DIABETES TYPE 2 AS A RISK FACTOR OF NEURODEGENERATION DEVELOPMENT AND COGNITIVE IMPAIRMENT IN DB/DB MICE

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DB/DB MICE AS A MODEL OF DIABETES T2

Diabetes T2 is a serious problem of health all over the world.
One of the important problem is neurodegeneration development,
and search of new approaches for prevention and treatment of this process.
Several experimental models were developed of diabetes T2, among them

– genetic model in db/db mice, related to leptin deficiency.

The aim: to investigate neurodegenerative disturbances in db/db mice and evaluate the effect of trehalose on neurodegeneration development.

ЗАГОЛОВОК

The **acoustic startle reflex (ASR)** is a short and intense defensive reaction in response to a loud and unexpected acoustic stimulus. The ASR can be modulated through sensorimotor gating processes, such as **prepulse inhibition (PPI)**, a neurological phenomenon in which a weak pre-stimulus inhibits the reaction to a startling stimulus. The reduction of the amplitude of ASR reflects the ability of the CNS to adapt to a salient sensory stimulus when a preceding weaker signal is perceived so that attention may be focused on more salient features of the environment. Reduced PPI, which is thought to reflect dysfunction of sensorimotor gating, is reported in patients with psychiatric disorders, such as schizophrenia, bipolar disorder, and post-traumatic stress disorder (PTSD), and in animal models of these disorders. (Shoji, Miyakawa, 2018; Hormigo, López, 2019).

METHODS

Pre-pulse inhibition (PPI) test

The test for pre-stimulus inhibition of the flinching reaction (PPI) was performed in a sound-attenuating chamber SR-Lab Startle Response System. Background noise was 65 dB. A session was initiated with a 3-min acclimation period followed by ten presentations of startle pulses-alone (110 dB) – Blocks 1. Trial types for the PPI included four different prepulse intensities (72, 78, 82, 86 dB); each prepulse preceded the startle pulse (110 dB) by a 40-ms inter-stimulus interval and was presented ten times in random order (Blocks 2 and 3). Inter-trial intervals varied from 5 to 25 s. Block 4 contained the exact ten startle pulses trials as Block 1.

Calculate the %PPI for each prepulse intensity: %PPI = 100 × [(pulse-alone) – (prepulse + pulse)]/pulse-alone where the pulse-alone is the average of pulse-alone values from Blocks 2 and 3. A measure of habituation to the sound signal = 100 ×[(pulse-alone from Blocks 4 - pulse-alone from Blocks 1)/ pulse-alone from Blocks 1].

Statistical analysis. Results are presented as mean ± S.E.M. and were analyzed using a two-way ANOVA followed by a post-hoc Fischer's LSD test. $p<0.05$ was regarded as statistically significant.

RESULTS

PPI of the ASR

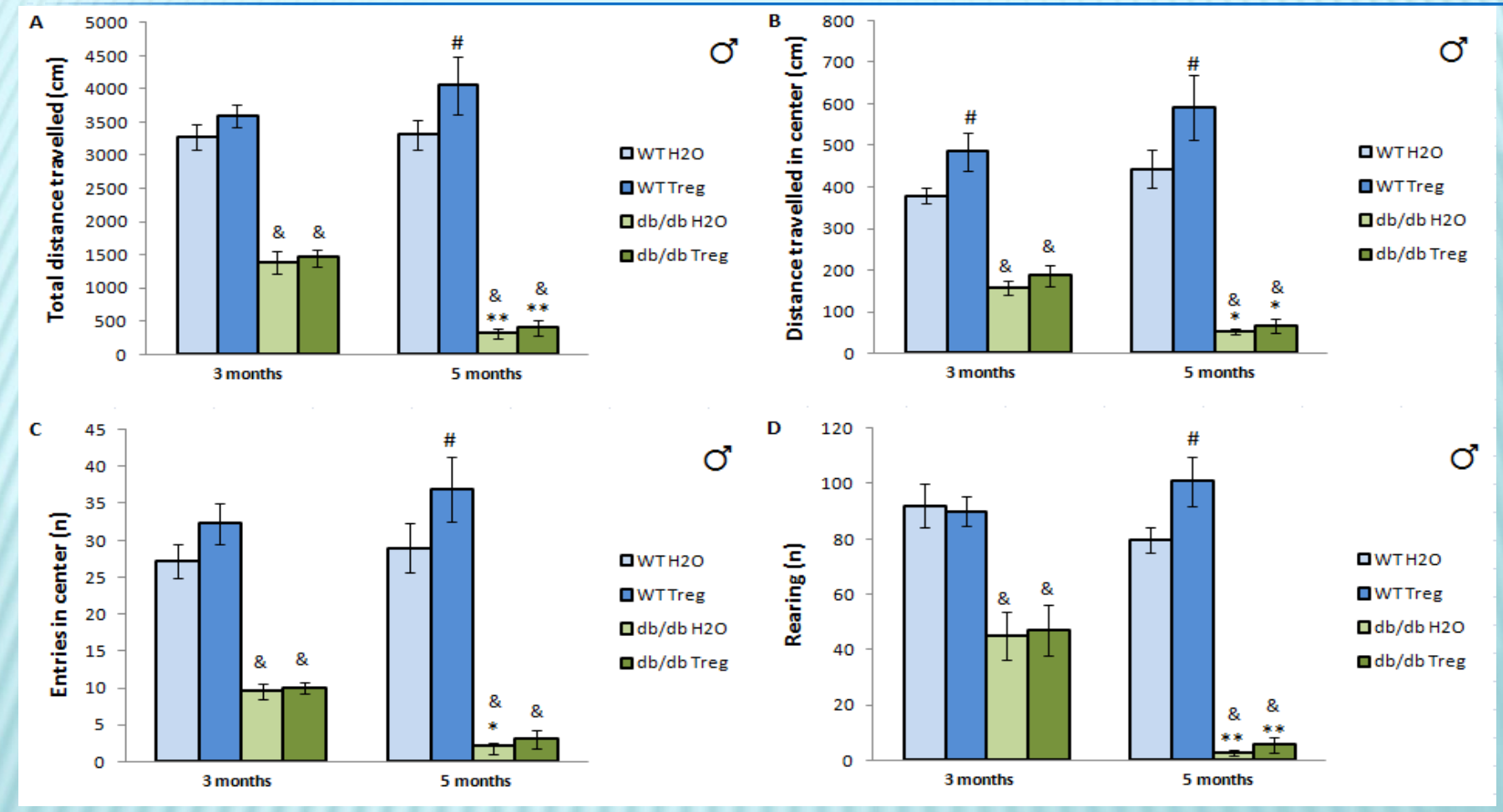
A significant decrease in % PPI of the ASR in db/db mice vs WT was observed (Fig.1). Calculated by two-way ANOVA the results show genotype effect on PPI for all prepulse intensities: 72 dB ($p<0.01$; $F=9.72$), 78dB ($p<0.01$; $F=7.35$), 82 dB ($p<0.001$; $F=13.98$), 86 dB ($p<0.05$; $F=4.05$), Global ($p<0.01$; $F=10.21$). Trehalose did not have a significant influence on PPI in WT and db/db mice (drug factor: Global ($p=0.53$; $F=0.41$).

