**Supporting information**

**Supporting table**

**S2 Table. Nodes and links with references.**

|  |  |  |
| --- | --- | --- |
| **Nodes** | **3 Letter Code** | **Outgoing Links** |
| Activin A | ata | btc1(1) | ctk0(2) | adp0(3) | ins1(4) |   |   |   |   |   |   |   |   |   |   |
| Adiponectin | and | ffa0(5) | inr0(6) | fty1(7–9) | tri0(5) | ata1(10) | ina1(11,12) | fdi0(13) |   |   |   |   |   |   |   |
| Adipose Tissue | adp | ctk1(14) | and1(15) | lep1(16–19) | sfr1(20,21) | ata1(3) | tnf1(22) |   |   |   |   |   |   |   |   |
| Aggression# | agr | cts1(23,24) | chl0(25) | egf1(24,26,27) | et11(28) | ngf1(29–33) | bdn1(34) | dop1(35,36) | ser0(35,36) | edp1(37,38) | cck1(39) | tet1(23) | igf1(40,41) |   |   |
| α-Melanocyte Stimulating Hormone (α- MSH) | msh | tri0(42) | ina1(42,43) | agr1(44–46) | msl1(47) | adp0(43) | ctk0(48) | fdi0(42,49,50) |   |   |   |   |   |   |   |
| Angiogenesis | ang | bgl1\* |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Anti-oxidants | aox | inr0(51) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Arginine Vasopressin | avp | agr1(52) | cfn1(53–55) | ins1(56) | gng1(57) |   |   |   |   |   |   |   |   |   |   |
| β-Adrenergic Receptors | bar | adp0(58,59) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| β Cells | btc | ins1(60) |  gap1(61) |   |   |   |   |   |   |   |   |   |   |   |   |
| Bone Strength/ Bone Mass | ost | ocl1(62) |   |  |  |  |  |  |  |  |  |  |  |  |  |
| Brain-Derived Neurotrophic Factor (BDNF) | bdn | btc1(63) | ina1(64–66) | cfn1(67) | ser1(68) | fdi0(64,67,69) |   |   |   |   |   |   |   |   |   |
| Brain Glucose | bgl | cfn1(70) | fdi0(71,72) |   |  |  |  |  |  |  |  |  |  |  |  |
| Cholecystokinin | cck | ina1(73) | fdi0(74–80) | gst0(81) | ins1(82) |  |  |  |  |  |  |  |  |  |  |
| Cholesterol | chl | ser1(83) | inr1(84) | agr0(83,85) | cfn1(86) |  |  |  |  |  |  |  |  |  |  |
| Cocaine and Amphetamine Regulated Transcript (CART) | car | fdi0(87,88) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Cognitive Functions | cfn | bgl0\* | dip1\* |   |   |   |   |   |   |   |   |   |   |   |   |
| Cortico-Releasing Hormone (CRH) | crh | fdi0(89) | cts1(90–95) | agr0(96,97) | ins1(56) | edp1(98,99) |   |  |  |  |  |  |  |  |  |
| Corticosteroids | cts | tri0(100,101) | gng1(102–104) | ina0(105–112) | agr0(113) | inr0(114–117) | ffa1(100,101) | ins0(118,119) |   |   |   |   |   |   |   |
| Cytokines | ctk | edp1(99,120) | crh1(121–123) | lep1(124,125) | inr1\* | oxy1(126) | avp1(126) | ina0(127,128) | klt0(129) | et11(130) |   |   |   |   |   |
| Diplomat Behaviour## | dip | ins1(131) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Dopamine | dop | nep0(132) | agr1(132,133) | ost1(134) | ocl1(135) | ina1(136) | ins0(137,138) | fdi0(137,139) | msl1(140) | lep0(141) | il61(141) | and1(141) | ffa0(137) | tri0(137) | pgl0(137) |
| Endorphins | edp | bdn1(142) | ina1(143) | agr0(144) | fdi1/0(50,145,146) |   |   |   |  |  |  |  |  |  |  |
| Endothelin-1 | et1 | ghr1(147,148) | ina0(149–151) | agr1(28) | ins1(152) | lep1(153) | vdl0(154–156) |   |  |  |  |  |  |  |  |
