CONCLUSIONS

In summary, the study focused on the role of endogeneous SARM1 induced in the presence of the mitochondrial complex I inhibitor rotenone in the regulation of mitochondrial homeostasis, its clearance and subsequent neurodegeneration using both in vitro cellular and in vivo *Drosophila melanogaster* models.

The major findings of the study are:

1. SARM1 is responsible for rotenone induced neuronal cell death and deregulation of the ETC genes.

    - SARM1 causes rotenone induced cell death in SH-SY5Y cells.
    - Rotenone mediated upregulation of SARM1 is also associated with loss of mitochondrial membrane potential.
    - Rotenone treatment results in de-regulation of ETC complex genes in SH-SY5Y cells.
    - In the absence of SARM1, rotenone treatment reverses cell death and ETC complex gene expression.
    - Over expression of SARM1 results in cell death and de-regulation of ETC complex genes.
    - NR or nimodipine administration reduces cellular stress that may lead to partial reversal of SARM1 expression, deregulation of ETC genes and subsequent cell death. This suggests that accumulated cellular stress following lowering of NAD^+ levels via the TIR domain of SARM1 and higher calcium influx may play a role in SARM1 mediated cell death via deregulation of ETC complex gene at the mitochondria.

2. ROS is not the executioner of rotenone induced cell death and the inflammation-autophagy axis may lead to induction of endogenous SARM1 and subsequent apoptosis following rotenone treatment.

    - Rotenone induced ROS generation is not the sole player in SARM1 mediated cell death.

- SARM1 induction and subsequent cell death is rotenone specific, as other ETC complex inhibitors do not result in SARM1 upregulation.

- Rotenone treatment in SH-SY5Y cells leads to blockage of autophagic flux that may results in SARM1 induction which could induce apoptosis further.

- Rotenone mediated inflammatory responses may trigger SARM1 upregulation in these cells.

3. dSarm signalling network causes motor deficits and reduced lifespan in rotenone treated w^{1118} flies.

    - In vivo studies using aging w^{1118} flies showed that activation of the dSarm signalling network results in rapid loss of dopaminergic neurons of w^{1118} flies that eventually leads to motor deficits and reduced lifespan in the rotenone-treated flies.

    - This effect could be partially reversed in the presence of the anti-inflammatory molecule resveratrol indicating that targeting the inflammation induced dSarm pathway could play an important role in the age-associated neuronal loss (Fig.5.1).

    - The aging model established in flies will help us better understand the increased susceptibility to age-dependent progressive loss of dopaminergic neurons following rotenone exposure.

    - Thus, targeting SARM1 or the use of anti-inflammatory compounds to reduce its levels could open up cost-effective exciting avenues in the treatment of PD and other age-associated neurodegenerative diseases.

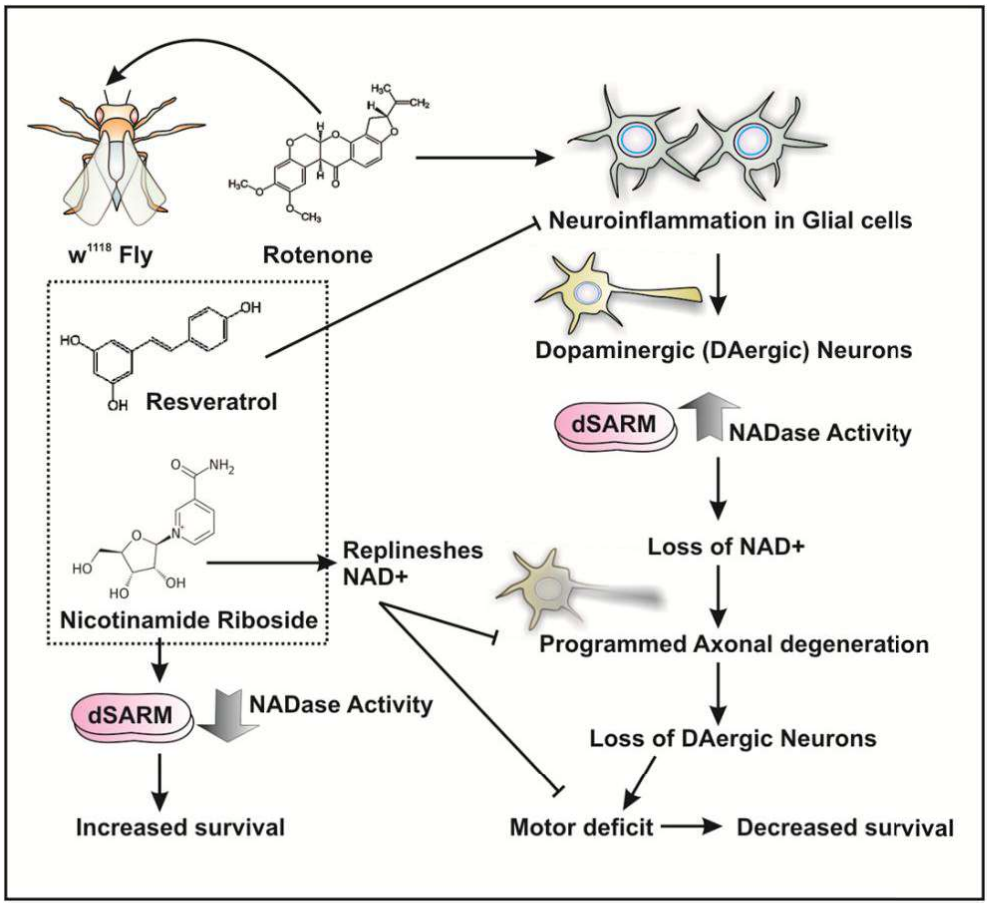

Fig. 73. Proposed model for study with Drosophila as the model system. Exposure to rotenone (pesticide) stimulates production of *Eiger* in the brain milieu of w^{1118} flies that further mediates the increased expression of the *Ect4* or *dSarm* (NADase) from dopaminergic neurons. This, in turn, induces the rapid loss of these neurons that ultimately leads to severe motor deficits and loss of survival. Presence of the anti-inflammatory molecule resveratrol or the NAD^+ supplement NR can partially reverse rotenone-induced neurotoxicity