PBPK model for prediction and simulation of melatonin pharmacokinetics

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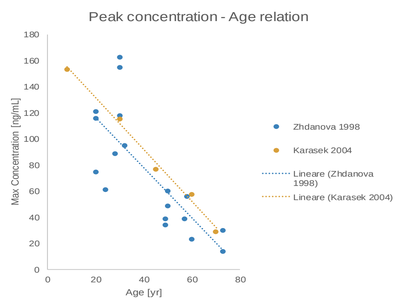
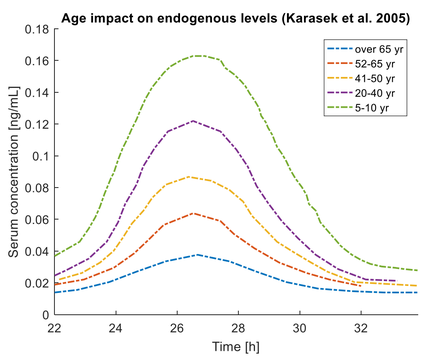
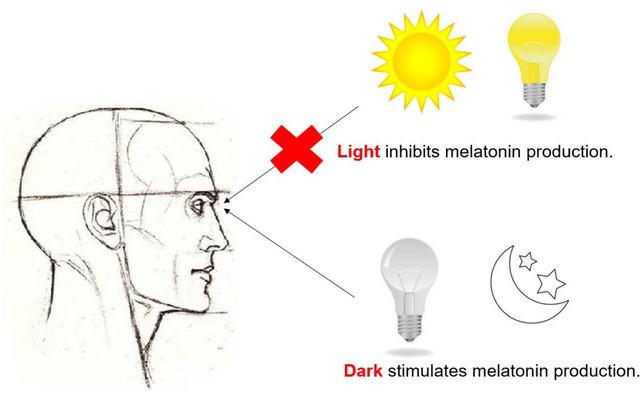
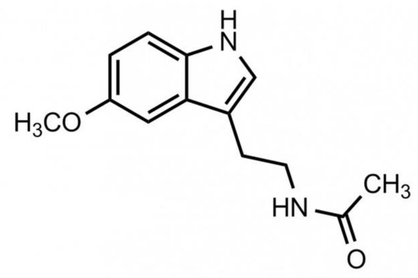
Introduction

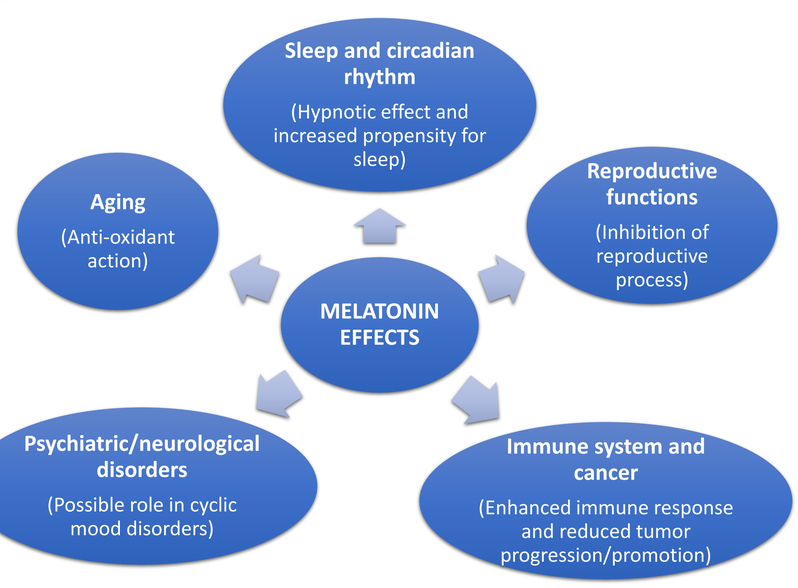
- **Melatonin** is a **biogenic amine** that is found in animals, plants and microbes. Aaron B. Lerner of Yale University is credited for naming the hormone and for defining its chemical structure in 1958.
- In humans, melatonin is produced mainly by the **pineal gland** starting from tryptophan which is converted to serotonin. Serotonin conversion to melatonin involves two different enzymes (SNAT and HIOMT) whose activity rise soon **after the onset of darkness** following the release of the neurotransmitter norepinephrine from sympathetic neurons terminating on the pineal parenchymal cells. In fact, melatonin production follows a **circadian** rhythm (**day-night cycle**).
- Endogenous concentrations of melatonin **decrease with age**.











