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Apkopoti fundamentālie pētījumi par meldonija (mildronāta) farmakoloģiskajiem efektiem un izskaidroti tā uzkrāšanās mehānismi organismā

Latvijas Zinātņu akadēmijas nozīmīgākie sasniegumi zinātnē 2016. gadā

LZA akadēmiķe **Maija Dambrova**, *Dr.pharm.* **Marina Makrecka-Kūka**, *Dr.pharm.* **Reinis Vilšķērsts**, *Dr.pharm.* **Elīna Makarova**, *Dr.pharm.* **Jānis Kūka**, LZA korespondētājloceklis **Edgars Liepiņš**
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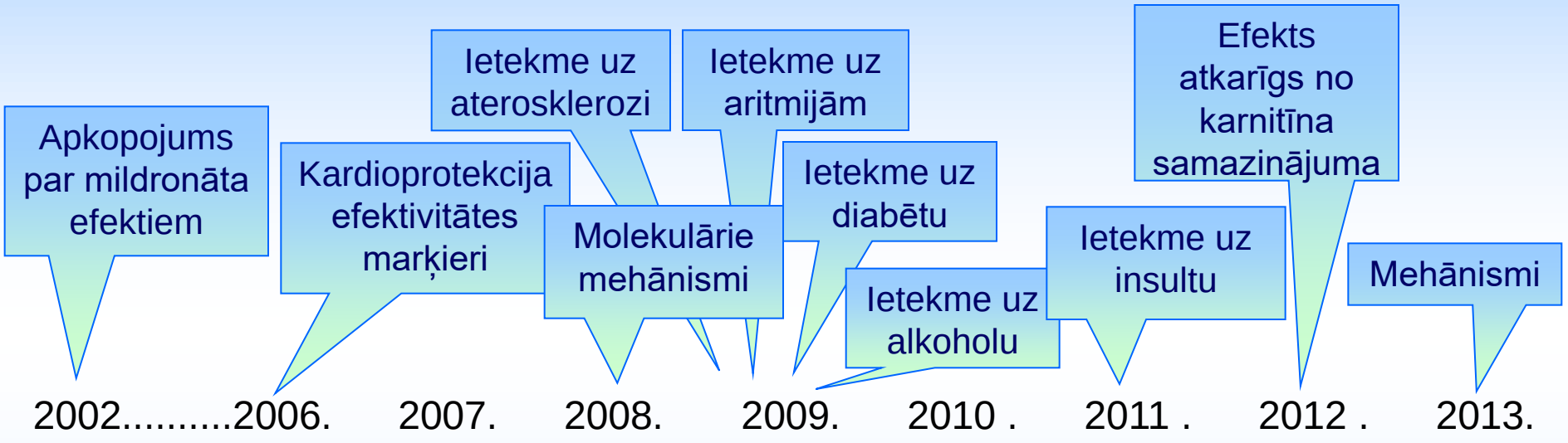
Mildronāta darbības mehānismu noskaidrošana



Farmakoloģisko īpašību izpēte

Molekulāro mehānismu izpēte

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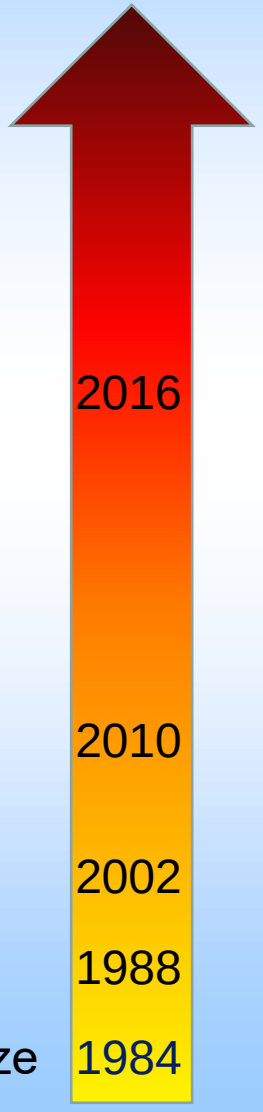
Meldonija mehānismu pētījumi



Liepinsh E, et al**.** Carnitine and γ-butyrobetaine stimulate elimination of meldonium due to competition for OCTN2-mediated transport. *Basic & Clin Pharmacol & Toxicol*. **2017** Doi: 10.1111/bcpt.12729

Liepinsh E, Dambrova M. The unusual pharmacokinetics of meldonium: Implications for doping. *Pharmacol Res*. **2016**; 111:100.

Dambrova M, Liepinsh E. Response to comment by Sergei V. Jargin: "Meldonium (Mildronate): primum non nocere". *Pharmacol Res*. **2016**; 114:295-296.

Dambrova M, Makrecka-Kuka M, Vilskersts R, Makarova E, Kuka J, Liepinsh E. Pharmacological effects of meldonium: biochemical mechanisms and biomarkers of cardiometabolic activity. *Pharmacol Res*. **2016** 113(B):771-780.

