (AD) model flies. In this data we have utilized the 3-day old fly data as young control flies and the 20-day old fly data as aged diseased flies. The data up to 10% false discovery rate (FDR) only was used.

We have obtained the data from GEO database and literature to ensure their reliability. The data utilised for the *in silico* work has been collected from previously published works and is analyzed through published, and frequently used reliable end-user bioinformatics software.

Gene Ontology

Functional interpretation for each data set was performed individually through DAVID (<https://david.ncifcrf.gov/>). It is a free online tool used for gene ontology studies (Dennis et al. 2003). *Drosophila melanogaster* was selected as the background, and all other parameters were kept in default mode. Venn diagram was also generated to deduce the overlap between the two datasets using InteractiVenn online tool. We explored the ageing data set and insulin resistant data set to find the common genes.

Comparison With Human Data

The data sets analyzed through REACTOME database within the human genome display TRKB mediated signalling pathway. Specifically, the pathways enhanced in age-related gene set show correlations to TRKB signalling pathways mediated through BDNF, NTF3, and NTF4 (Supplementary data 2a, 2b). In comparison, the high sugar-fed fly data from gene enrichment analysis revealed the involvement of GABA, NTF3, NTF4, TRKB and BDNF (Supplementary data 3). BDNF and other neurotropic factors NTF3 and NTF 4 are essential players of neural plasticity and survival. When the axons of the distal segment of nerves degenerate due to damage in the peripheral nerves, the axons of the proximal segment start budding; that gradually grow and eventually forms a connection with the target organ to restore its function. In the absence of NTF, the proximal segment begins to degenerate rapidly, and the cell body dies. BDNF mainly acts through TRKB pathway and plays a vital role in learning and memory. TRKB acts as a receptor for the neurotropic ligand BDNF and NT4 (Firuzi et al. 2015). BDNF can also inhibit the phosphorylation of the GABA receptor (Xiao and Le 2016; Porcher et al. 2018; Xiang et al. 2019). Modulation in TRKB signalling, and its transactivation can lead to neuronal damages. Therefore, proper TRKB signalling is required for learning and memory. This modulation is the cause of age-related neurodegenerative diseases observed in humans and *drosophila*. Next, we analyzed data from Alzheimer's disease (AD) to identify the common genes between insulin resistant/obese flies and AD flies.

Fly Husbandry And Diet Preparation

Wild type *Drosophila melanogaster* flies (Canton-S) were reared at controlled temperature $25^{\circ}\text{C} \pm 1^{\circ}\text{C}$ and light:dark cycle (12:12 hours). Flies were maintained in 300 ml polypropylene bottles containing 30 ml of maintenance diet (MM diet) (10% semolina (w/v), 10% jaggery (w/v), 1.5% agar (w/v), 3% methyl paraben (v/v), and 0.3% propionic acid (v/v) (Chattopadhyay et al. 2015). Eggs were collected and transferred to a new bottle. Newly emerging flies were segregated based on sex. Then, these flies were transferred to 2 different diets: (1) standard Sucrose-Yeast diet (SYD) (10% sucrose (w/v), 10% yeast extract (w/v), 2% agar (w/v), 3% methyl paraben (v/v), and 0.3% propionic acid (v/v) (Chattopadhyay et al. 2015). (2) High fat diet (HFD) (10% sucrose, 10% yeast extract, 2% palmitate, 2% Tween-80 and 1.5% agar, 3% methylparaben and 0.3% propionic acid). For sesamol-conjugated lipoic acid-derivative supplementation, the compound was dissolved in 0.5% DMSO and added into SYD and HFD at final concentrations of 30 μM , and 60 μM by proper mixing. Standard control diets contained only water as a vehicle.

Memory Assay

Age matched *drosophila* flies were sorted into a group of 10 flies based on their sex for each set. An in-house T-maze apparatus was built, and a modified protocol from JOVE was used for this assay (Malik and Hodge 2014). All the experiments were conducted under dim red light to block the visual inputs for the flies. We introduced the flies to a training tube attached to the T-maze. They were then allowed to adapt to the tube and airflow for 2 minutes. Then the first odour (yeast) was introduced in one of the arms of the T-maze with a 60-V shock (consisting of 1.25-sec pulses with 3.75-sec interpulse intervals) for a total duration of 1 minute. We calculated the time with a stopwatch. While doing this, we attached only one arm and removed the other arm. We followed the same way while introducing the second odour. The flies were given a 30 sec rest period and then introduced to the second odour (banana) for 60 sec without any shock. Then again, we gave a rest period of 30 sec, and the flies were finally moved from the training chamber into the central chamber of the T-maze for 90 sec. Then both the tubes were fitted into the bottom of the apparatus to form the T-maze.

