12. DISTRIBUTION OF SP, CGRP, AND VIP IN THE GUINEA PIG NASAL MUCOSA SENSITIZED BY TOLUENE DIISOCYANATE (TDI)

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Toluene diisocyanate (TDI) is known to induce clinical symptoms of respiratory hypersensitivity in the mammals including man. Present immunohistochemical study has demonstrated in the Guinea pig that TDI treatment resulted in increase in number and intensity of Substance P (SP) and Calcitonin Gene Related Peptide (CGRP)-like immunoreactive fibers in the nasal mucosa, while failed to cause changes in the distribution of Vasoactive Intestinal Peptide (VIP) immunoreactive fibers.

Introduction It has been demonstrated that stimulation of the sensory nerve fibers in the nasal mucosa of mammals including human causes inflammation. It is likely that this effect is due to the release of neuroactive substances from the endings of sensory nerve fibers. In fact release of SP and CGRP in the nasal mucosa was confirmed pharmacologically in the animals whose nasal mucosa sensory fibers were stimulated. However, it is still unclear whether or not SP and CGRP are reflexly released or they are produced actively from the nerve endings in this animal. Accordingly, in the present study, we have attempted to elucidate the changes of SP, CGRP and VIP immunoreactive fibers in the nasal mucosa after treatment with TDI which is known to cause respiratory hypersensitivity.

Material and Methods Guinea pig weighing about 250—300g were used in this study. Animals were divided into 2 groups: one treated by TDI and an other was a control group. The sensitization process was done by local and daily application of 10% TDI solution to the nasal mucosa for 5 days. After 3 weeks of observation, application of 10% TDI sol. was repeated for another 5 days period. One week after the final application, 5% TDI sol. was applied locally for provocation test once a week for 7 weeks. Animals showing a positive reaction (sneezing, rhinorrhea) to the provocation test were selected and nasal mucosa samples were subjected to immunohistochemistry.

Results In the control animals, many SP and CGRP fibers were seen in the nasal mucosa. In the lamina propria, a number of immunoreactive fibers were associated with blood vessels and seromucous glands. Several fibers often left the lamina propria to enter the epithelium. VIP fibers showed a similar distribution pattern to those of SP and CGRP, but very few fibers entered the epithelium. TDI...
treatment resulted in marked increase in number and intensity of SP and CGRP fibers in the lamina propria and in the epithelium, while no clear changes could be detected in the distribution of VIP fibers in the TDI treated animals.

Discussion It has been reported that activation of sensory fibers by local irritation of nasal mucosa using a chemical irritant, causes release of SP or CGRP from the nerve endings. In well accordance with these findings, present immunocytochemical analysis demonstrated the increase in number and intensity of SP and CGRP fibers in the Guinea pig nasal mucosa treated by TDI. Considering the present findings, production of SP and CGRP in the sensory neurons increases in the TDI treated animals. Our findings suggest that TDI treatment resulted in increase of blood flow and glandular secretion, because 1) most of SP and CGRP fibers were located around blood vessels and glands, 2) both SP and CGRP are known to be strong vasodilators and they have been found to be stimulant of airway mucous secretion.

On the other hand, TDI treatment failed to cause changes of VIP fibers both around blood vessels and glands and within the epithelium, suggesting that TDI doesn't give an influence on the VIPergic nor in sensory fibers of Guinea pig nasal mucosa.

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13. 反回神経の変性及び再生過程における形態学的観察

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末梢神経は損傷されると損傷部より末梢側はワーラー変性におけるが中枢側は逆行性変性をおこす。一方では末梢神経特有の強い再生能力を示すことが報告されている。しかし、反回神経のように同一神経が拮抗筋を支配している場合には再生が正確に行われないと機能回復にいろいろの障害が生じるのは臨床的あるいは生理学的にも知られている。今回われわれは転移とシュワリア細胞などの細胞成分のみを除去する目的で結腸損傷をモルモットの反回神経に加えその変性と再生の過程を観察した。末梢部神経の光顕、電顕的変化及びHRP標識法を用いて延髄の内聴神経を支配する運動神経の再配列を観察した。

3日後に反回神経の損傷部より末梢側では損傷後軸索がほぼ完全に消失し脳神の破壊が見られたが2週後には無数ないし有数の細い再生軸索が多数観察された一方、この再生過程において再生神経線維の形態は変形が著しく完全な神経配列回復の難しさが推測された。反回運動神経の再配列は神経損傷後モルモットの筋にHRPを注入した結果、3ヶ月から標識細胞が見え、標識細胞は徐々に増える陽化で6ヶ月には正常対照群の後筋支配運動神経の数とはほぼ同じレベルとなった。しかし再生運動神経細胞体の分布を見ると本来の後筋支配領域以外の細胞体からの投射がおこっていることが確認された。反回神経の運動神経には強い再生能が見られるが、再生神経は正しく再支配することは限らず正常な機能回復によって障害となることが推定される。