Liepinsh E, et al.. Decreased acylcarnitine content improves insulin sensitivity in experimental mice models of insulin resistance. *Pharmacol Res*. **2016** 113(B):788-795

Liepinsh E, et al. Long-chain acylcarnitines determine ischemia-reperfusion induced damage in heart mitochondria. *Biochemical J*. **2016** 473(9):1191-202.

Liepinsh E, Selective inhibition of OCTN2 is more effective than inhibition of Gamma-butyrobetaine dioxygenase to decrease the availability of L-carnitine and to reduce myocardial infarct size. *Pharmacological Research*, **2014**; 85:33-38.

Liepinsh E, et al. Activated peroxisomal fatty acid metabolism improves cardiac recovery in ischemia-reperfusion. *Naunyn Schmiedebergs Arch Pharmacol*. **2013**;386(6):541-50.

Tars K , et al. Crystal structure of human gamma-butyrobetaine hydroxylase. *Biochem Biophys Res Commun*. **2010**; 398(4):634-9.

Dambrova M, Liepinsh E, Kalvinsh I.Mildronate: cardioprotective action through carnitine-lowering effect. *Trends Cardiovasc Med*. **2002**;12(6):275-9.

Simkhovich BZ, et al. Regulation of the carnitine-dependent fatty acid metabolism. *Biochem Pharmacol*. **1988** Jan 15;37(2):195-202.

