

Abstract

Although there is a renewed interest in the therapeutic potential of cannabinoids, pharmacological and physiological characterisation of these promising compounds is currently not well documented in the respiratory system. The aim of this study is to increase our understanding of possible roles of cannabinoids in the airways.

Apart from CB₁ and CB₂ receptor-mediated actions, cannabinoid compounds can also target TRPV₁ receptors, ion channels or the orphan GPR55. In isolated guinea-pig bronchi, WIN55212-2 probably exerted its inhibitory effect on sensory nerves through CB₂-like receptors. VIR did not act prejunctionally but its excitatory action was mediated through TRPV₁ receptors. Δ⁹-THC activated sensory nerves presumably involving CB₁ receptors. It was speculated that GPR55 might be activated by VIR and antagonized by CBD. CBD revealed multiple mechanisms of actions: it antagonized effects mediated by TRPV₁ and NK₂ receptors, modulated mast cell function and showed anti-allergic activity in an in vitro model of bronchial asthma.

In a human bronchial epithelial cell line the functional expression of CB₁ receptors could not be confirmed. Cannabinoids examined in this study were ineffective to induce signal transduction which would be linked to ion channel activity or to intracellular Ca²⁺ changes. Only VIR might trigger a CB₁ receptor-independent signalling pathway in these cells.

In conclusion, the findings presented in this thesis reflect the diversity of cannabinoid pharmacology in the airways. They show for the first time that CBD has the ability to reduce antigen-induced bronchoconstriction, indicating relevance in bronchial asthma.

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Publications

Abstracts

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Abbreviation

AC	Adenylate cyclase
ACh	Acetylcholine
AEA	Anandamide
2-AG	2-arachidonoylglycerol
AMT	AEA membrane transporter
ANS	Autonomic nervous system
APC	Antigen presenting cell
ASM	Airway smooth muscle
BAL	Bronchoalveolar lavage
bFGF	Basic fibroblast growth factor
BSA	Bovine serum albumin
$[Ca^{2+}]_i$	Intracellular calcium concentration
CB ₁	Cannabinoid receptor 1
CB ₂	Cannabinoid receptor 2
CCE	Capacitative Ca ²⁺ entry
CCh	Carbachol
cDNA	Complementary DNA
CFTR	Cystic fibrosis transmembrane conductance regulator
CGRP	Calcitonin gene related peptide
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CPS	Capsaicin
CysLTs	Cysteinyl leukotrienes
DEPC water	Diethylpyrocarbonate water

DMSO	Dimethyl sulfoxide
dNTPs	Deoxynucleotide triphosphates
EAR	Early asthmatic response
EB	Eosinophilic bronchitis
EDTA	Ethylenediaminetetraacetic acid
EFS	Electrical-field stimulation
EGRF	Epidermal growth factor receptor
EMTU	Epithelial mesenchymal trophic unit
eNANC	Excitatory non-adrenergic non-cholinergic
ETI	5,8,11-Eicosatriynoic acid
ETYA	5,8,11,14-Eicosatetraynoic acid
FAAH	Fatty acid amide hydrolase
FBS	Fetal bovine serum
FcεRI	High-affinity IgE Fc receptor
FEV ₁	Forced expiratory volume in one second
FLIPR	Fluorescence imaging plate reader
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GIRK	Inwardly rectifying potassium channel
GPBP	Guinea-pig bronchial preparation
GPCR	G-protein coupled receptor
GPCRs	G-protein coupled receptors
16HBE	Human bronchial epithelial cell line
16HBE14o-	Human bronchial epithelial cell line
5-HT	Serotonin
IFN-γ	Interferon-γ

IgE	Immunoglobulin E
IL-2	Interleukin 2
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-9	Interleukin 9
IL-13	Interleukin 13
IP ₃	Inositol 1,4,5-trisphosphate
K ⁺ _{Ca}	Calcium-activated potassium channel
LAR	Late asthmatic response
5-LO	5-Lipoxygenase
LTB ₄	Leukotriene B ₄
LTs	Leukotrienes
MAPK	Mitogen-activated protein kinase
Maxi-K ⁺ channels	Large conductance Ca ²⁺ -activated K ⁺ channels
MIP-1α	Macrophage inflammatory protein-1alfa
NA	Noradrenaline
NANC	Non-adrenergic non-cholinergic
NEP	Neutral endopeptidase
NGF	Nerve growth factor
NKA	Neurokinin A
NKB	Neurokinin B
NO	Nitric oxide
NPY	Neuropeptide tyrosine
OEA	Oleylethanolamide
OVA	Ovalbumin

PBS	Phosphate buffered saline
PEA	Palmitoylethanolamide
PGs	Prostaglandins
PGE ₂	Prostaglandin E ₂
PKA	Protein kinase A
PLC	Phospholipase C
PMSF	Phenylmethanesulphonyl fluoride
Pt	Platinum
PTX	Pertussis toxin
RAR	Rapidly-adapting receptor
RBL-2H3	Rat basophilic leukemia cells
SAR	Slowly-adapting receptor
SCF	Stem cell factor
SDS-PAGE	Sodium dodecyl sulphate-polyacrylamide gel electrophoresis
SEM	Standard error of the mean
SP	Substance P
SYK	Spleen tyrosine kinase
TEMED	N,N,N',N'-Tetramethylethylenediamine
TGF- β	Tissue growth factor- β
Δ^9 -THC	(-)- Δ^9 -Tetrahydrocannabinol
Th2 lymphocytes	T helper 2 lymphocytes
TJs	Tight junctions
TNF- α	Tumor-necrosis factor- α
Tris	Trishydroxymethylaminomethane
TrkA	Tyrosine kinase receptor

TRPV ₁	Transient receptor potential vanilloid-1
TTX	Tetrodotoxin
VIP	Vasoactive intestinal peptide
VIR	Virodhamine