| Epidermal Growth Factor (EGF) | egf | btc1(157,158) | bdn1(159) | ina1(160) | fty1(161–164) | noc0(165) |   |   |   |   |   |   |   |   |   |
| Erythropoeitin | epo | ang1(166,167) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Exercise# | exe | adp0(168) |  il61(169) |  |  |  |  |  |  |  |  |  |  |  |  |
| Fertility+ | fty | egf1(170) | otg1(171) | oxy1(172) |   |   |   |   |   |   |   |   |   |   |   |
| Food Intake | fdi | adp1(173) | agr0(174) | msl1\* | ffa1\* | ins1(175) | pgl1\* |   |  |  |  |  |  |  |  |
| Free Fatty Acids | ffa | inj0(176) | ina0(176–179) | bdn0(177) | gng1(180) |   |   |   |   |   |   |   |   |   |   |
| γ-Aminobutyric acid (GABA brain) | gab | grh1(181) | agr1/0(182–184) | fdi1/0(185–188) |  |  |  |  |  |   |   |   |   |   |   |
| GABA pancreas | gap | inr0(189) | btc1(190) |  |  |  |  |  |  |  |  |  |  |  |  |
| Gastrin | gst | btc1(191) | agr1(192) | ina1(193) | adp0(193) |   |   |   |   |   |   |   |   |   |   |
| Ghrelin | ghr | agr1(194) | fdi1(195–201) | hgh1(147,197,198,202–206) | ins1(207) | gab1(208,209) | et10(210) |   |   |   |   |   |   |   |   |
| Glucagon++ | glg | gng1(211–213) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Glucagon-Like Peptide-1 (GLP-1) | glp | ins1(214,215) | btc1(215,216) | glg0(217) | gmo0(218) | fdi0(218) | ina1(218) | ost1(219) |  |  |  |  |  |  |  |
| Gluconeogenesis | gng | pgl1(211,213) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Glucose Transporter-1 (GLUT-1) | gt1 | bgl1(220) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Gonadotropin-Releasing Hormone (GnRH) | grh | tet1(221,222) |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Growth Hormone | hgh | msl1(223–225) | agr1(226) | ins1(227,228) | ina0(227–232) | igf1(228,231,233–235) | fty1(233) |   |   |   |   |   |   |   |   |
| Gut Motility | gmo | glp1\* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histamine | hst | fdi0(236–239) | agr1(240) |   |   |   |   |   |   |   |   |   |   |   |   |
| Inflammatory Response$ | inr | ina0(241) |   |   |   |   |   |   |   |   |   |   |   |  |  |
| Injury (Growth Factors) | inj | btc1(242,243) | hst1(244) | adp0(245) | ins0(245) | inr0(246) | ina1(245) | agr0(247) | ang1(248) |   |   |   |   |  |  |
| Insulin | ins | btc1(158) | lep1(16,249) | klt1(250) | egf1(161,251) | cfn1(252–256) | et11(257) | grh1(258) | ktg0(259) | and0(260,261) | nox1(262,263) | gmo1(264) |   |  |  |
| Insulin Action$$ | ina | pgl0(265,266) | gng0(212,267,268) | msl1(269) | ost1(270,271) | adp1(272,273) | tri1(274,275) |   |   |   |   |   |   |  |  |
| Insulin-like Growth Factor (IGF-1) | igf | ina1(234,276–283) | btc1(284) | fdi0(266,283) | adp0(277,283) | msl1(285–288) | ins0(282,289) | hgh0(290–292) | ost1(290) | ctk0(293) | tnf0(293) |   |   |   |   |
| Interleukin-6 (IL-6) | il6 | agr0(294) | ina0(295,296) | adp0(297) |  fdi0(298) |  inr0(299) |  glp1(300) |   |   |   |   |   |   |   |   |
| Keto Acids | ktg | cfn1(301) | ins1(302,303) | inr0(304) |   |   |   |   |   |   |   |   |   |   |   |