ASR

There were significant difference between the db/db mice and WT mice in the ASR (genotype effect: $p<0.01$; $F=10.86$). Post-hoc test showed a significant increase the ASR in db/db-H2O mice vs WT ($p<0.05$). In db/db mice that consumed trehalose, the ASR did not differ from the WT mice (Fig. 2).

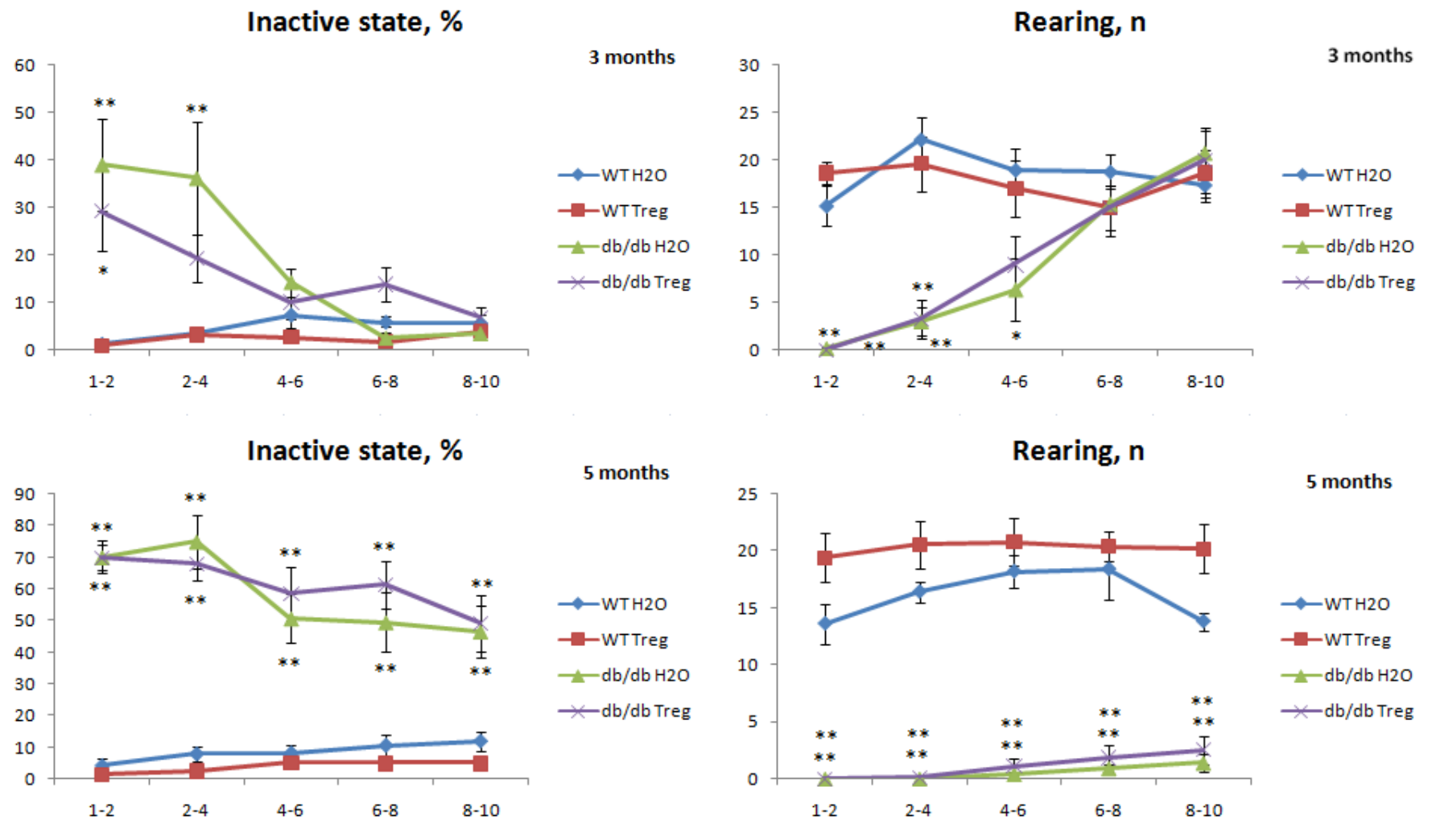
Differences in the habituation reaction to the sound signal were revealed in WT and db/db mice (Fig. 3). In WT mice ASR declined from block 1 to block 4 by more than 40%, while in db/db mice increased by 17% ($p<0.05$ vs WT mice). In db/db mice that consumed trehalose, the ASR decreased by 17%.

