Amylin affects pain-related behaviors associated with the formalin test

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Abstract: Amylin is a peptide secreted by the pancreatic beta-cells and is also expressed in sensory neurons of the dorsal root ganglia. Literature points to a possible nociceptive action of amylin. This study aims to clarify potential anti- or pro-nociceptive effects of amylin administration on the formalin test, a model of acute and sustained pain of chemical origin. We evaluated the effect of a subcutaneous amylin injection (20 or 50\,µg/kg) or saline (control) in adult male Wistar rats 20 min before a subcutaneous formalin injection into the hindpaw. Nociceptive behavior scoring was performed for 60 min to evaluate the time spent in focused pain-related activity towards the injected paw, time spent in non-focused pain-related activity and number of involuntary jerks/flinches of the paw. c-Fos immunolabeling of nociceptive-responsive neurons in L4-5 spinal cord dorsal horn sections was analyzed on the same rats.

The 20\,µg/kg amylin dose significantly increased the number of paw jerks in the acute pain phase (first 5 min) of the formalin test. Animals injected with 50 \,µg/kg amylin displayed a significantly higher number of paw jerks 15 min post-formalin injection, which corresponds to the interphase period (10-15 min), and a longer time spent in non-focused and total pain-related activities at 20 and 25 min, which corresponds to the beginning of the second phase. There was a statistically significant reduction in the number of c-Fos-positive neurons in L4-5 spinal cord dorsal horn sections of 50\,µg/kg amylin-treated animals, which was limited to laminae I-II and V-VI.

Data suggest that amylin affects pain processing. The increase in paw jerks observed in the acute phase and in the interphase (a period in which autoanalgesic mechanisms take place in response to noxious
chemical stimulus) are indicative of hyperexcitability. Amylin may affect the inhibitory mechanisms normally occurring in the interphase. The higher amylin dose anticipated and exacerbated the beginning of the second phase of sustained/tonic pain, which suggests a role of amylin in tonic pain modulation. Additionally, 50μg/kg amylin reduced the number of spinal cord neurons activated by the noxious stimulus (c-Fos expression), which suggests that amylin ultimately attenuated the degree of noxious input to supraspinal areas. Taken together, results indicate that amylin modulates pain and may have affected the nociceptive system at different levels of the pain matrix at distinct time points. Ongoing studies with intrathecal amylin and amylin-receptor antagonist administration suggest the existence of relevant spinal cord-mediated mechanisms.

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