| Klotho | klt | fty0(305,306) | ins1(307) | aox1(308) | ang1(309) | inr0(310,311) | adp1(312,313) | ina0(312,314) |   |   |   |   |   |   |   |
| Leptin | lep | inr1(17) | car1(111,315,316) | ang1(317–320) | cfn1(321) | et11(322,323) | ffa0(324) | ser1/0(325,326) |   |   |   |   |   |   |   |
| Leptin Action$$ | lpa | fdi0(316,327–330) | adp0(329–331) | tri0(327,330) |   |   |   |   |   |   |   |   |   |   |   |
| Melatonin | mlt | agr1(332) | ina1(333–337) | adp0(338–341) | msl1(342,343) | ost1(341,344) | ocl1(344) | lep0(345,346) | ins0(339,340,345,346) | pgl0(338) | tri0(338,346) |   |   |   |   |
| Muscle Strength/ Muscle Mass | msl | agr1(347) | ina1(347) | inr0(299) |   |   |   |   |   |   |   |   |   |   |   |
| Myostatin | myo | msl0(348–353) | ina0(353–356) | adp1(351,353,355,356) | tnf1(355) |   |   |   |   |   |   |   |   |   |   |
| Nerve Growth Factor (NGF) | ngf | bdn1(159,357) | noc1(358–360) |   |   |   |   |   |   |   |   |   |   |   |   |
| Nitric Oxide | nox | vdl1(262,361) | ang1(248,362) | nep0(363) | dop0(363) | agr1/0(364–369) |   |   |   |   |   |   |   |   |   |
| Nociception | noc | ina0(370) |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nor-epinephrine | nep | agr0(132) | ina0(371) | crh1(372) |   |   |   |   |   |   |   |   |   |   |   |
| Oestrogen | otg | ocl1(373) | hgh1(374–376) | fty1(377) | fdi0(378) | agr1(379–385) | gmo0(386) | ang1(387–390) | ina1/0(391–393) | inr1/0(390,394) |   |   |   |   |   |
| Osteocalcin | ocl | ina1(395–397) | glp1(398) | ins1(395,396) | and1(395,396) | tet1(399,400) |   |   |   |   |   |   |   |   |   |
| Oxytocin | oxy | agr1/0(401–404) | adp0(405,406) | fdi0(407) | gng1(57) | glg1(408) | cts1/0(409–411) | noc0(412) |   |   |   |   |   |   |   |
| Plasma Glucose | pgl | ins1(413) | bgl1(414) | glg0(415) | ghr0(416) | gt10(220,417) | ata1(2) |   |   |   |   |   |   |   |   |
| Secreted Frizzled-Related Protein 5 (SFRP-5) | sfr | adp1/0(21,418) | inr0(418) |   |   |   |   |   |   |   |   |   |   |   |   |
| Serotonin | ser | cfn1(419–425) | dop0(426) | ost0(427–430) | agr0(367,431–440) | inr1(441–445) | fdi0(446–450) | ina0(371,451–453) |   |   |   |   |   |   |   |
| Symapathetic Stimulation | sys | gng1(211) | ina1(454) | adp0(455,456) | egf1(457) |   |   |   |   |   |   |   |   |   |   |
| Testosterone | tet | dip0(458) | aox1(459) | epo1(460) | agr1(369,379,380,385) | ang1(461) | edp0(462) | msh0(462) | egf1(161,463) | myo0(464) | msl1(465,466) | ocl1(373) | adp0(467–471) | ina1/0(468,469,472) |   |
| Triglycerides | tri | adp1(473) | ina0(473) |  |  |  |  |  |  |  |  |  |  |  |  |
| Tumor necrosis factor-α (TNF-α) | tnf | nep0(474) | inr1(475) | ina0(295,476) | ata1(477,478) | il61(479,480) | lep1(124,125,249,250,259) | klt0(129,481) | et11(482) |   |   |   |   |   |   |
| Vasodilation | vdl | bgl1\* | ina1(483) |   |   |   |   |   |   |   |   |   |   |   |   |
| Vitamin B12 | v12 | hgh1(235) | noc0(484) | ost1(235) | igf1(235) | inr0(484) |   |  |  |  |  |  |  |  |  |
| Vitamin D3 | vd3 | ina1(485,486) | ost1(487) | agr1(488) | ins1(486,489) |   |   |   |   |   |   |   |   |   |   |