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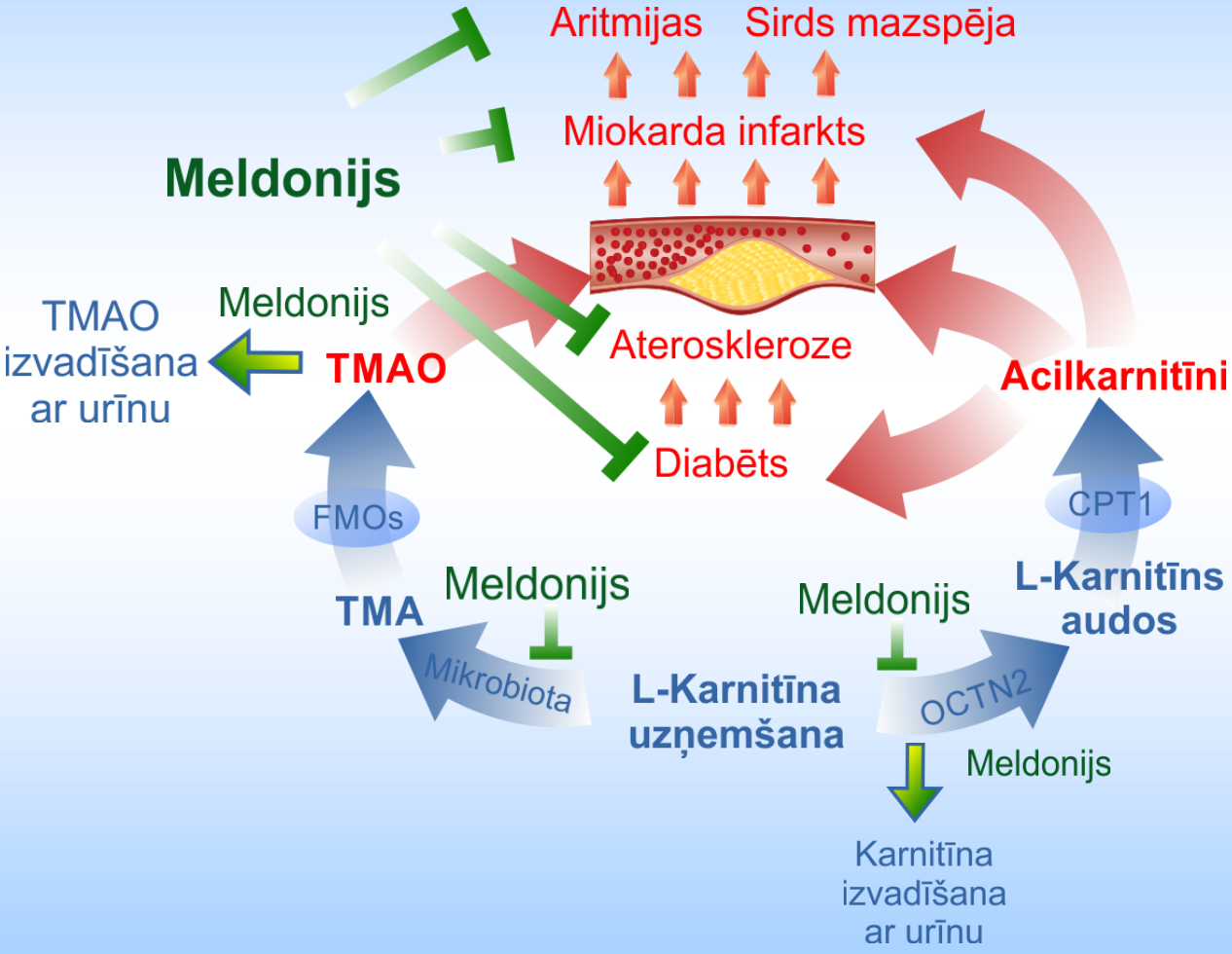