Short Term Memory Retention

The flies were simultaneously exposed to both the odours and were allowed to move towards them. The test was conducted for 120 sec to allow maximum (80%) mobility. The memory retention analysis was recorded for 3 times with a gap of 10 minutes and the average was utilized as the final result. We recorded the flies that avoided the punishing chamber odour against the total number of flies as the percentage of flies retaining short term memory.

Long Term Memory Retention

We trained batches of flies in 2 cycles of spaced training with a 6-hour inter-cycle interval. Then long term memory was evaluated, 12-hour after the training. Six-hour interval was considered because one-cycle training in *drosophila* leads to the formation of a labile-phase of memory detected for up to 7 hrs.

Results And Discussion

Gene and genome analysis

Drosophila has served as a model organism for many human diseases and disorders due to its homology with *Homo sapiens*. We have analyzed the GEO database and published literature to obtain data for genomic comparison between ageing flies and insulin resistant obese flies. Insulin resistance led by inflammation is the root cause of many metabolic diseases. Recently, insulin resistance has been marked as a characteristic feature of the normal ageing process. Normal ageing is accompanied by fat deposition and lipid accumulation in the abdomen and visceral compartments leading to age enhanced insulin resistance or hyperinsulinemia (Ryan 2000; Refaie et al. 2006). The data obtained from the literature survey and GEO database revealed 482 genes that are differentially expressed during the process of aging and also insulin resistance during obesity lead to the modulation of 1267 genes. The data sets were analysed for their gene ontologies (Supplementary data 1). We observed that the top ranked biological process affected by the aging process were cytoskeleton and synapse organisation, immune responses and metabolic processes. The gene ontology analysis of obese/insulin resistant sample data revealed the modulation of receptor signals and signal transduction, synaptic transmissions and organization, cytoskeleton organisation and circadian rhythm entrainment. Most of the metabolic pathways, hippo signalling pathways, fatty acid biosynthesis-related pathways, cytokine-mediated pathways, and neural receptor-ligand interacting pathways were regulated by the listed gene sets. We observed that the genes listed in ageing data and the gene list of insulin resistant obese data had a few similarities based on their gene ontology. These similarities between these two data sets provoked us to investigate the common genes between these two datasets. Among the reported genes, 98 genes were common (Table 1) in both aging as well as insulin resistant conditions (Fig. 2).

Further a comparison between the fly model and human in general was performed. The similarities within pathways were obtained by comparing the *Drosophila* genome with the human genome using REACTOME database (<https://reactome.org/>) (Fig. 1).

The Relation Between Insulin Resistance/obesity And Ad

The comparison between the data sets of AD and the insulin resistant/ obese model revealed that there is a significant number of genes that commonly regulate both the diseases (Supplementary data 4). The functional annotation and the analysis of enrichment clusters for the standard gene sets revealed their involvement in the stimulus, metabolic, biosynthesis, and synapse related biological processes (Supplementary data 4, Fig. 3). The biological functions related to these common genes majorly included synaptic communication, reflexes towards the light, sound, mechanistic, and, abiotic stimulus (Table 2). When these common genes were analyzed against human data, many neurological diseases were predicted for this dataset (Fig. 4). There are genes that can commonly regulate and affect the occurrence / maintenance of both the diseases and might be associated with the ageing process also. Thus, we next attempted to search the literature for phytochemicals that might retard the ageing process and the

related neurological disorders. Since our data showed the enrichment for TRKB related pathway, we focused this survey on TRKB modulations.

Phytochemical Survey

Our *in silico* analysis revealed the TRKB pathway as a link between insulin resistance/obesity, aging and Alzheimer disease, targeted by the list of common genes. Alzheimer is a disease of memory loss and TRKB/BDNF pathway is an important pathway mediating neuronal plasticity and survivorship. This pathway has been reported to play an important role in controlling memory retention and progression of Alzheimer disease (J. Allen, J. Watson and Dawbarn, 2011; Wang et al., 2019). This pathway is modulated mainly by oxidative stress, Nrf2, and PI3K/AKT and ERK signalling. Therefore, our next attempt was to explore compounds that might enhance the activity of this pathway.

There are a few phytochemicals that can regulate both or any one of the molecules (TRKB, BDNF) (Hannan et al. 2020).