BEHAVIOR OF WT AND DB/DB MALE MICE IN OPEN FIELD TEST, THE INFLUENCE OF TREHALOSE



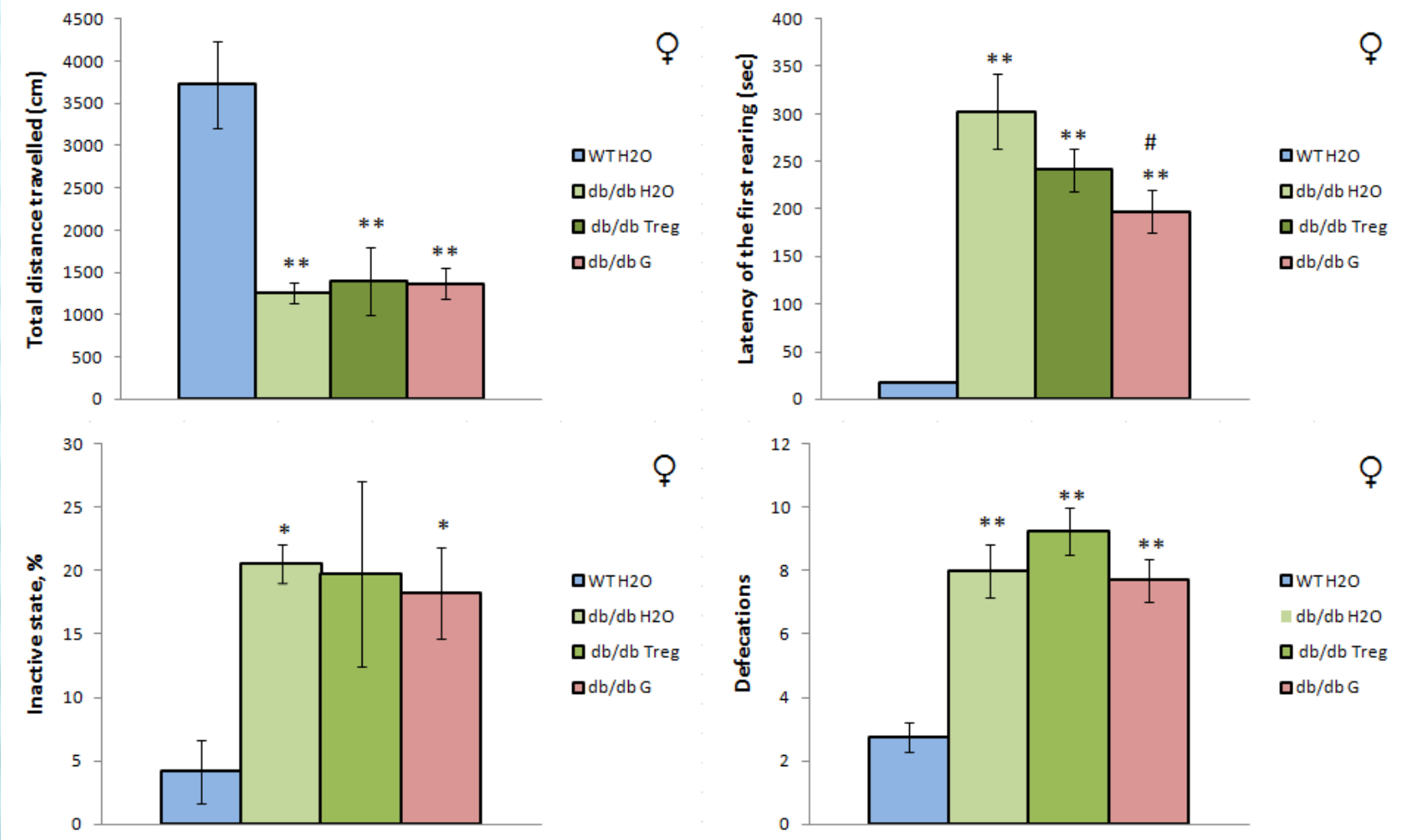
* p<0.05,** p<0.001 - 3 month vs 5 month old mice,
& p<0.001 - db/db vs WT,
# p<0.05 - trehalose vs H_2O.

