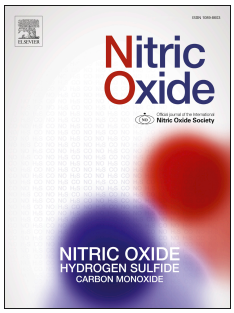
Accepted Manuscript



A high fat diet induces sex-specific differences in hepatic lipid metabolism and nitrite/nitrate in rats

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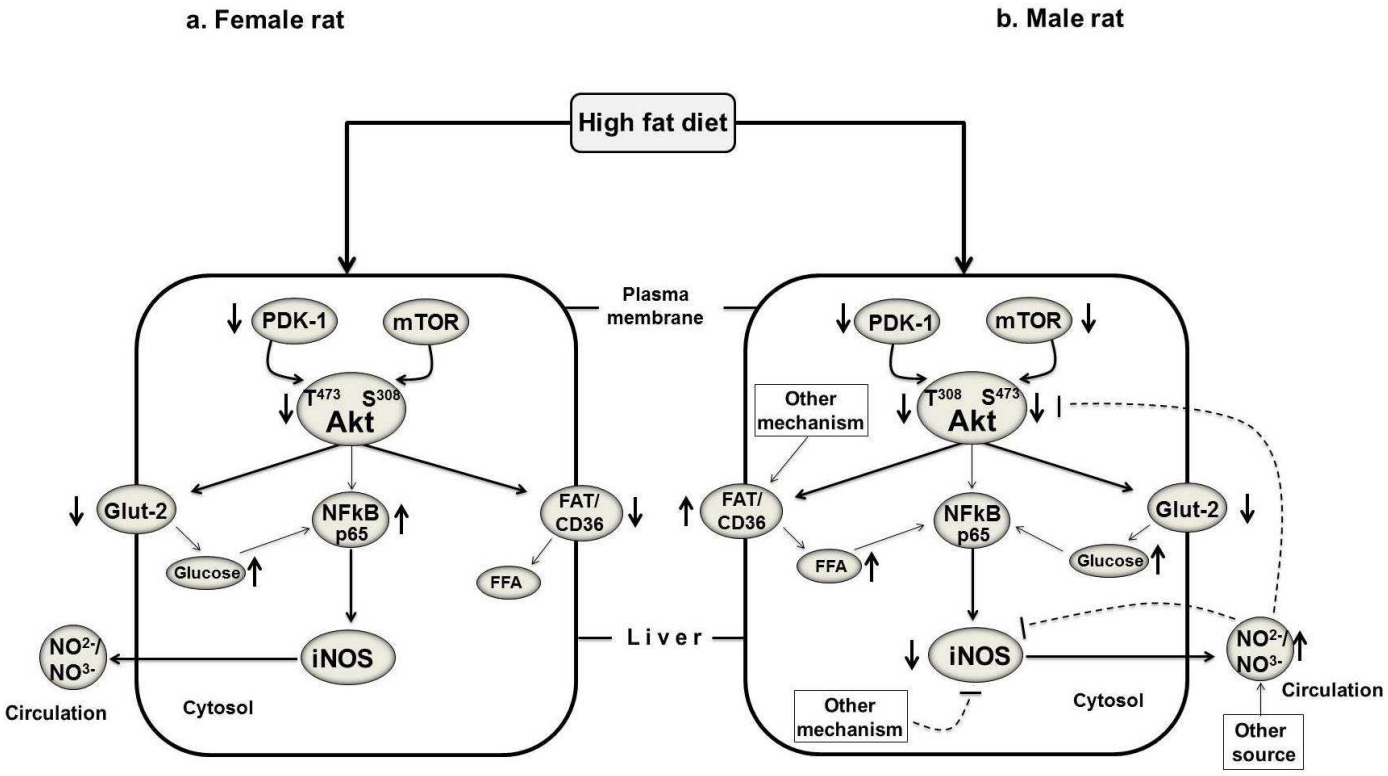
Graphical abstract



The proposed mechanism by which a HF diet induces altered hepatic lipid metabolism and affects regulation of hepatic iNOS expression and nitrite/nitrate production in a sex-specific manner in rats. Altered hepatic lipid metabolism caused by a HF diet influence iNOS/NO pathway and thus promotes IR by attenuating insulin action. This is likely a consequence of decreased Akt activation by PDK-1 and mTOR, which further allows regulation of glucose and FFA membrane transporters. Differences in HF-fed female and male rats in IR manifestation, insulin signalling disturbance, iNOS induction and nitrite/nitrate production is likely due to protective effects of estradiol which mitigate effects of a HF diet on insulin action. Among other mechanisms, large amounts of nitrite/nitrate produced in other tissues may easily enter the liver and inhibit iNOS protein expression, but also disturb insulin action. Akt, protein kinase B; FAT/CD36, fatty acid translocase/cluster of differentiation 36; FFA, free fatty acids; Glut-2, glucose transporter 2; IR, insulin resistance; p65, p65 subunit of nuclear factor κB; iNOS, inducible nitric oxide (NO) synthase; mTOR, mammalian target of rapamycin; NO^{2-}/NO^{3-}, nitrite/nitrate; PDK-1, phosphoinositide-dependent kinase-1.