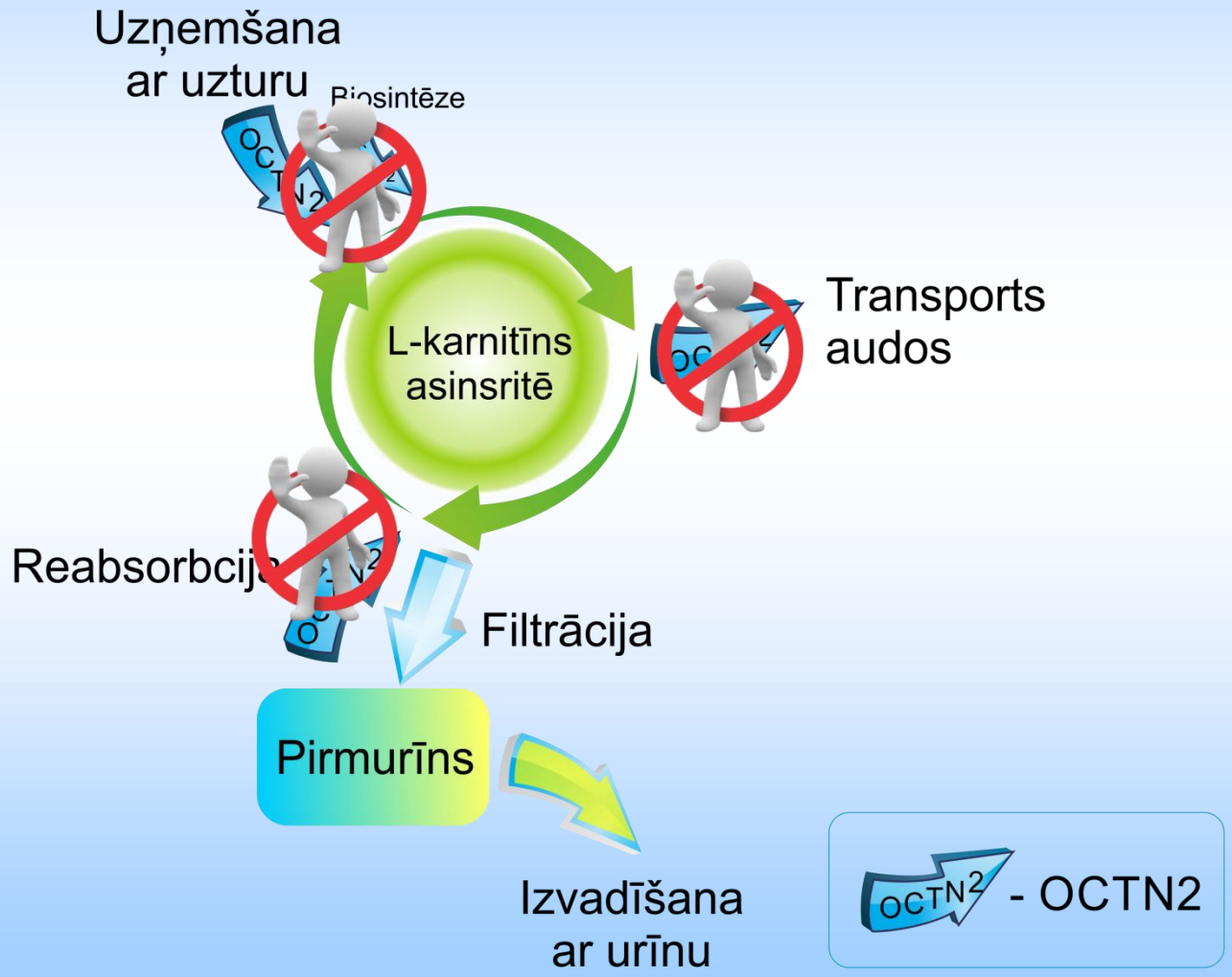
Meldonija darbības mehānismi