THE DYNAMICS OF BEHAVIOR OF DB/DB MALE MICE IN OPEN FIELD TEST AT TWO-MINUTE INTERVALS



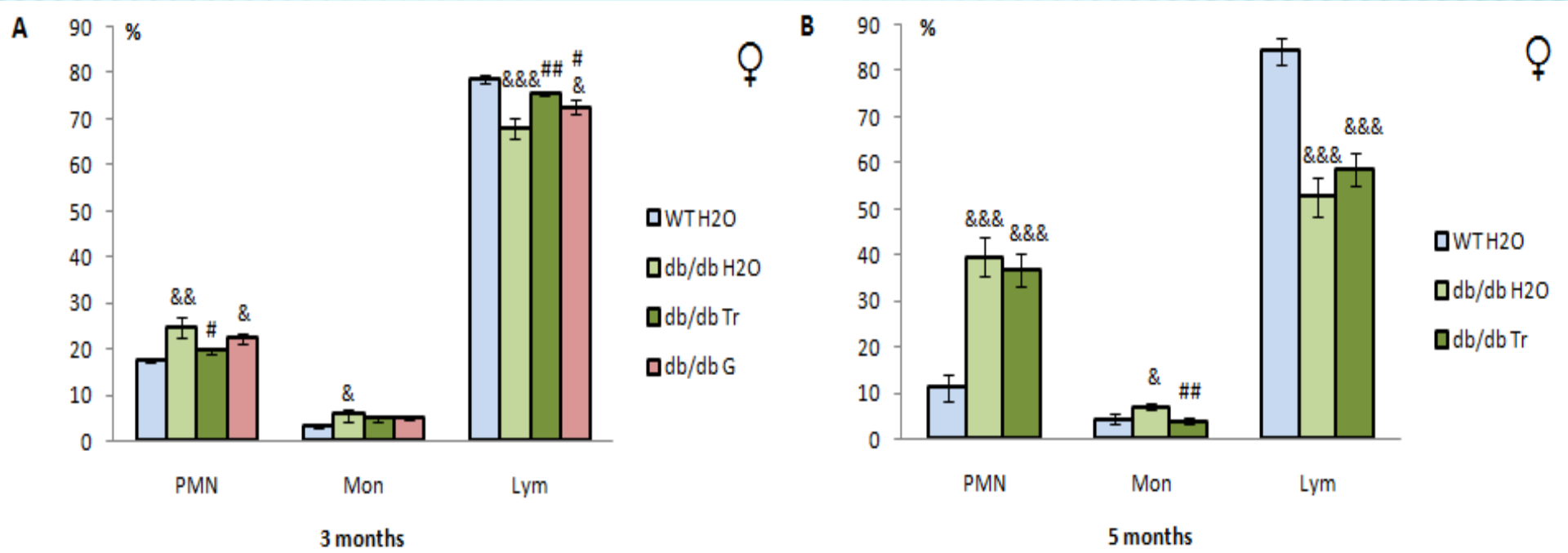
* p<0.01,** p<0.001 db/db vs WT mice

BEHAVIOR OF WT AND DB/DB FEMALE MICE IN OPEN FIELD TEST, THE INFLUENCE OF TREHALOSE (TREG) AND LIRAGLUTIDE (G) .



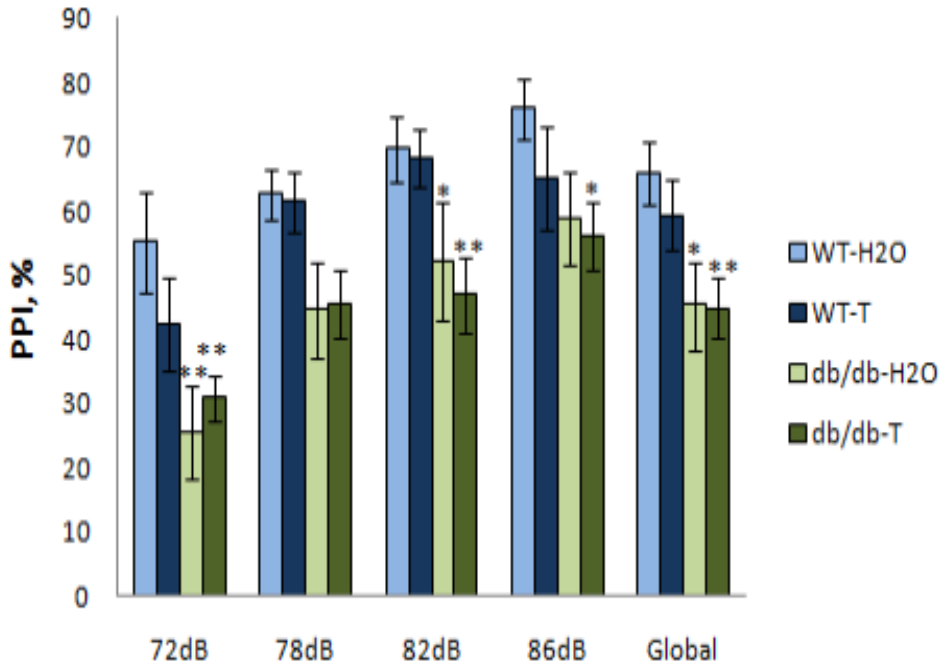
* p<0.05,** p<0.001 - db/db vs WT mice,
# p<0.05 - trehalose vs H2O in db/db mice.

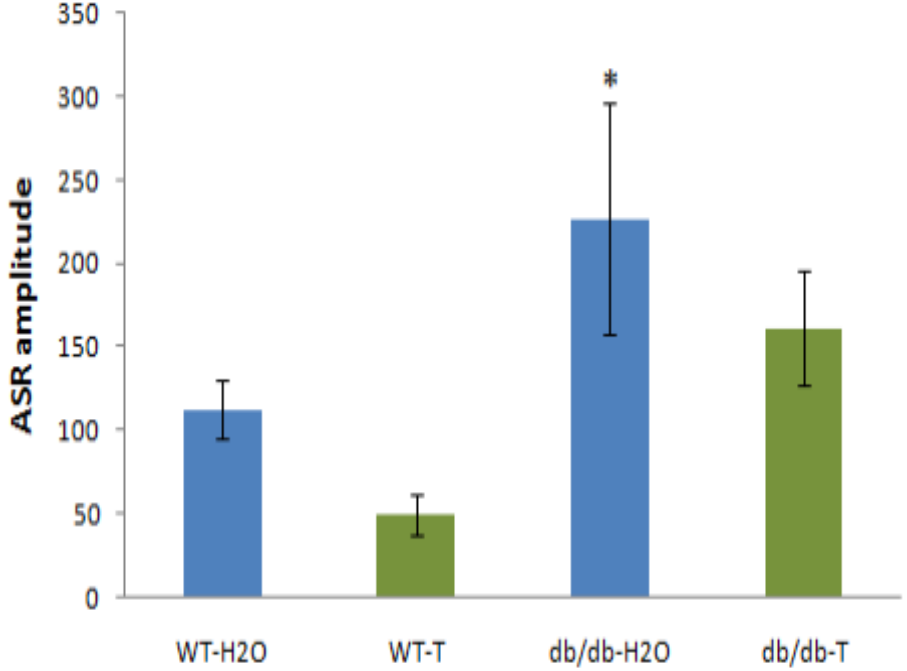
RELATIVE LEUKOCYTE NUMBER IN PERIPHERAL BLOOD IN 3- (A) AND 5-MONTH (B) OLD WT AND DB/DB FEMALE MICE, THE INFLUENCE OF TREHALOSE (TR) AND LIRAGLUTIDE (G)



& p<0.05, && p<0.01, &&& p<0.001 - db/db vs WT,
# p<0.05; ## p<0.01 - trehalose (or liraglutide) vs H2O in db/db mice.

