## Dendrimeric derivatives of nociceptin/orphanin FQ: in vivo studies

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Dendrimeric derivatives of the peptide nociceptin/orphanin FQ (N/OFQ) were prepared with a novel chemical strategy named peptide welding technology (PWT). Four N/OFQ sequences were linked to three different core moieties obtaining PWT1-N/OFQ, PWT2-N/OFQ, and PWT3-N/OFQ. In the present study the in vivo actions of PWT derivatives of N/OFQ were investigated on mouse locomotor activity in comparison to the native peptide sequence. The following parameters were measured in CD-1 mice: i) cumulative distance travelled (total distance in m that the animal travelled during the test), ii) immobility time (the animal is considered immobile when 90% of it remains in the same place for a minimum of 2.5 s) and iii) number of rearings (the number of beam breaks due to vertical movements). During the 120 min following intracerebroventricular (icv) injection N/OFQ (0.1 – 10 nmol, icv) produced biphasic effects: at low doses the peptide elicited short lasting stimulatory effects, while at higher doses it produced robust inhibitory effects. PWT derivatives of N/OFQ (2.5 – 250 pmol) mimicked N/OFQ effects being however approximately 40 fold more potent and showing slower onset of action and prolonged effects. Thus, in order to investigate the duration of action of PWT derivatives, the same parameters were measured during overnight experiments. Mice were injected at 11 AM and their locomotor activity was measured from 3 PM to 9 AM of the following day. Mice injected with N/OFQ (10 nmol) displayed a locomotor behaviour similar to that of saline injected mice. On the contrary, animals treated with PWT derivatives (250 pmol) displayed statistically significant reduced distance travelled and rearings associated with increased immobility time for the whole observation time. Finally, the in vivo effects of PWT2-N/OFQ has been investigated in wild type (NOP(+/+)) and NOP receptor knockout mice (NOP(-/-)). PWT2-N/OFQ (250 pmol) produced a statistically significant reduction of distance travelled and rearings in NOP(+/+) but not in NOP(-/-) mice. Collectively these findings demonstrated that PWT derivatives of N/OFQ displayed full agonist activity, high selectivity for the NOP receptor, higher potency, and a dramatic increase of in vivo duration of action compared to the natural peptide.