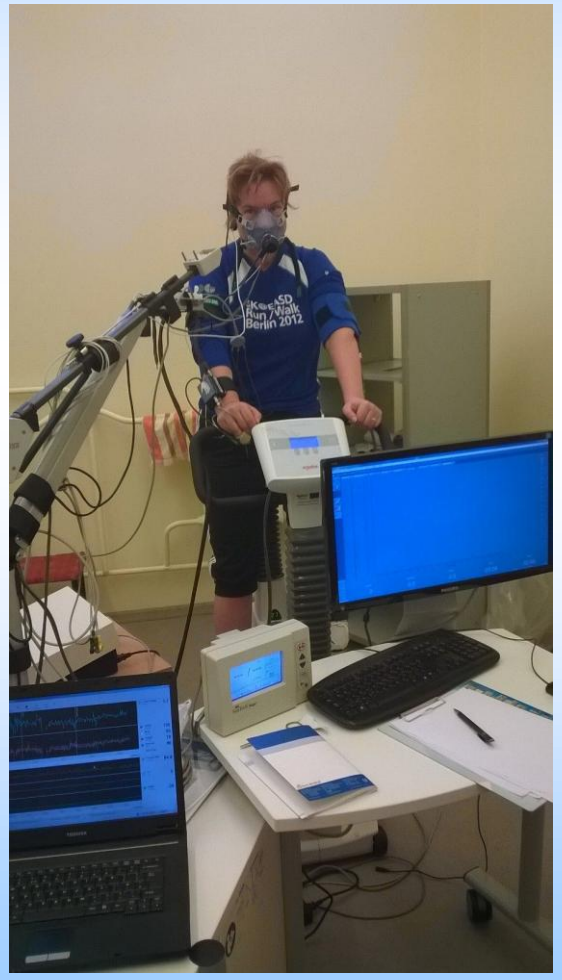
Dambrova et al. *Pharmacol Res*. **2016** 113(B):771-780.

L-Karnitīna un meldonija konkurence pie transportproteīna OCTN2



Dambrova M., *Pharmacological Research* **2016**

Meldonija farmakokinētika cilvēkos



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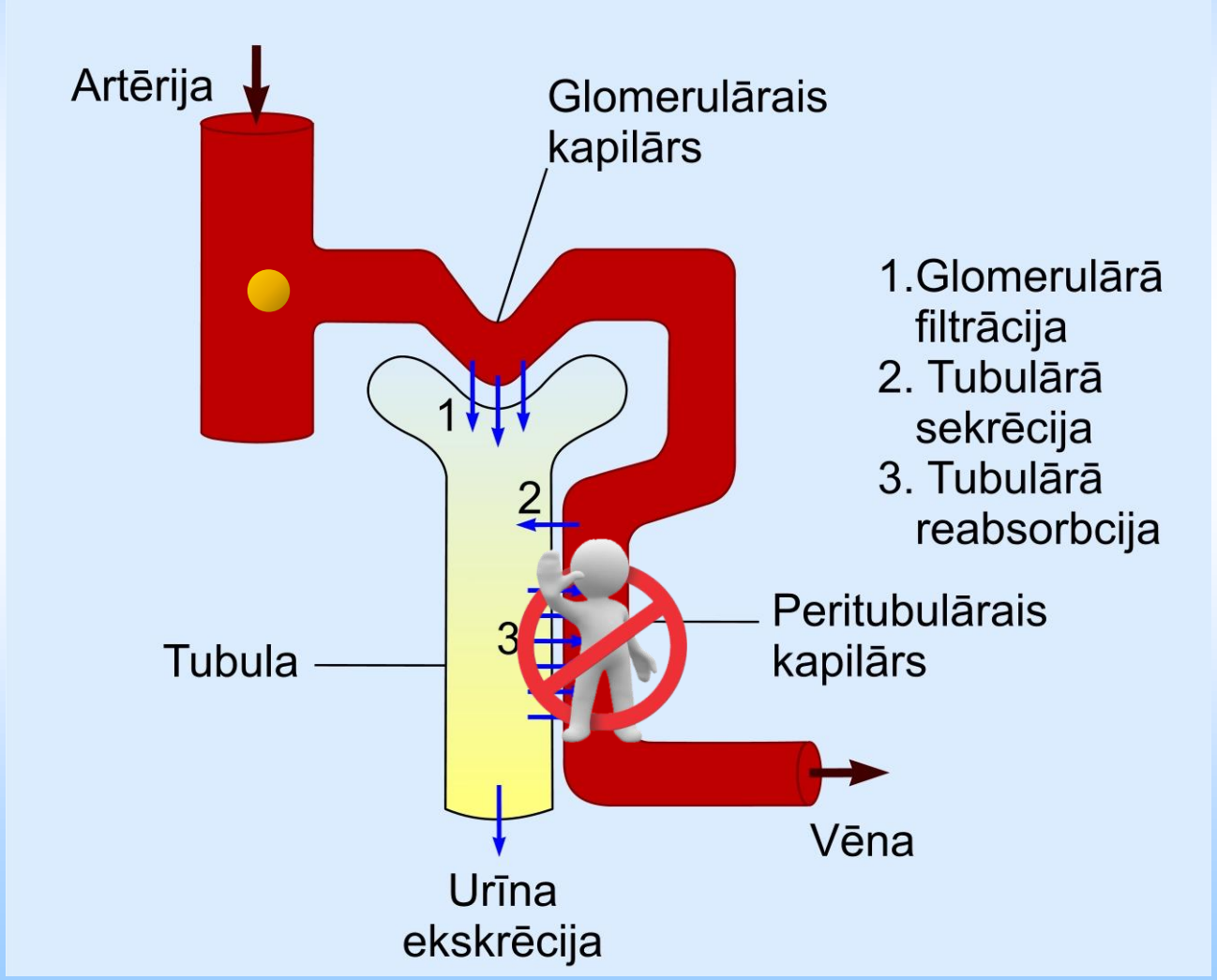
Invited perspective