PREPULSE INHIBITION (PPI) AND ACOUSTIC STARTLE REFLEX (ASR)





*p<0.05; **p<0.01 – vs WT-H_2O.

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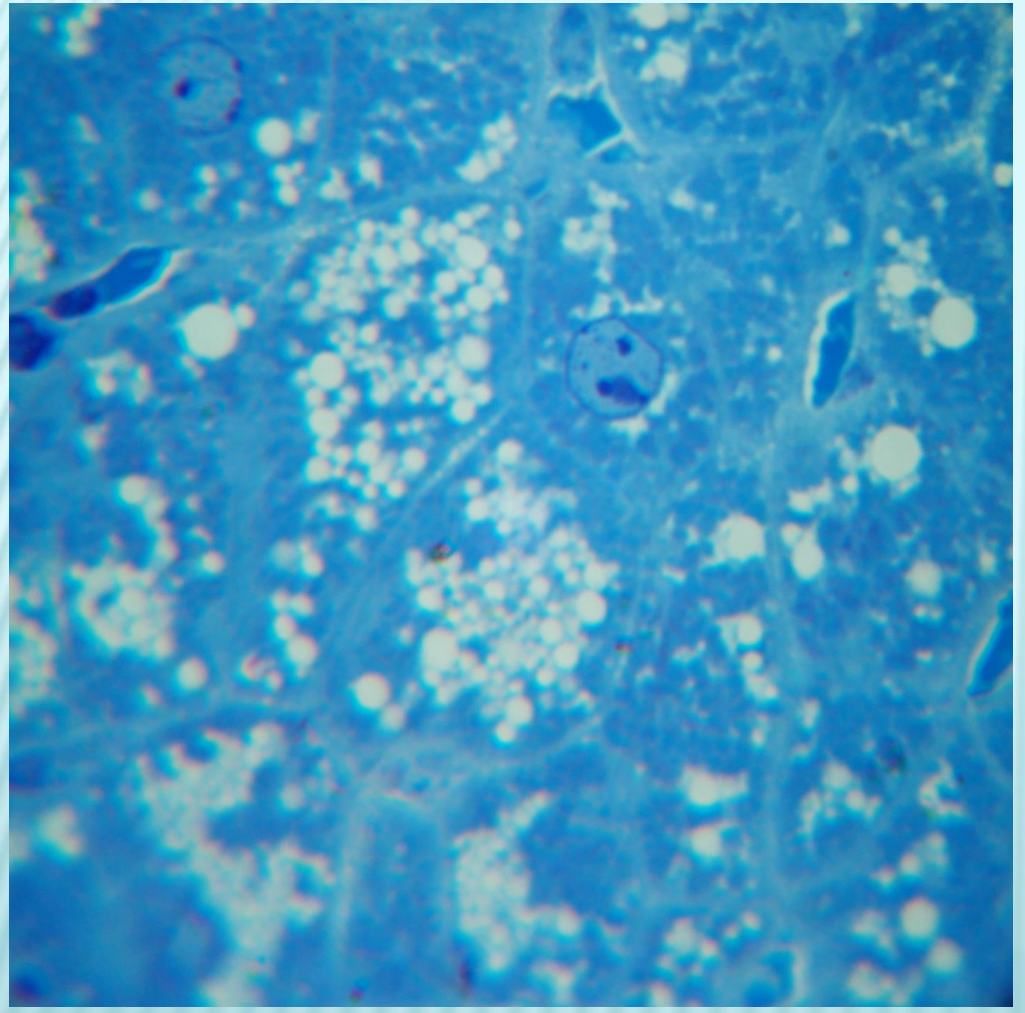

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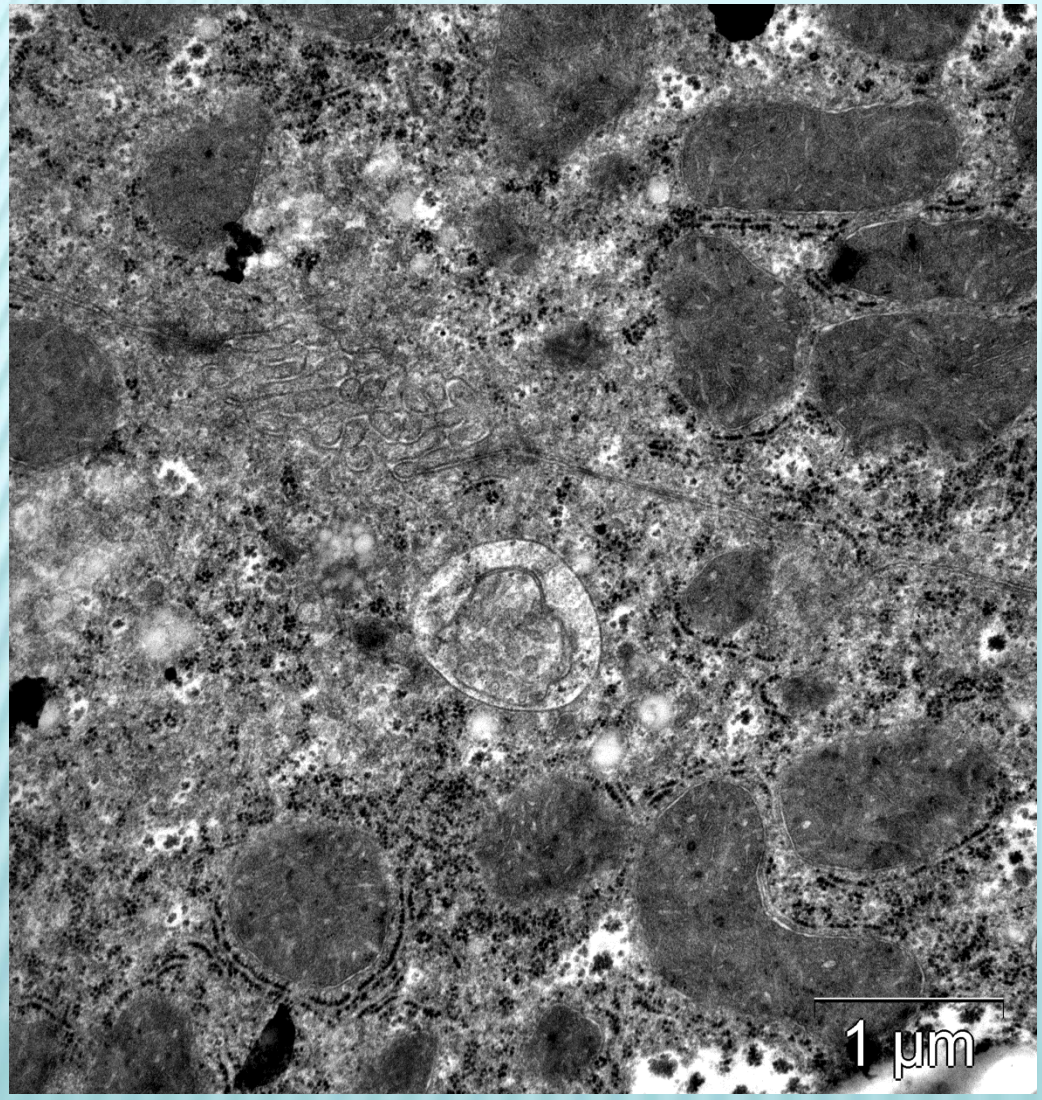

