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授与した学位	博　士
専攻分野の名称	学　術
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学位授与の要件	自然科学研究科生体機能科学専攻 （学位規則第４条第１項該当）
学位論文の題目	Establishment of new evaluation method for allergic rhinitis and its application （アレルギー性鼻炎の新しい評価方法の開発とその応用）
論文審査委員	教授　亀井千晃　　教授　川﨑　博己　教授　合田　榮一

学位論文内容の要旨

Allergic rhinitis is the inflammatory condition of nasal mucosa characterized by sneezing, nasal itch and nasal congestion etc. in human. Histamine released from the mast cells of nasal mucosa during antigen-antibody reaction induces nasal behavior in human and animals, and the response is mainly occurred through H_1 receptor located at the sensory nerves. In a large number of studies, nasal behavior induced by antigen was measured with naked eye observation but the main disadvantage is a lack of objectivity. Therefore, the present study was undertaken to establish a new evaluation method for allergic rhinitis by measuring the EEG at the olfactory bulb. The effects of some H_1 receptor antagonists on the EEG and behavioral changes induced by histamine were also studied. The topical application of histamine into the nasal cavity resulted in a significant and dose-related increase of sneezing and nasal rubbing. The EEG spike at the olfactory bulb was also observed to be in parallel with the sneezing. In addition, there was an intimate relationship between the EEG spike and sneezing; however, no correlation was observed between the EEG spike and nasal rubbing. All the H_1 receptor antagonists used in this study caused an inhibition not only sneezing but also EEG spike at the same dose level. Therefore, these findings suggest that the EEG spike observed in the olfactory bulb is an objective and reliable indication of sneezing induced by allergic rhinitis in rats.

It was also reported that not only histamine is associated in the genesis of nasal allergic symptoms but also other chemical mediators are involved in these responses. Thus, in the present study, the role of substance P in nasal allergic symptoms was also investigated. It was found that exogenous substance P caused a significant and dose-related increase of nasal behavior and EEG spikes in rats. L-732,138, a selective tachykinin NK_1 receptor antagonist caused a significant and dose-dependent inhibition of nasal allergic symptoms and EEG spike induced by both substance P and antigen. Moreover, antigen-induced nasal allergic symptoms and EEG spike was also significantly inhibited by H_1-antagonists used. On other hand, these H_1-antagonists had no effects on nasal allergic symptoms and EEG spike induced by exogenous substance P. Therefore, from these results, it can be concluded that substance P also participates in nasal allergic symptoms and H_1-antagonists tested do not possess NK_1 receptor antagonistic activity.

In a number of studies, it has been indicated that prostaglandins are released from the activated mast cells and implicated in the genesis of nasal allergic reaction. Prostaglandins are the active metabolites of arachidonic acid catalyzed by cyclooxygenase (COX). Thus, in the present study, the involvement of COX-2 in nasal inflammation was studied. An allergic rhinitis model was developed by the repeated topical application of antigen into the nasal cavities in the sensitized rats. The severity of nasal inflammation was evaluated by measuring the nasal behavior and EEG spike after antigen challenge. Antigen caused a significant increase of nasal behavior and EEG spike at a dose of 50 μg. Etodolac and ramatroban caused a significant and dose-related inhibition of nasal behavior and EEG spike induced by antigen in rats. On the other hand, indomethacin and zafirlukast had no effects on the responses induced by antigen even at a higher dose. Therefore, it can be concluded that COX-2 is contributed in the allergic nasal inflammation in actively sensitized rats.

Finally, the role of PGD_2 in histamine-induced nasal allergic symptoms was also investigated in this study. It was found that at a dose lower than 1000 nmol, histamine did not provoke the nasal allergic symptoms in rats. PGD_2 also caused no increase of nasal allergic symptoms in rats even at a dose of 10 nmol. On the other hand, co-administration of histamine and PGD_2 at a dose in which they do not individually induce nasal symptoms caused a significant and dose-related increase of nasal symptoms in rats. Chlorpheniramine and cyproheptadine caused a significant and dose-related inhibition of nasal allergic symptoms induced by the simultaneous application of histamine and PGD_2 in rats. Moreover, the nasal allergic symptoms induced by the simultaneous application of histamine and PGD_2 were also significantly inhibited by BW A868C and ramatroban. From these results, it can be suggested that PGD_2 enhance the action of histamine in inducing the nasal allergic symptoms and the action of PGD_2 is occurred through DP_1 and $CRTH_2$ receptor.

論文審査結果の要旨

本研究はラットのアレルギー性鼻炎により生ずるくしゃみおよび鼻掻き行動より客観的な指標を見い出し，その指標を元に，アレルギー性鼻炎に関する各種化学メディエーターの効果とその作用機序を明らかにする目的で行われた．より客観的なアレルギー性鼻炎の指標として，くしゃみが認められる時に，嗅球から spike 波がみられることを見い出した．このくしゃみと spike 波は相関したが，鼻掻き行動とspike 波は相関しなかった．このくしゃみとspike 波は第一世代の抗ヒスタミン薬で抑制され，鼻掻き行動の抑制より強力であった．次に， substance P 点鼻により生ずるくしゃみと spike 波は，ヒスタミンとは関連なく知覚神経の C-fiber に存在する tachykinin NK_1 receptor に関与することを見出した．最後にヒスタミンにより生ずるくしゃみと spike 波に対する prostaglandin D_2 の関与について検討した結果，プロスタグランジンは，自身の受容体を活性化する以外にヒスタミンの効果を亢めることを見出した．

本研究は，アレルギー性鼻炎の客観的な新しい評価方法を開発した点ならびに，それらを用いて，各種化学メディエーターの関与を見出した点で有意義であり，博士（学術）の学位に値すると判断した．