The unusual pharmacokinetics of meldonium: Implications for doping

In the only long-term study of meldonium treatment in healthy volunteers, we demonstrated that after 4 weeks of treatment with the clinically suggested dose (500 mg twice a day), the concentration of meldonium in plasma reached approximately 20 μM (7 μg/ml) [3]. At the time, we did not report that the washout of meldonium was monitored 4 weeks after the end of the treatment, when the plasma concentration of meldonium was 1.15 ± 0.6 μM (0.2 ± 0.1 μg/ml), which is well above the established detection limit in plasma [3]. In addition, we found that the plasma concentrations of meldonium at the end of the 4-week treatment period correlated with the concentrations found after the washout period, which suggests that the complete elimination time is longer in individuals with higher initial concentrations.

The urine concentrations of meldonium during treatment were 150-fold higher than those in plasma and reached approximately 3000 μM/ml (500 μg/ml) [3], indicating that approximately 60% of meldonium is excreted. The meldonium concentration measured in the WADA monitoring programme in 2015 was in the range of 0.1–1428 μg/ml [4]. The upper concentrations found in the monitoring programme indicate that doses up to 3 times higher than those suggested for therapy were used by athletes. According to

Karnitīna filtrācija, ekskrēcija un reabsorbcija: meldonijs inhibē



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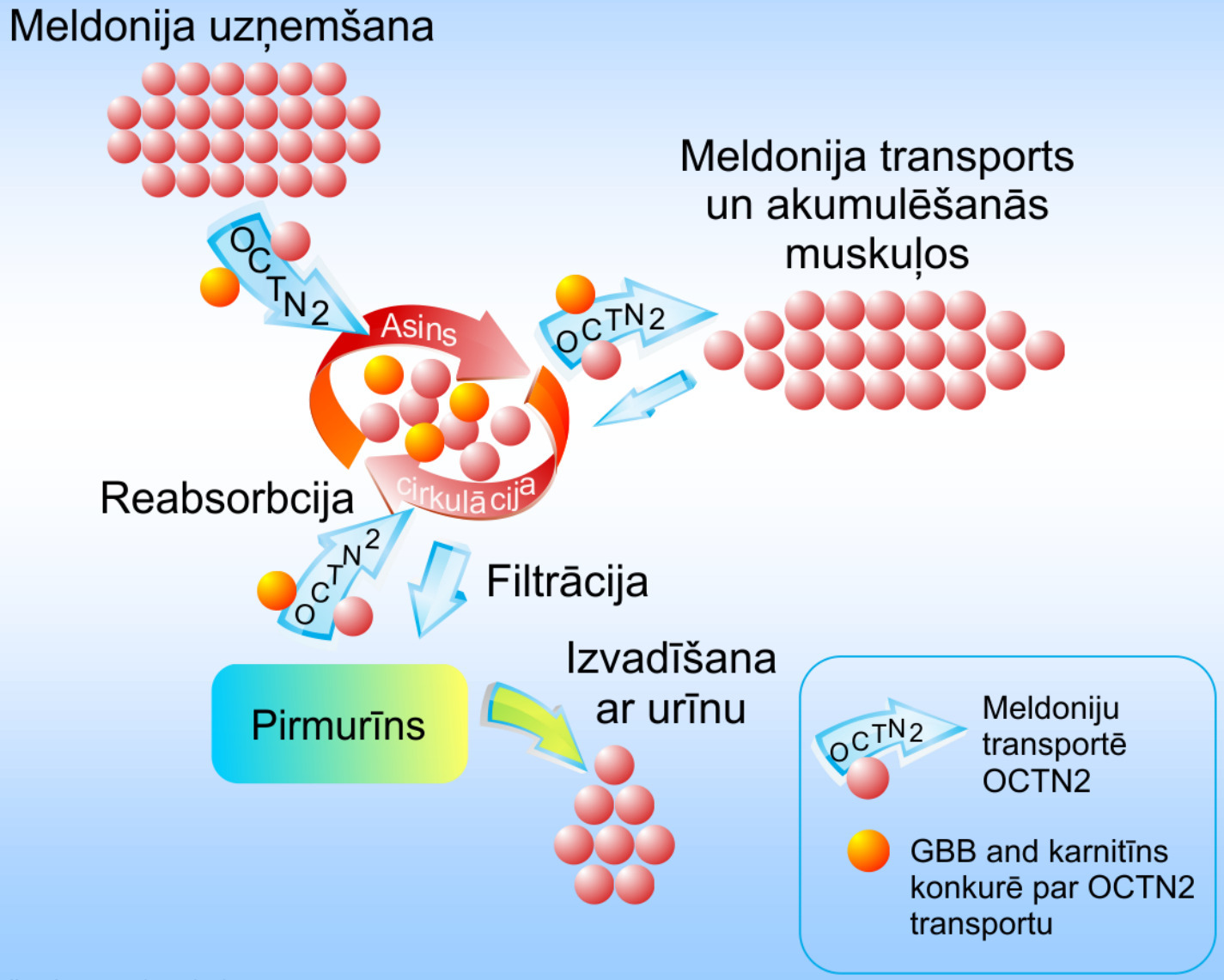
Meldonijs akumulējas muskuļos