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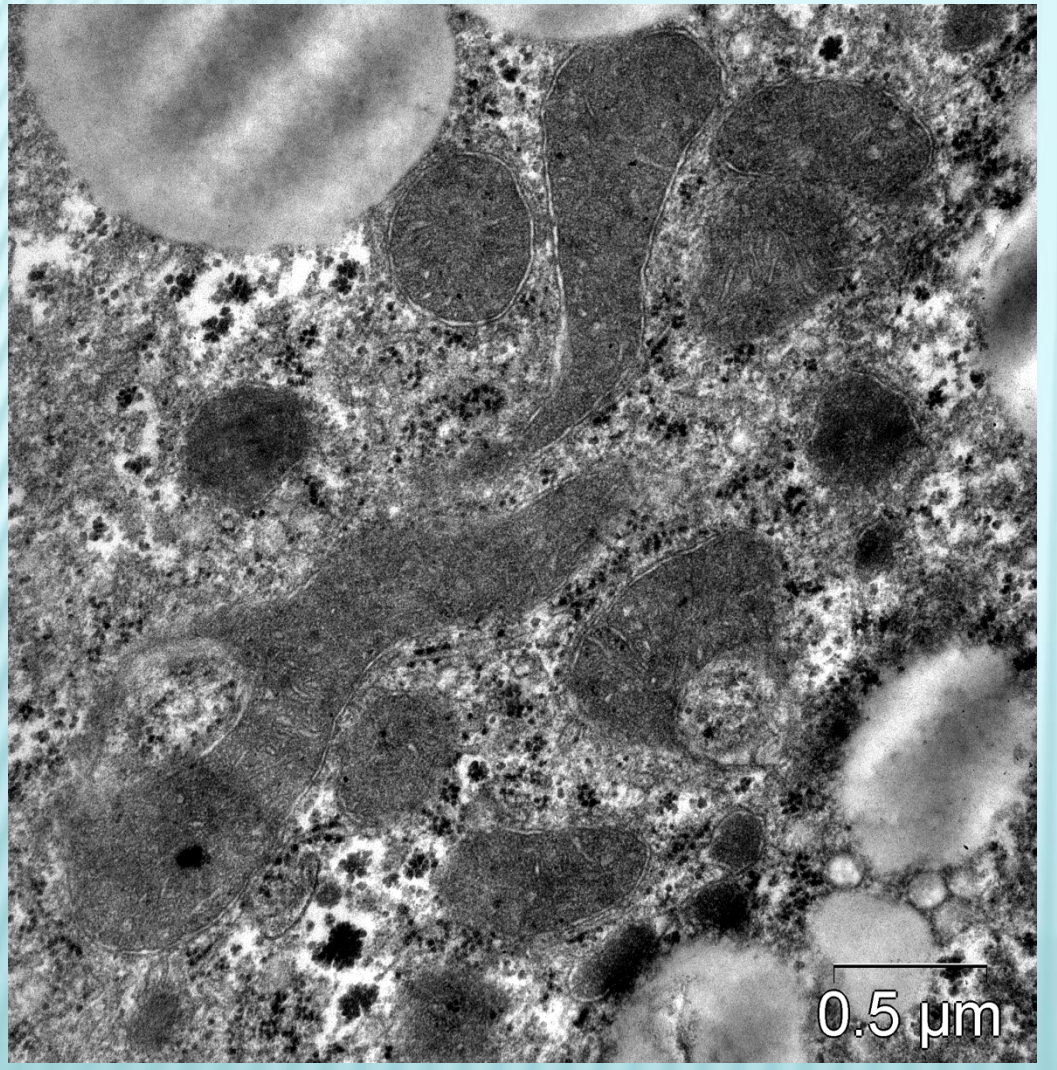