Polyphenols constitute a significant class of phytochemicals that are abundantly present and have proven therapeutic effects against several pathological conditions, including neurodegenerative diseases. Phenolic compounds produced via malonate–acetate pathway, the shikimic acid pathway, and the isoprenoid pathway. The shikimic acid pathway yields three aromatic amino acids that are essential precursors of plant phenolics: tyrosine, tryptophan, and phenylalanine. Phenylalanine converts to salicylic acid, cinnamic acid, *p*-coumaric acid, *p*-hydroxybenzoic acid, sinapic acid, caffeic acid, and ferulic acid. The malonate–acetate pathway is similar to the fatty acid synthesis pathway. It involves sequential additions of malonyl-CoA to create a polyketide chain, which cyclizes to form a phenolic ring structure. Such structures like acetyl-CoA, malonyl-CoA, and *p*-coumaric acid yield chalcone. Chalcone can undergo various modifications to produce a variety of isoflavones, flavanones, flavon-3-ols, flavones, and anthocyanidins.

Some phenolics are produced by combining the products from both the malonate–acetate and shikimic pathways. About 8000 different types of plant phenolics are known (Stewart and Stewart 2008), and characterized by the presence of repeated phenolic structural units. They are mainly of natural origin (from fruits, vegetables, and spices), but they can also be produced synthetically, semi-synthetically, or organically (as in beverages, chocolates, and wines). Out of 8000 polyphenols, about 3000 are flavonoids in nature (Stewart and Stewart 2008). Other than flavonoids, there are phenolic acids, stilbenes, and lignans that form the subset of polyphenolic compounds (Pandey and Rizvi 2009).

Flavonoids

Tea is rich in polyphenol content. Other than its antioxidant nature, they are reported of being neuroprotective as well. They attenuate the inhibition of the TRKB/Akt signalling pathway and also restore the pro-BDNF expression in cytotoxic cells (Yang et al. 2020). Flavonoid 7,8-DHF (7,8-dihydroxyflavone) target the PI3-AKT-ERK/CREB pathway to upregulate TRKB dimerization and

phosphorylation (Jang et al. 2010). This compound acts as an agonist for TRKB. The flavonoid, 7,8,3-trihydroxyflavone, produces similar effects by phosphorylating ERK and TRKB receptors (Yu et al. 2013). Another polyphenolic flavonoid, diosmetin is capable of weakly inducing phosphorylation of TRKB (Moosavi et al. 2015). Flavanonol compound, astilbin upregulates BDNF and activates ERK and Akt pathways (Lv et al. 2014).

Non & Flavonoid Polyphenols

The neuroprotective role of polyphenols is carried out by activating the pathways such as PKC-ERK1/2, PI3K/Akt, MAPK, and Akt-ERK1/2; that regulate cell proliferation and growth, translation, transcription, and survival. These polyphenols bind Trk receptors to activate the protein kinase cascades, CREB, and increase the expression of Bcl-xL, Bcl-2, and neurotrophic factors like BDNF, NT4/5 & NT3 and NGF (Huang and Reichardt 2003). A decrease in neurotrophic factor is an indication of neurodegenerative diseases, characterizing its physiological attributes (Sharma 2017). 2,3,5,4'-tetrahydroxystilbene-2-O- β -D-glucoside (THSG) adapts PI3/Akt signalling pathway to provide neuroprotective effects (Yang et al. 2014). Another stilbene, resveratrol is capable of inducing the release of BDNF in a time-dependent and dose-dependent manner. Neuroprotective effect of resveratrol is hindered due to the blockage of neurotrophins (Zhang et al. 2012). Resveratrol, baicalein, and rosmarinic acid (a caffeic acid ester) also arbitrate BDNF-ERK-mediated neurotrophic action (Moosavi et al. 2015). Another polyphenol, ferulic acid, also mediates the CREB-BDNF signalling pathway (Yabe et al. 2010). Chrysin also modulates BDNF production and scavenges free radicals (Souza et al. 2015). Polyphenols such as curcumin target PI3K-Akt/CREB-ERK and insulin signalling pathways, thereby upregulating BDNF (Zhang et al. 2015). Topiramate increases BDNF expression and enhances the phosphorylation of TRKB (Mao et al. 2015). Polyphenol, harpagoside regulates the PI3K-Akt-ERK pathway to enhance the activity and expression of BDNF (Li et al. 2015). Oleuropein, an olive derived polyphenol was reported to increase the levels of BDNF and NGF levels in serum. Contradicting reports show reduced levels of BDNF in the hippocampus (Carito et al. 2014). Some phenolic compounds and non-phenolic compounds induce BDNF expression (Zhang and Tang 2006; Hoi et al. 2010; Zhang et al. 2011; Yuan et al. 2014; Sharma 2017).

