Table S.1 – Animal characterization

	6-months old		12-months old	
	Control	**GK**	**Control**	**GK**
Body Weight (g)	471,60 ± 15,14	370,00 ± 6,09****	512,50 ± 15,11	415,00 ± 6,75****
Glucose (mg/dl)	117,40 ± 9,89	212,00 ± 18,30**	121,40 ± 10,28	269,10 ± 18,77****

Animal´s characterization table. Data represents mean ± SEM from 6 independent animals. Statistical significance: ****p<0.0001 when compared with age-matched controls counterparts. GK- Goto-kakizaki rats.

S.1- Prolonged high glucose conditions lead to decreased mitochondrial membrane potential with an increase in mitochondrial ROS production.

Previous work from our lab has clearly demonstrated that mitochondrial dysfunction is a key component of brain dysfunction under diabetic conditions however, the mechanisms underlying the appearance of mitochondrial anomalies in such conditions remain elusive. Thus, and after establishing the veracity of our hypothesis "brain WWOX alterations occur under T2D-brain conditions" we try to elucidate if WWOX-mitochondria interactions can be in the genesis of T2D-associated neurodegenerative events. We started by performing a screening in glucose concentrations and incubation times in order to establish the optimal work conditions. Here, we clearly demonstrated that only a chronic (48h) incubation with 25mM glucose can induced a decrease in mitochondrial membrane potential (ΔΨm) and cell viability (Fig. 2A and 2B). Further, although a slight increase in mitochondrial ROS production can already be observed after 24h of incubation it is only statistically significant after 48h of incubation (Fig. 2C).

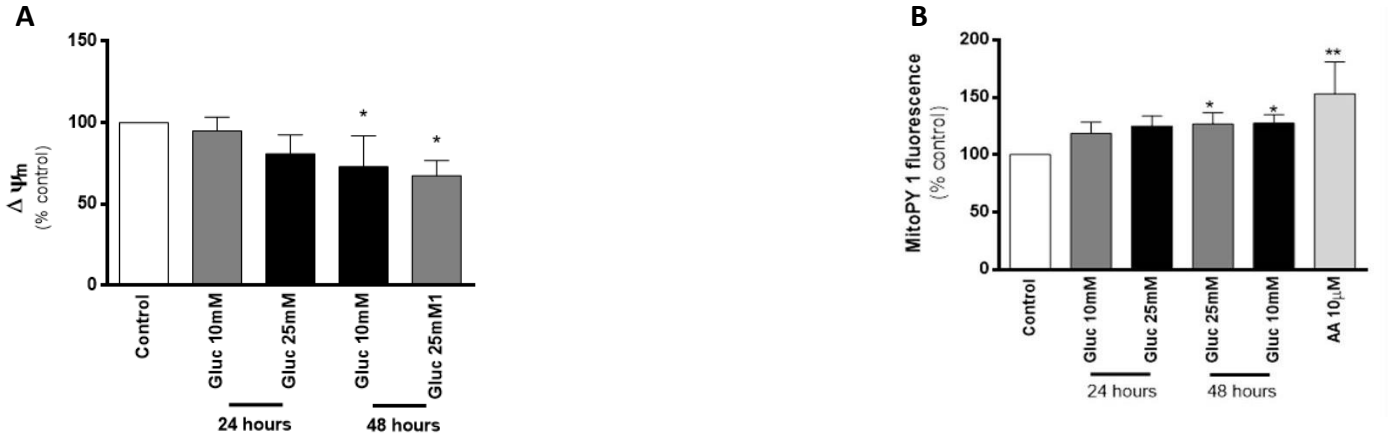

Figure S.1- The effect of high glucose in mitochondria and cell viability. (A) mitochondrial membrane potential (ΔΨm) and; (B) mitochondrial ROS production. Data shown represent mean ± SEM from 6-8 experiments. Statistical significance: *p<0.05; **p<0.01 when compared with control condition.

