Precocious involvement of prokineticin system in diabetic neuropathic pain in mice

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Neuropathic pain is defined as a pain sensation arising from a lesion or disease in the nervous system characterized by sensory loss and spontaneous pain together with sensory gain such as allodynia (pain resulting from stimuli that are normally innocuous). It is well demonstrated that neuropathic pain development is due to a pathological interaction between neuronal and immune cells and recently emerging researches have suggested a possible role of a new family of chemokines, named prokineticins (PKs), in the crosstalk between neurons, glia and immune cells in pain condition. PKs signal through two GPCRs (PKR1 and PKR2) widely distributed in all tissues, including nervous and immune system cells, and are involved in many biological activities such as angiogenesis, pain transmission, inflammation-related pain and immune processes. Since diabetes is an increasingly widespread disease affecting millions people in the world and neuropathic pain represents one of the most common and disabling long-term complications in diabetic patients, here we investigated the role of PKs system in a mouse model of diabetic painful neuropathy evaluating the effect of the PKRs antagonist PC1.

Diabetic painful neuropathy was induced in C57/BL6 mice using Streptozotocin (STZ, i.p. 200 mg/Kg). Mice were injected with PC1 (s.c. 150 µg/Kg, twice-daily for 14 days) either 14 days after STZ, when hyperglycaemia and mechanical allodynia (measured by Dynamic Plantar Aesthesiometer) were already fully developed, or at the same time of STZ to evaluate a potential role of PKs system in the onset of neuropathic pain. As controls, diabetic mice treated with saline and normal mice treated with either PC1 or saline were used.

The levels of PK2 and PKRs in spinal cords and sciatic nerves from STZ, PC1-STZ treated mice and controls were measured by RT-PCR. As mounting data show a critical role of cytokines in neuropathic pain we have also analyzed IL-1ß and IL-10 production in the same tissues from different animal groups by means of RT-PCR and ELISA. Finally, to understand if the PKs system was implicated also in the onset and progression of diabetes we evaluated the effect of the antagonist on insulin secretion measuring the levels of circulating insulin by ELISA and pancreatic IL-1ß and IL-10 levels by means of RT-PCR and ELISA in STZ, PC1-STZ and control mice.

PK2 levels were already elevated in both spinal cord and sciatic nerve fourteen days after STZ and high levels of PK2 were still observed 28 days from STZ. At this time point also PKR2 was significantly up regulated. In the same tissues, 14 days after STZ, an augmentation of IL-1ß was present while IL-10 levels significantly increased only in spinal cord. High levels of IL-1ß were still present 28 days after STZ both in spinal cord and sciatic nerve; on the contrary IL-10 levels appeared lower than controls. Moreover 14 days after STZ administration we observed a drastic reduction of circulating insulin in STZ mice and a decrease of pancreatic IL-1ß and IL-10. PC1 treatment induced a significant relief of painful symptoms. In fact the PKRs antagonist prevented the development of allodynia when administered together with STZ, and reverted allodynia when animals were treated in presence of a full developed neuropathic pain. Early PC1 administration, i.e. when administered together with STZ, slightly reduced hyperglycaemia and restored pancreatic IL-1ß and IL-10 to baseline levels in STZ mice but did not affect the pro/anti-inflammatory cytokine balance in the nervous system. However, a full restoration of this balance was observed when PC1 was given to animals 14 days after STZ, in fact 28 days after diabetes induction we observed a decrease of IL-1ß and an augmentation of IL-10. No significant effect of PC1 on insulin production was observed.

Our data show a clear implication of PKs system in diabetic painful neuropathy and suggest its potential role also in diabetes.