Memory Retention

Flies were treated with two different concentrations of sesamol-conjugated lipoic acid derivative (30 μ M and 60 μ M) with three different diets: Maintenance Diet (MD), High-Fat Diet (HFD), and normal Sucrose Yeast Diet (SYD). In HFD, short term memory retention increased after the exposure to sesamol-conjugated lipoic acid derivative (Fig. 5). As the concentration increases, the retention was observed to have a gradual decrease in males. This indicates that up to a threshold point, the compound increases the memory retention in the drosophila males. But it decreases after crossing the threshold level. However, in the case of females, it showed an increase in short term memory retention, which increased gradually giving a positive response at all the concentrations. Thus, the threshold level of the compound is different for males and females.

But, in SYD, both males and females had an increase in short term memory retention, due to the administration of the sesamol-conjugated lipoic acid derivative (Fig. 6). Therefore, the memory retention was better in flies fed with normal diet. The females showed a better memory retention potential when compared to males. This is in accordance with the previously published data that states the difference in memory retention based on sexes. Many earlier studies have reported that females are better in memory retention as compared to males (Lowe, 2003; Loprinzi and Frith, 2018). Our data also represents the same conclusion. Further, our data indicates that diet also plays a pivotal role in memory retention. High fat diet consumption is capable of reducing the memorizing capability, and also reduces the therapeutic effect of drugs that might aid in memory retention.

The flies retained their long term memory at all the concentrations in both the diets even after 12 hours. This indicates that the sesamol conjugated lipoic acid derivative helps in retaining the memory at both short term duration as well as long term duration. Deterioration in long term memory retention is a physiological ailment in Alzheimer disease patients.

Conclusion

The TRKB-BDNF signalling pathway is known to regulate neurodegenerative diseases through a neuroprotective mechanism. Many factors can cause neurodegeneration, and ageing is one of the prominent factors. Neurodegeneration, memory loss, abdominal and visceral adiposity are characteristics of ageing. Specifically, hypertrophic adiposity is observed mostly in men (Palmer¹ and Kirkland 2017). Men are also most vulnerable to diabetes and cardiac myopathies (Mancuso and Bouchard 2019). The data obtained from insulin resistant obese male flies revealed that TRKB signalling is essential in reducing the effects of ageing and insulin resistance. Further, there are many phytochemicals which are used to treat neurological disorders by targeting TRKB signalling. They can be used to reduce the effects of ageing and insulin resistance. This is achieved by targeting the TRK receptors through activation of PI3K/Akt, ERK, CREB pathways, Nrf2 pathway; upregulation of antioxidant and detoxifying enzymes. In support of this observation, we also observed many genes, that are common between obesity related insulin resistance and AD. These genes might be responsible for regulating both diseases together. Insulin resistance is a well-known link between obesity and diabetes, but it is recently, linked to AD (De La Monte 2009; Ferreira et al. 2018). These reports are consistent with our observations on bioinformatic analysis and drosophila memory assay. The NGF and BDNF are early targets of the disease which ultimately leads to the symptoms of dementia and memory loss. BDNF/TRKB is a vital component of long term memory potentiation (J. Allen, J. Watson and Dawbarn, 2011; Wang et al., 2019). Since, our compound is able to show enhanced long-term memory retention in AD patients, we have attempted to relate this data to AD. We conclude that this data can be used as preliminary data to further investigate the pathway and molecular mechanisms adapted by this compound and establish it as a therapeutic agent for AD. We also hypothesize that this compound might be enhancing memory retention through BDNF/TRKB pathway. But a more insightful approach towards these genes might give a clear link between AD, ageing, insulin resistance, and obesity. Also, a better understanding of the neurotropic

effects and the molecular mechanisms of action for these compounds could help to design better dietary supplements to mitigate the effects of ageing.

Abbreviations

Nrf2

nuclear factor erythroid 2–related factor 2

NFκB

Nuclear Factor kappa-light-chain-enhancer of activated B cells

BDNF

Brain-derived neurotrophic factor

GEO

Gene Expression Omnibus

AD

Alzheimer's disease

TRKB

tropomyosin-related kinase B

SYD

Sugar yeast diet

HFD

High fat diet

NTF

neurotrophic factor

GABA

Gamma aminobutyric acid

PI3K

Phosphatidylinositol 3-kinases

AKT

Protein kinase B

ERK

Extracellular signal-regulated kinase

CREB

cAMP-response element binding protein

PKC

Protein kinase C

MAPK

mitogen-activated protein kinase

Bcl-xL

B-cell lymphoma-extra large

Bcl-2

B-cell lymphoma 2
NT4
Neurotrophin 4

Declarations

Ethics approval and consent to participate

This work did not require any ethics approval and consent to participate.

