THE ROLE OF SUBSTANCE P IN THE NEUROGENIC INFLAMMATION: EFFECTS ON HUMAN NEUTROPHILS AND ENDOTHELIAL CELLS

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Substance P (SP), a neuropeptide belonging to the tachykinin (NK) family, has been evaluated as a major mediator of neurogenic inflammation [1]. SP and the other mammalian tachykinins, NKA and NKB, interact with three receptor types (NK1, NK2 and NK3) that have been identified by molecular cloning and sequence analysis [2]. SP acts primarily by the activation of NK-1 receptor, while NKA is the preferred natural agonist for NK-2 receptor and NKB the preferred agonist for the NK-3 receptor. When it is released by primary sensory nerves in peripheral tissues following axon reflexes, SP induces vasodilatation and plasma extravation and exerts different effects on cells involved in the inflammatory response [3]. When the ability of SP to modulate the function of inflammatory cells was evaluated, the laboratory contributed through the original observation that SP primed human neutrophils (PMNs) challenged by PAF or FMLP, thus amplifying the cell response (O2-. production) to the above stimuli. In the concentration range tested SP by itself did not work [4]. These data have been recently extended to PMNs exposed to a chemokine, interleukin-8 (rIL-8). SP enhanced, in a dose- and time-dependent way, the rise in cytosolic free calcium concentration, [Ca2+]i, evoked by rIL-8. The maximum effect was at 3X10-6 M after 3 min incubation. SP priming effects were abolished by exposing PMNs to a calcium-free medium supplemented with EGTA. The selective NK-1 receptor agonist, [Sar9,Met(O2)11]SP, mimicked the effects of SP, that were not reproduced by the selective NK-2 receptor agonist, [(Ala8]-neurokinin A (4-10) or the selective NK-3 agonist, senktide. Two selective NK-1 antagonists, CP 96,345 and L 703,606, dose dependently, inhibited SP priming effects. These results suggest that SP priming effects on PMNs are mediated by NK-1 receptors [5].
Leukocyte adhesion to vascular endothelium is a key event in the migration of inflammatory cells, such as PMNs, from the circulation into tissue. The adhesion of PMNs to the endothelial lining has to be regarded as an important parameter of PMN activation that occurs during the inflammatory response. Therefore, to further extend the study on SP modulation of PMN activity, we have tested whether or not SP exerts pro-adhesive effects. SP was coincubated with PMNs and confluent monolayers of endothelial cells isolated from the human umbilical vein (HUVEC). The adhesion was quantitated by computerized microimaging fluorescence analysis [6]. SP (10-18–10-6M) exerted proadhesive effects, that were depicted by two bell-shaped dose-response curves, the first one in the range 10-18–10-12M (maximum at 10-15–10-14M, a mean two-fold increase over control) and the second one in the range 10-12–10-6M (maximum 10-11–10-10 M, a mean one-fold increase over control). SP was more active than NKA; NKB did not work. SP effects were reproduced by the NK1-agonist [Sar9,Met(O2)11]SP, while the NK2-agonist [(Ala8]-neurokinin A (4-10) mimicked the effects of SP only in the range 10-12–10-6M. The NK3-agonist, senktide, was inactive. The antagonism by CP 96,345 and SR 48,confirmed that SP proadhesive effect were mediated by NK1 and NK2 receptor, the NK2 receptor being activated by higher concentrations of the tachykinin.

These data extend previous findings on SP modulation of PMN activity and confirm the role played by the enuropeptide in the inflammatory event.

References

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