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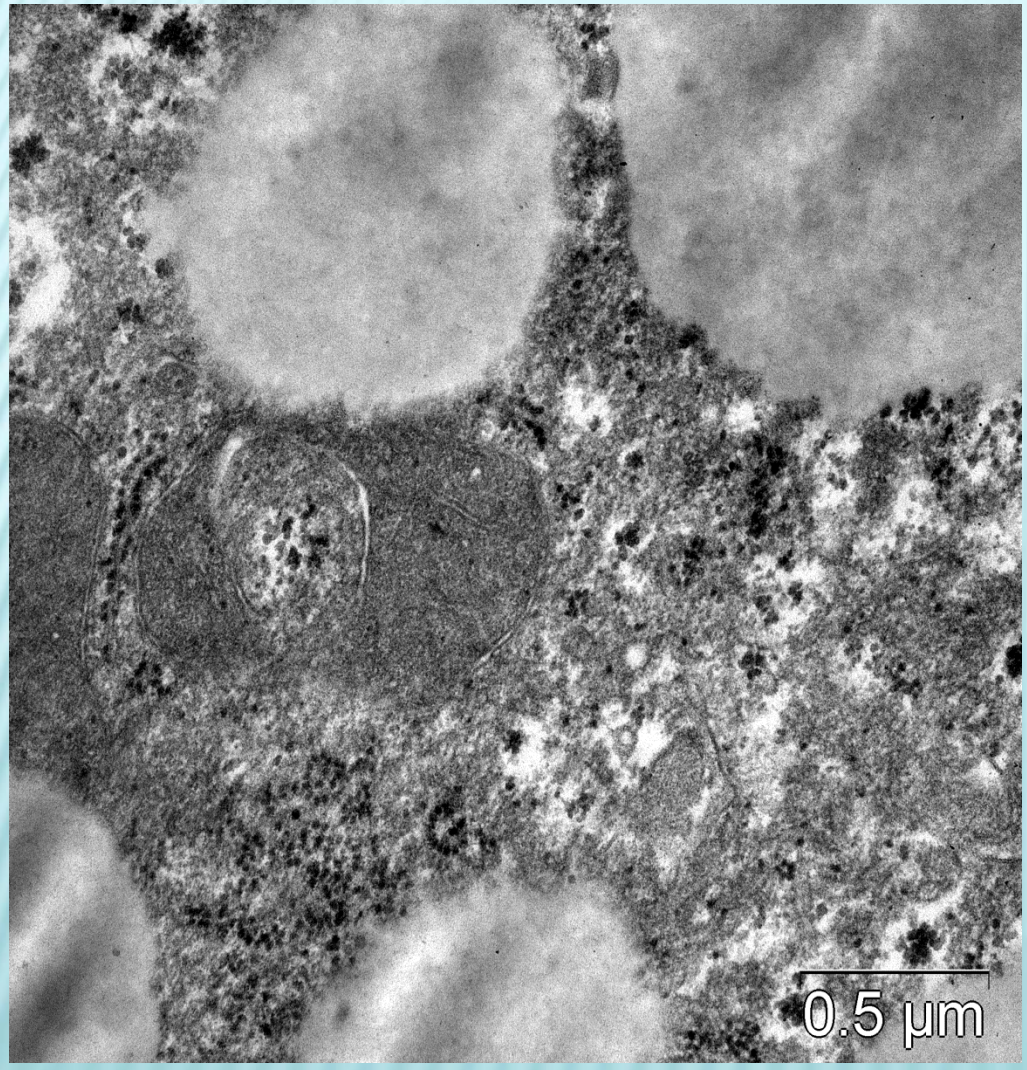

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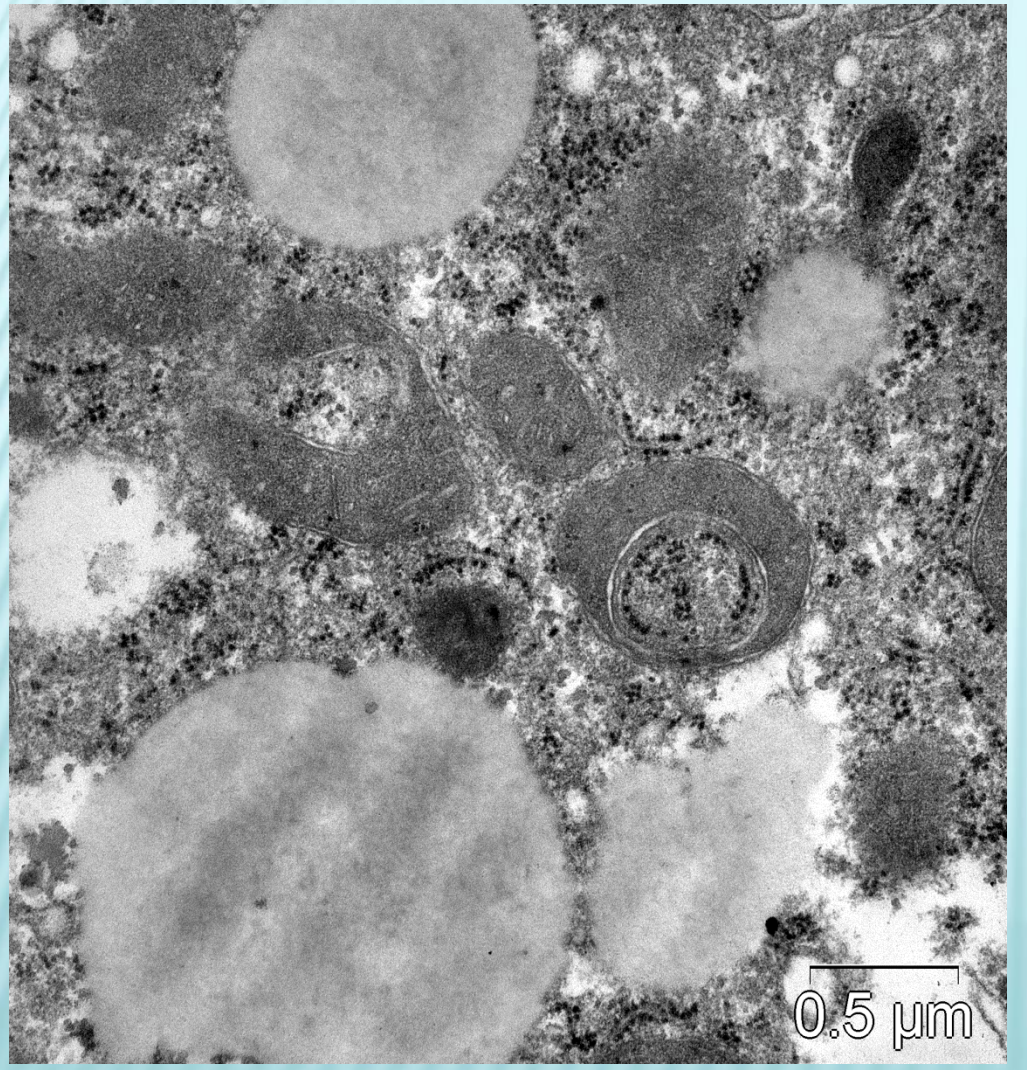