S.2 -Hyperglycemia leads to increased p53 levels and caspase3 activation

Furthermore, we also observed that an increase in p53 levels occurs in early stages of the incubation while caspases activation seems to occur only 48h after the beginning of high glucose incubation

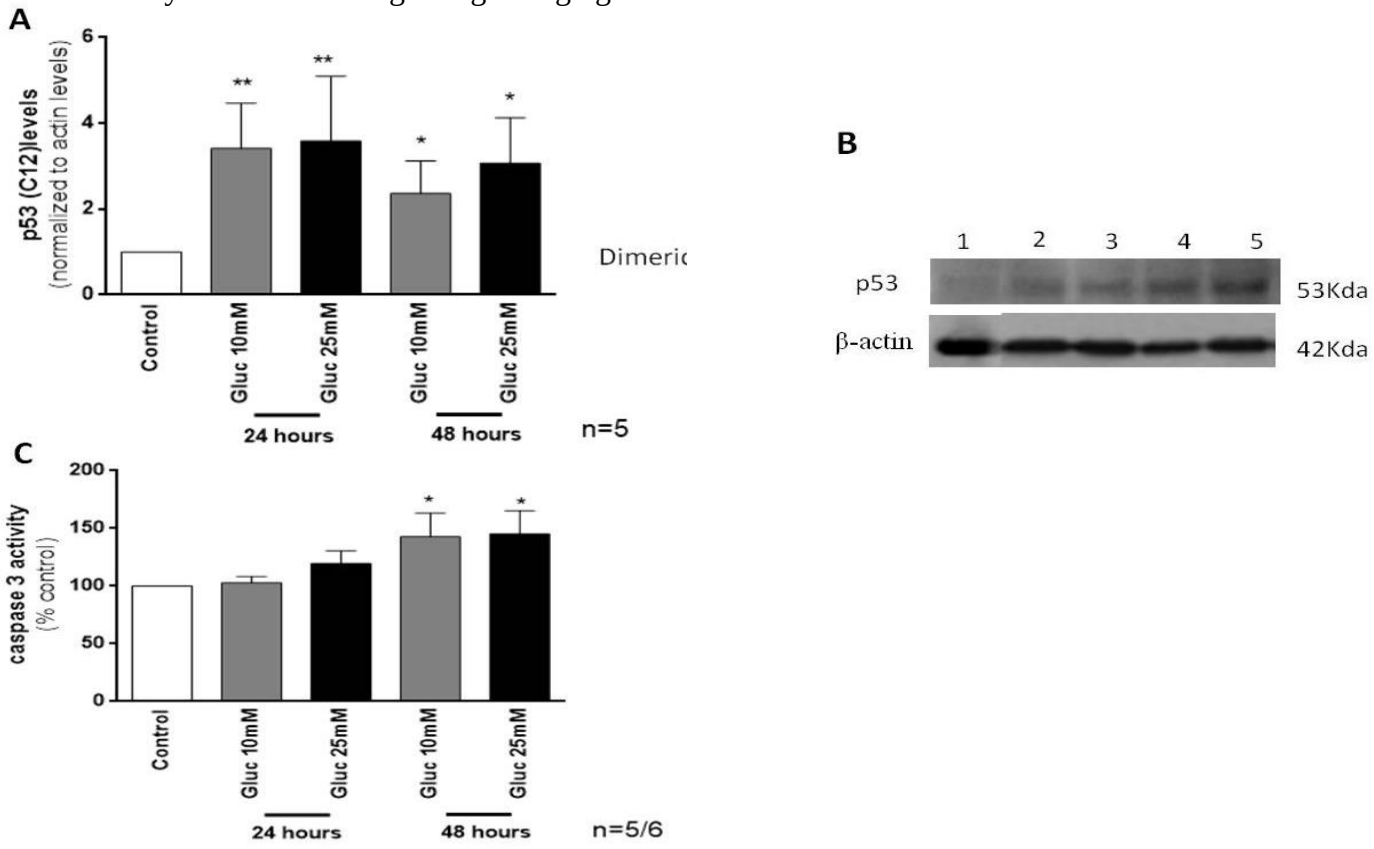

Figure S.2- The effect of high glucose in p53 and caspase 3 activation. (A) P53 levels; (B) Western blot representative images and; (C) caspase 3 activity. Data shown represent mean ± SEM from 5/6 independent experiments. Statistical significance: *p<0.05 when compared with control condition