Early nutrition reprograms the hepatic Circadian Clock: Permanent deregulation of metabolism

Cristina Garcia-Beltran(1), Sílvia Ribó(1), Susana G Kalko (2), Antonio Fernández (3), Laura Martínez-Guinó(1), Judith Cebrià(1), Thais Pentinat(1), Débora Martínez(1), Carles Lerín(1), Mario Vallejo(3), Rubén Díaz(1), Josep Jiménez-Chillarón(1)

(1) Hospital Sant Joan de Déu, (2) Hospital Clínico de Barcelona-IDIBAPS, (3) Instituto de Investigaciones Biomédicas Alberto Sols (CSIC/UAM) and Ciber de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM)

Developmental programming of health and disease

Environmental stimuli acting during critical windows of development, including fetal and/or early postnatal periods, can induce permanent alterations in cell/tissue structure and function thereby increasing the risk of disease in adult life.

1. Mouse model of neonatal overfeeding ("childhood obesity")
2. Insulin action is primarily impaired in the liver
3. Circadian Rhythm expression is altered in liver of ON mice
4. Expression of the Circadian Clock is altered in the liver of ON mice
5. Rhythmic expression of circadian genes is altered over the light/dark cycle
6. The hepatic Circadian Clock is already altered during early development
7. Expression of CCGs is altered in livers from ON mice
8. Neonatal overfeeding moderately alters physiologic rhythmicity of ON mice

RESULTS

AIMS

We have previously developed a mouse model or neonatal overfeeding and late onset of disease.

Objective: To explore molecular mechanisms that may contribute to explain long-term programming of disease (Gene expression profiling, Affymetrix).

SUMMARY

1. Neonatal overnutrition alters the expression of the hepatic circadian clock. No major defects are observed in hypothalamus and eWAT.
2. Altered expression of the hepatic clock occurs early in development well before ON mice develop metabolic abnormalities. This implies that altered clock is mediated by nutritional signals.
3. Diurnal rhythmicity of Clock Controlled Genes, which display metabolic outcomes, is altered in livers from ON mice.
4. ON mice show a defect in the RER characterized by a shift in the diurnal cycle

CONCLUSION

Early malnutrition permanently de-regulates the hepatic circadian clock, which, secondarily may contribute to late onset of obesity and diabetes