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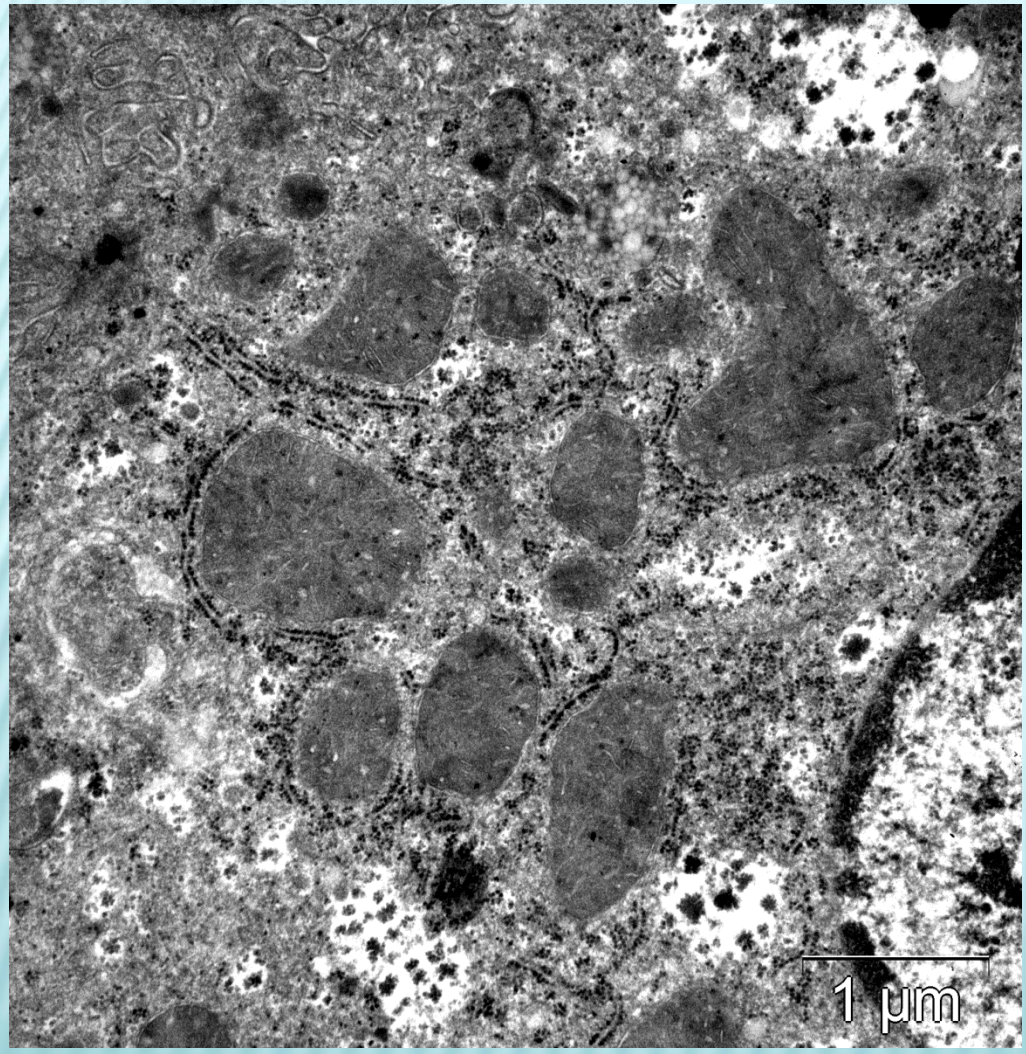

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EFFECT OF TREHALOSE ON BLOOD GLUCOSE LEVEL IN DB/DB MICE

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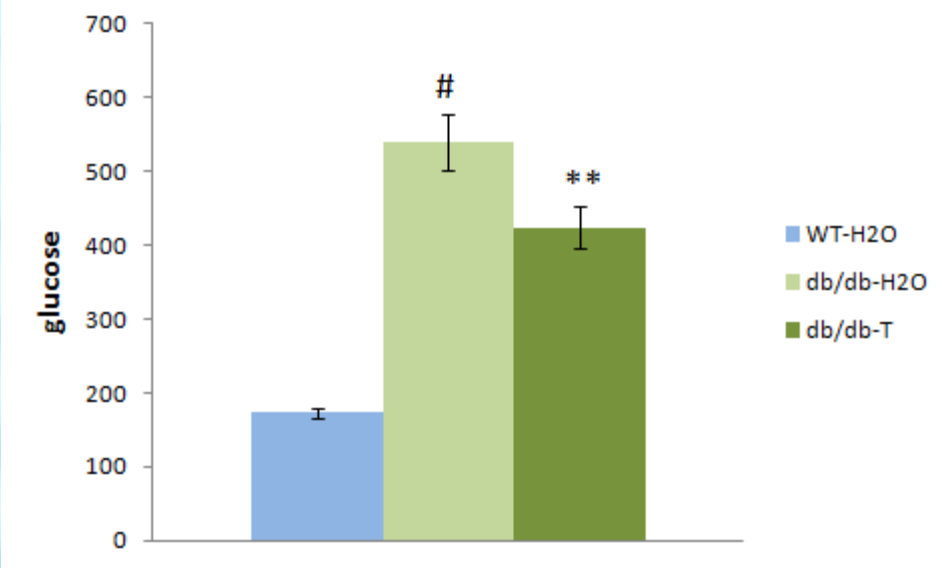

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