Consent for publication

Author consent is obtained

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

P.S, P.J, R.D, and K.T conceived, designed, and directed the study. P.J. and R.D. conducted synthesis. P.S, K.P, S.Y, S.D, and Y.S conducted experiments with drosophila. P.S, K.T were involved in writing and discussion of the manuscript.

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Tables

Table 1

The genes that were observed to be differentially expressed among the ageing flies and the high-sugar fed insulin-resistant obese flies are listed here as the common genes

Shared genes between ageing and high-sugar fed insulin-resistant obese flies	
CG4213	CG17633
CG13947	CG5853
Lsp1beta	CG13138
CG5080	Pim
CG31928	CG5096
CG31926	CG7300
CG31661	CG6724
CG17239	CG31869
CG17234	CG12517
Send1	CG16743
CG31681	CG14915
CG3597	Vm32E
Daw	Vha100-5
Odd	CG5867
Bsg25A	Vm34Ca
Elba3	CG16956
CG3036	CG31813
Jon25Biii	Ance
Jon25Bii	NimB2
Jon25Bi	CG43333
CG14036	Send2
Qtc	CG31775
CG14022	CG42586
CG14014	CG15263
Vm26Ab	CG15255
Vm26Ac	CG15254

Shared genes between ageing and high-sugar fed insulin-resistant obese flies	
Vm26Aa	CG15253
Psd	CG7631
CG13992	CG6870
Kr-h1	ninaD
Tig	CG33120
CG9527	CG10623
CG15818	CG10650
CG5958	AMD
Uro	Fon
LKR	CG13084
Tg	CG13083
Mur29B	FBP
Peritrophin-15b	CG17571
Peritrophin-15a	CG33510
CG13091	CG8677
Tsp29Fa	CG7881
Tsp29Fb	Cyp6w1
Mco1	CG1942
CG13113	CG12825
CG13114	Odc1
CG3841	Mal-A1
Mal-A3	Mal-A6
Mal-A4	Mal-A7

Table 2

Biological functions related to the common gene list of Alzheimer's disease and obesity related insulin resistance models of drosophila flies. This data was obtained through GeneMANIA.

Biological Function	FDR	Genes in network
detection of light stimulus	2.92E-07	14
Phototransduction	4.96E-07	13
detection of external stimulus	5.07E-07	14
detection of abiotic stimulus	5.07E-07	14
Rhabdomere	1.37042E-05	10
response to light stimulus	3.14106E-05	17
photoreceptor activity	0.000216117	6
response to radiation	0.000216117	17
cellular response to radiation	0.009136754	8
sensory perception of sound	0.013069066	9
cellular response to abiotic stimulus	0.027025423	8
cellular response to light stimulus	0.038283938	7
detection of visible light	0.046789133	6
sensory perception of mechanical stimulus	0.055660088	9
synapse assembly	0.074724231	12
detection of stimulus	0.083505031	15

Figures

Figure 1

Genome-wide representation of the similarities between pathways adopted by drosophila and humans in general. The data obtained through the REACTOME database. It is observable that most of the metabolic and regulatory pathways are similar in both organisms.

Figure 2

Venn diagram representing the number of intersecting genes among ageing fly data and high-sugar diet-fed insulin-resistant obese fly data. The diagram was made using InteractiVenn web-based tool. It represents the genes in common (98 genes) from both the datasets, within the intersecting region and the genes unique (384 from aging dataset and 1138 from the insulin resistant/Obese dataset) for each dataset within the subset regions, respectively.

Figure 3

Cluster enrichment analysis for the common set of genes (amongst AD and insulin resistant/Obese data set) performed through METASCAPE. Kappa score 0.3 was applied as the threshold to prepare the clustergram through the inbuilt software algorithm. The chances of randomness decreases with an increase in the value of $-\log_{10}(P)$

Figure 4

Diseases related to the common genes (amongst AD and insulin resistant/Obese data set) as obtained from METASCAPE Human data. The chances of randomness decreases with an increase in the value of $-\log_{10}(P)$

Figure 5

Short term memory retention graph: flies treated with a High-Fat diet containing different concentrations of sesamol-conjugated lipoic acid derivative for 21 days and a set of flies treated with a maintenance media (MM) only were analyzed and represented as the percentage of flies capable of memory retention.

Figure 6

Short term memory retention graph. The flies treated with a Sucrose Yeast diet containing different concentrations of sesamol-conjugated lipoic acid derivative for 21 days, and a set of flies treated with maintenance media (MM) only were analyzed and represented as the percentage of flies capable of memory retention.

Supplementary Files

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