Liepinsh E et al, Basic Clin Pharmacol Toxicol. **2017**

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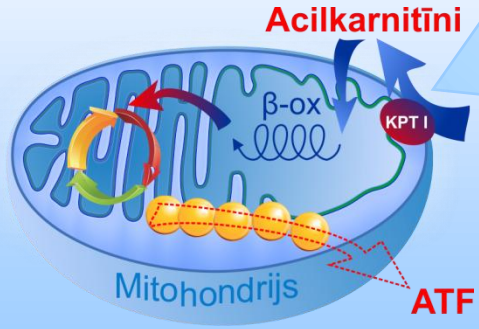
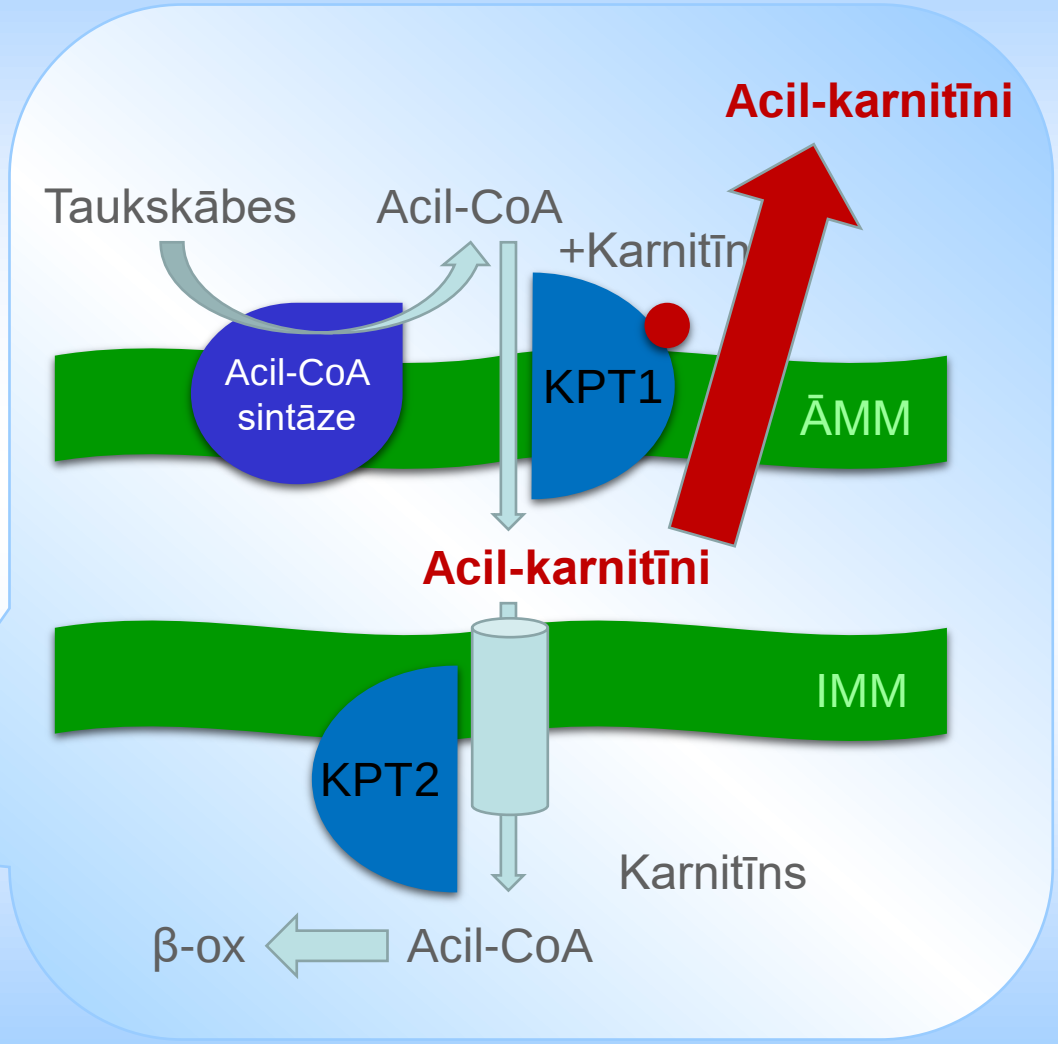
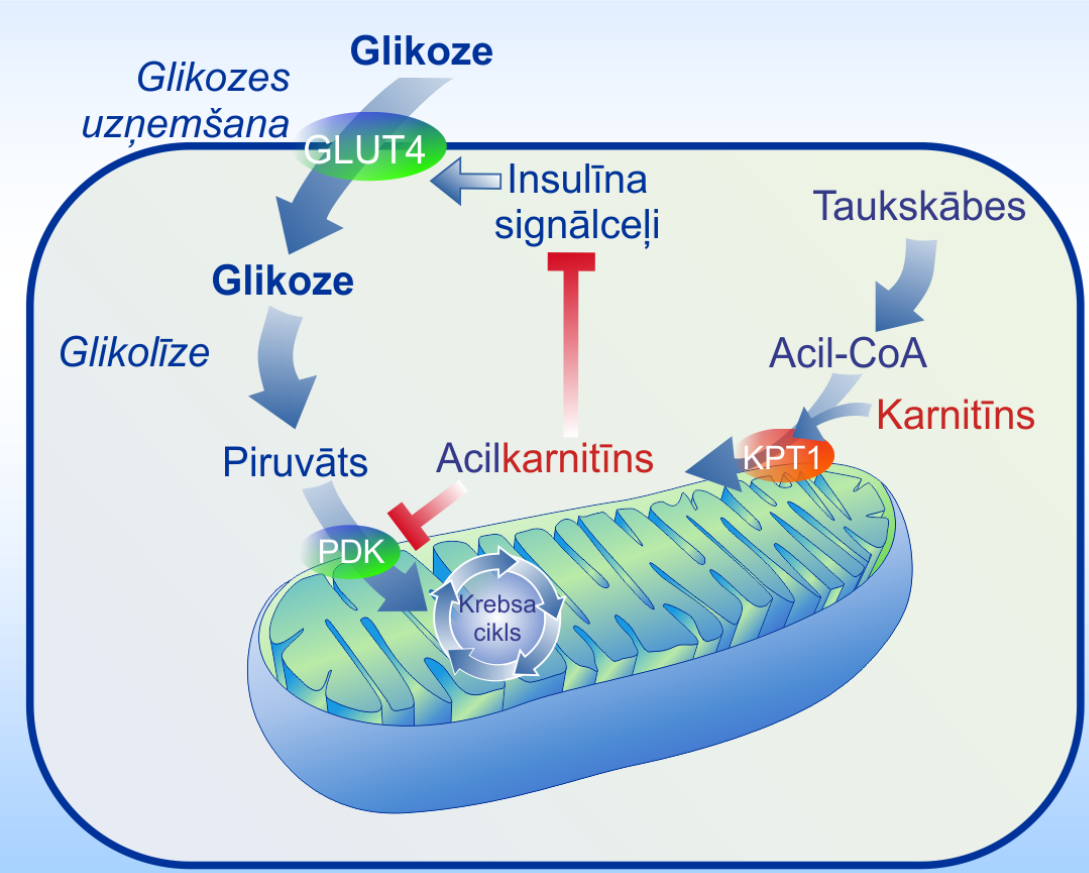
Acilkarnitīni un to metabolisms