Methods

Endogenous production

- Production of melatonin is described by a **periodic function** multiplied for a correction factor that accounts for the **age** of the patient.

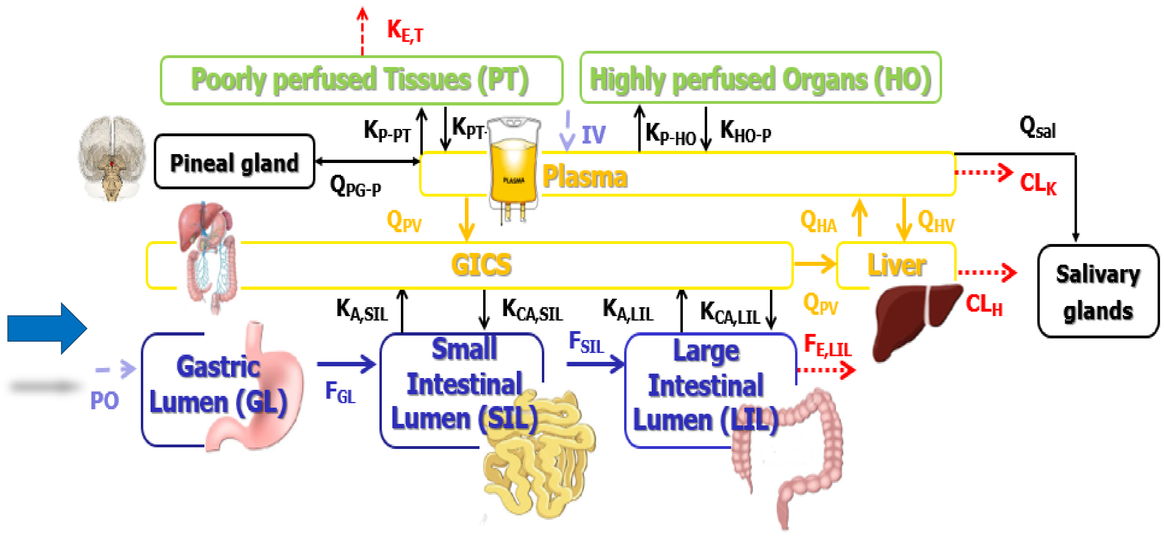
$$FC = \text{cost1} * \text{age} + \text{cost2}$$

$$f(T) = \frac{a0}{2} + a1\cos(\frac{2\pi t}{T} + \text{phi}) + a2\sin(\frac{2\pi t}{T} + \text{phi}) \qquad T = 24\ \text{h}$$

$$r_{prod} = f(T) * FC\ (age)$$

ADME processes and exogenous melatonin

- The **physiologically-based pharmacokinetic (PBPK)** model allows determining melatonin concentration in the different body organs and tissues, accounting for the processes of absorption, distribution, metabolism and elimination (**ADME**).
- In the figure, the rectangles indicate the **compartments** which are assimilated to the body parts, the black arrows indicate the **convective or diffusive fluxes** between the compartments; the dashed light blue arrows indicate the **routes of administration** and the red dashed arrows indicate the **metabolism/elimination pathways**.



Mathemathical formulation

- The model consists of **ordinary differential equations** representing the material balances of melatonin in the compartments. The general formulation of these **material balances** is the following:

