

# NEUROBEHAVIORAL DEVELOPMENT IN PACAP

## KNOCKOUT NEWBORN MICE

Kiss P<sup>1</sup>, Farkas J<sup>1</sup>, Matkovits A<sup>1</sup>, Horvath G<sup>1</sup>, Helyes Zs<sup>2</sup>, Kun J<sup>2</sup>, Hashimoto H<sup>3</sup>, Baba A<sup>3</sup>, Welke L<sup>4</sup>, Tamas A<sup>1</sup>, Reglodi D<sup>1</sup>

Departments of <sup>1</sup>Anatomy, <sup>2</sup>Pharmacology and Pharmacotherapeutics, University of Pecs, Hungary; <sup>3</sup>Graduate School of Pharmaceutical Sciences, Osaka University, Japan; <sup>4</sup>Ross University, Dominica

### Introduction

PACAP has been shown to play important roles during the development of the nervous system. We have previously shown that PACAP treatment enhances neurobehavioral development of newborn rats. PACAP deficient mice display several abnormalities, including alteration of cerebellar structure, behavioral abnormalities and cognitive deficits. The aim of the present study was to investigate whether the early neurobehavioral development is affected in PACAP knockout mice to have further insight to the effects of endogenous PACAP in early postnatal development.

### Animals and testing methods

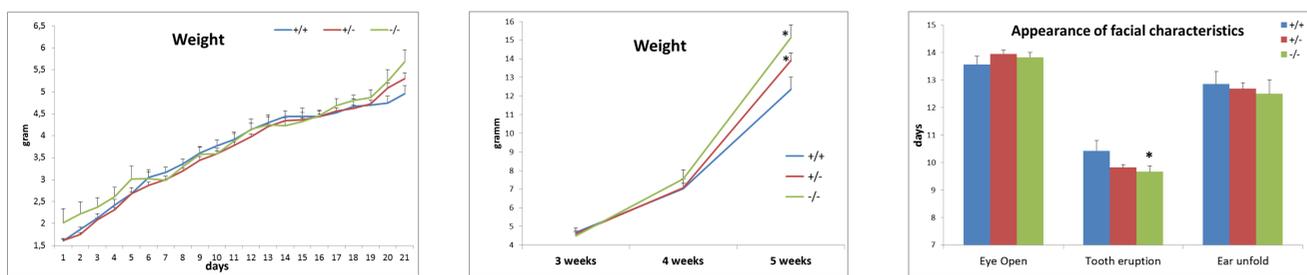
Litters composed of (1) wild type CD1 mice (+/+), (2) PACAP knockout mice (-/-) and (3) heterozygous mice (+/-) were used from day of birth to 5 weeks of age. Somatic and neurobehavioral development was tested daily during the first 3 weeks (appearance of negative geotaxis, sensory reflexes, righting reflexes, development of fore- and hindlimb grasp and placing, gait and auditory startle reflexes). Time to perform negative geotaxis, surface righting and gait reflexes was also measured. Motor coordination tests were performed on postnatal weeks 3-5.



Grid-walk and foot-fault test

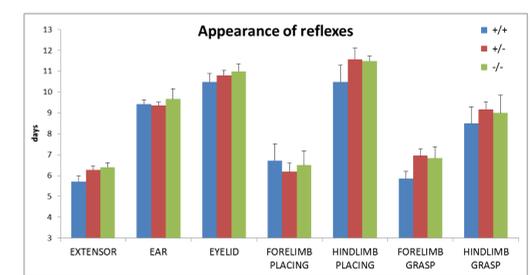
### Results

#### Somatic development



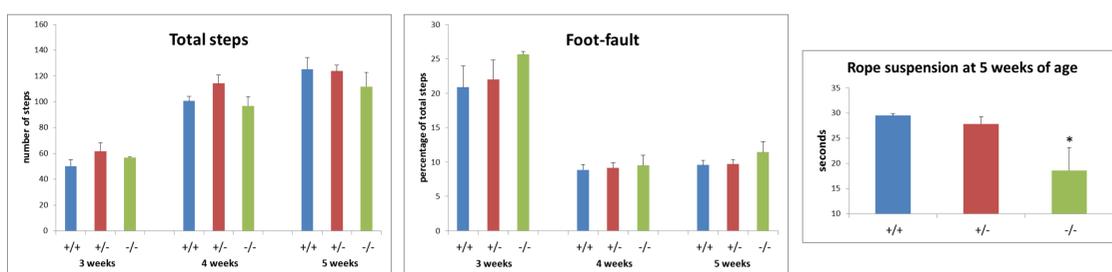
Daily examination of the somatic development (appearance of most important facial parameters) revealed no significant alterations in case of the visual and the auditory system, however, knockout as well as heterozygous animals showed a premature incisor outgrowth. Weight of knockout animals tended to be more than wild type mice's, but significant difference was only found at 5 weeks of age, where heterozygous animals weighed also more than wild-type littermates.

#### Neurological reflexes



There were no major differences found in the reflexes. In some cases, however, knockout animals displayed a slight delay in the appearance day of the reflexes.

#### Motor coordination

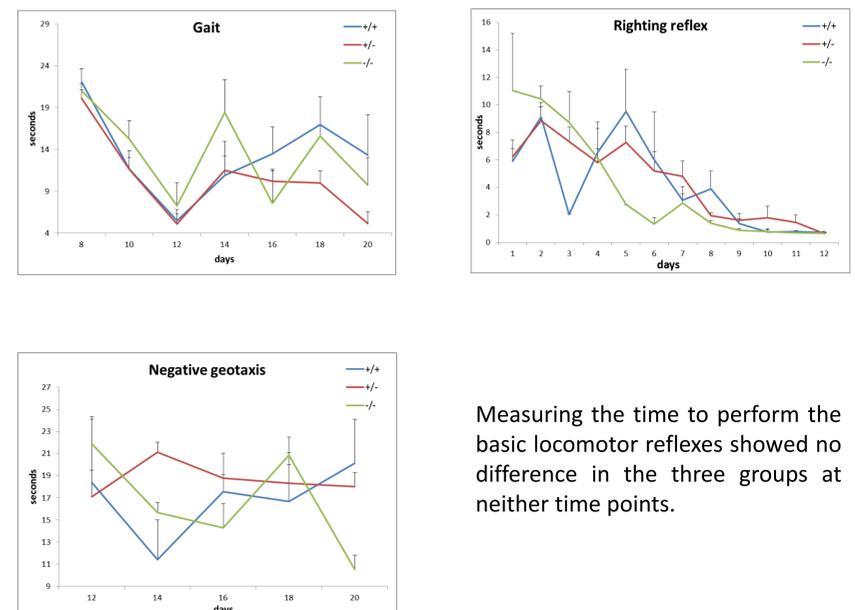


Motor coordination tests give data about the development of the more complex somatomotor systems, thus providing data about the maturation of neuronal circuits and muscular development. The most sensitive test is the foot-fault testing on an elevated grid platform.

Knockout animals moved about the same distance on the platform, but at the same time made slightly more mistakes with either limb.

Rope suspension test revealed a significant decrease in gripping strength in knockout animals compared to wild-type mice.

#### Reflex performance



Measuring the time to perform the basic locomotor reflexes showed no difference in the three groups at neither time points.

### Summary

Based on our findings, it seems that the endogenous deficiency in PACAP does not cause major developmental alterations. This is also in accordance with other observations showing that PACAP deficient mice have normal organ development. However, studies have proven that these mice are markedly more sensitive to harmful stimuli, pointing to the presence of subtle alterations in biochemical pathways necessary to cope with stressful stimuli.