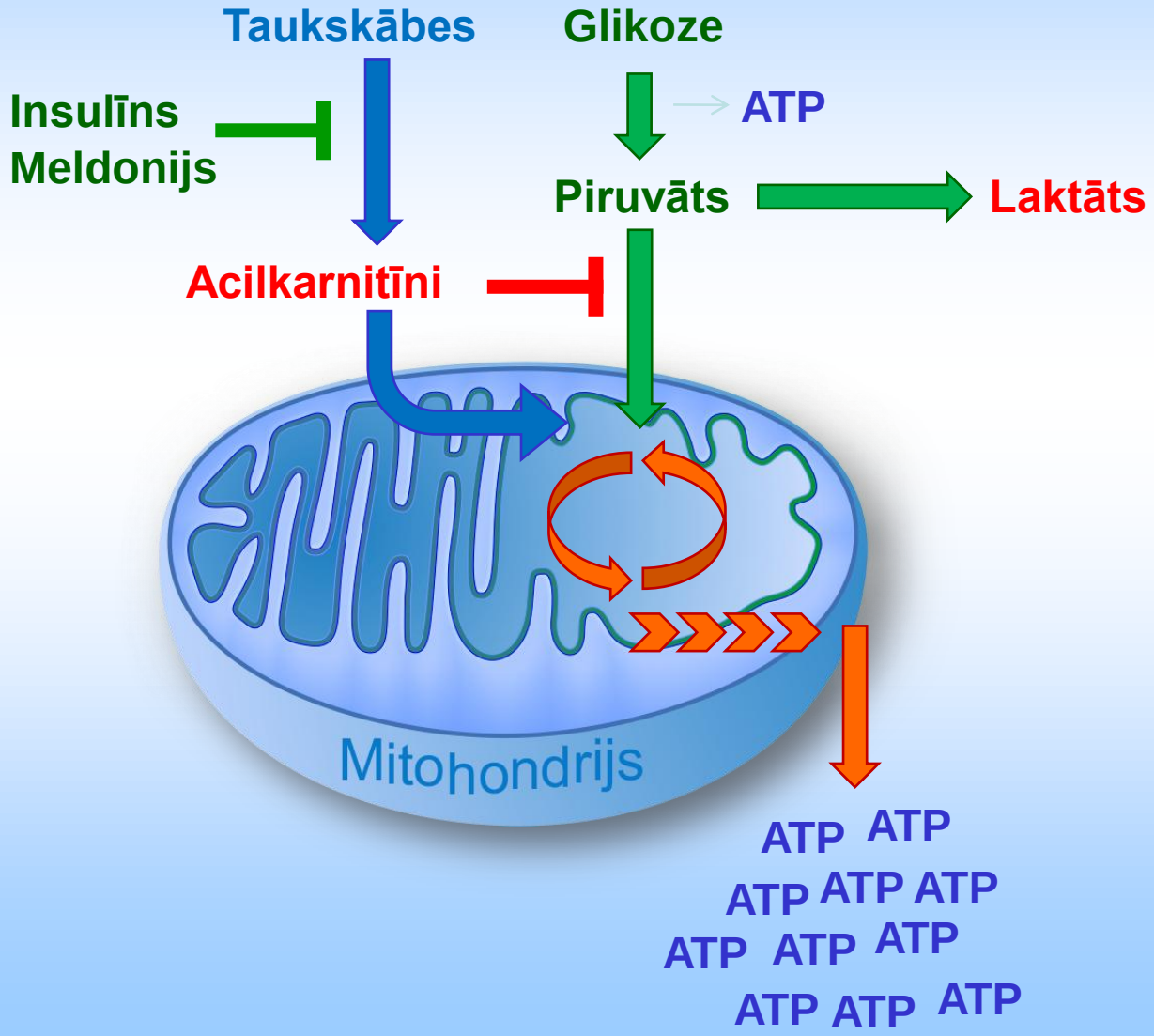


Acilkarnitīni kavē insulīna signālus un glikozes metabolismu



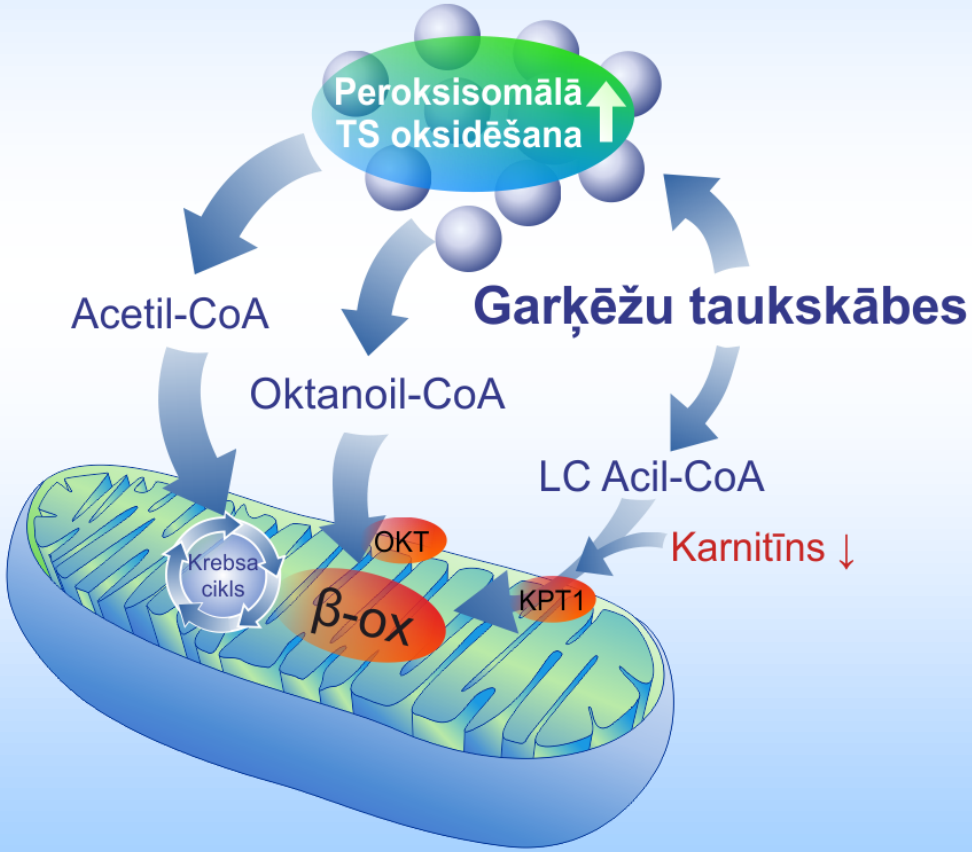
Dambrova M., *Pharmacological Research* **2016**

Meldonijs novērš acilkarnitīnu izraisīto glikozes metabolisma kavēšanu



Meldonijs pārslēdz taukskābju oksidāciju

no mitohondrijiem uz peroksisomām un pasargā mitohondrijus no kaitīgajiem taukskābju oksidēšanas starpproduktiem - acilkarnitīniem



Dambrova M., *Pharmacological Research* **2016**