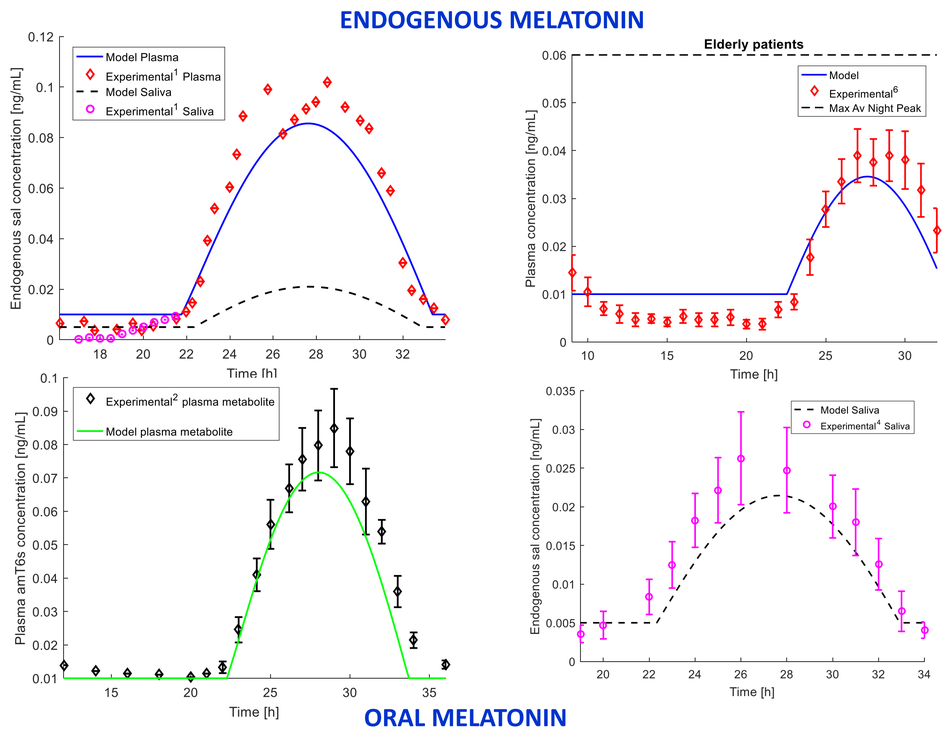
$$\frac{dn}{dt} = IN - OUT + PROD$$

Where in $\boldsymbol{IN}$ represents the fluxes entering the compartments or the input drug rate, $\boldsymbol{OUT}$ represents the fluxes exiting the compartments and $\boldsymbol{PROD}$ indicates the production rate, which is only present in the pineal gland compartment.

The model accounts for **the intravenous and oral (immediate and controlled release formulations) routes of administration.**

Results

- After **identification of the non-individualized parameters**, The model is **validated** with **experimental** data extracted from literature.
- The model results to be **reliable** in the prediction of the pharmacokinetics of endogenous melatonin, and exogenous melatonin administered via either enteral and parenteral route.



Conclusions

Intravenous administration

- The dose is administered to the systemic circulation immediately
- Reduced T_{max}
- Risk of high concentration peaks
- Complicated and expensive, possibly distressing

Per os administration

- Easy
- Possible slow-release formulation
- High inter-individual variability
- First-pass hepatic metabolism
- Slow absorption

The model can find multiple applications:

- Support in the **selection** of the **optimal route of administration/dosing regime** with the aim of producing either pharmacological or endogenous levels
- **Optimization** of the dosing regime through correlation with **pharmacodynamic indexes**
- **Individualization of the PK prediction** through introduction of correction factors (*e.g.,* renal disease; liver disease)

Future work will focus on the study of the **effects of melatonin on tumoral cells** and the development of models of the **target organs** of melatonin.

References

1. Benloucif, S., Burgess, H.J., Klerman, E.B., Lewy, A.J., Middleton, B., Murphy, P.J., Parry, B.L., Revell, V.L. (2008). Measuring Melatonin in Humans. Journal of Clinical Sleep Medicine : JCSM : official publication of the American Academy of Sleep Medicine, 4, 66-69.
2. Bojkowski, C.J., Arendt, J., Shih, M.C., Markey, S.P. (1987). Melatonin secretion in humans assessed by measuring its metabolite, 6-sulfatoxymelatonin. Clin Chem, 33, 1343-1348.
3. Gooneratne, N.S., Edwards, A.Y., Zhou, C., Cuellar, N., Grandner, M.A., Barrett, J.S. (2012). Melatonin pharmacokinetics following two different oral surge-sustained release doses in older a dults. J Pineal Res, 52, 437-445.
4. Laakso, M.-L., Hätönen, T., Stenberg, D., Alila, A., Smith, S. (1993). One-hour exposure to moderate illuminance (500 lux) shifts the human melatonin rhythm. Journal of Pineal Research, 15, 21-26.
5. Mallo, C., Zaidan, R., Galy, G., Vermeulen, E., Brun, J., Chazot, G., Claustrat, B. (1990). Pharmacokinetics of melatonin in man after intravenous infusion and bolus injection. Eur J Clin Pharmacol, 38, 297-301.
6. Zeitzer, J.M., Duffy, J.F., Lockley, S.W., Dijk, D.-J., Czeisler, C.A. (2007). Plasma Melatonin Rhythms In Young and Older Humans During Sleep, Sleep Deprivation, and Wake. Sleep, 30, 1437-443.