S2 Table Footnotes.

\*Logical interactions – Some interactions were added which did not have a specific reference, but were obvious, logical or evident. For example, food intake increases plasma glucose, plasma free fatty acids, muscle energy, or fat storage are such obvious links. It is also logical that increased capillary density would increase glucose transport. There were nine such logical interactions in the model for which references are not cited.

#Physical exercise versus physical aggression: We differentiated the two nodes exercise and physical aggression for the following reasons. The node exercise, here, refers to calorie consumption aspect of exercises reducing obesity. This is the classical concept of exercise which is generally prescribed to counter T2DM. However exercise also has a number of direct neuroendocrine effects which are less appreciated. Apart from calorie burning exercise has many behavioural components that trigger behavioural endocrine signals. For example running and chasing may be energetically the same but endocrinologically different. A number of studies show that insulin sensitivity can increase substantially by exercise even without loss of weight or total fat which demonstrates that exercise has direct effects on insulin sensitivity independent of weight loss(490–493). We therefore segregate the energy component and behavioural components of exercise which are labeled as exercise and physical aggression. These two nodes were treated as separate and independent nodes with exercise having links to energy pathway and aggression having links to behavioural pathways.

##Diplomat behaviour: Diplomat behavior refers to social manipulation and the ability to do so. Physical aggression and diplomat behaviourplay diametrically opposite roles in the pathophysiology of Type 2 Diabetes and related disorders (494,495). Insulin is shown to affect social behaviour in humans independent of glucose(496).

+Fertility: The node fertility refers to changes in menstrual cycle (if any)/ number of pregnancies/ litter size/ rate of abortion/ number of implantation sites/ uterine weight/ mammary gland size/ amount of milk produced or composition of milk in females; and number of successful (with ejaculation) copulations/ testis size/ testis weight/ epididymal weight/ seminal vesicle weight/ number of leydig cells/ number of sertoli cells/ germ cell apoptosis/ sperm count (at different stages of cell development) or sperm motility in males. Infertility is significantly associated with T2DM and a number of components of fertility are affected by insulin resistance and vice versa(497,498).

++Glucagon to insulin link is a self-negating link since both up-regulatory(499–502) and down-regulatory(503) effects have been demonstrated. Such self-negating links were generally filtered out. However since both molecules are believed to be central to glucose regulation, we simulated the model with both types of links separately. This did not affect bi-stability. In case of glucagon up-regulating insulin, both glucagon and insulin lay in the insulin resistant basin of attraction but in case of glucagon down-regulating insulin, glucagon changed the cluster and lay in the insulin sensitive basin of attraction. Apart from this there was no significant change in the attractor signatures or the basins of attraction in both the cases.

$Reactive oxygen species (ROS) is considered an important player in the pathophysiology of T2DM. During redundancy filtering ROS was filtered out since it was tightly linked to inflammation and both shared identical incoming and outgoing arrows. But since ROS is believed to be an important player, we simulated keeping ROS as a separate node. This change again did not affect bi-stability and up-regulation of ROS led to insulin resistant state.

$$Insulin action and leptin action are two nodes in the network which represent the action of insulin and leptin at the receptor level. When the state value of these nodes is +1, they represent the insulin sensitive or the leptin sensitive state and when their state value is -1, they represent the insulin resistant or the leptin resistant states respectively. Thus the action node represents the resistance sensitivity axis.

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