Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue1abst011.pdf

Selective CB2 agonist RO6839328 protects mouse kidneys from acute injury

Jürgen Fingerle[1], Sabine Grüner[1], Christian M Apfel[1], Christoph Ullmer[1], Jürgen Funk[3], Ivan Formentini[1], Atsushi Kimbara[2], Mark Roger-Evens[2], Stephan Röver[2], Matthias Nettekoven[2], Franz Schuler[3], Giorgio Ottaviani[3], Stefanie Bendels[2], Uwe Grether[2]. [1]F.Hoffmann-La Roche Ltd, Pharma Research & Early development, Discovery Biology, Grenzacherstr. 124, CH 4070 Basel, Switzerland, [2]F.Hoffmann-La Roche Ltd, Pharma Research & Early development, Medicinal Chemistry, Grenzacherstr. 124, CH 4070 Basel, Switzerland, [3]F.Hoffmann-La Roche Ltd, Pharma Research & Early development, Nonclinical Safety, Grenzacherstr. 124, CH 4070 Basel, Switzerland

Introduction: Agonists of the cannabinoid receptor 2 (CB2) have been shown in several models to exhibit protective effects in ischemic organs like liver and heart. Acute kidney injury is a significant clinical problem as a consequence of multiple conditions including inflammation, necrosis, reduced blood flow, and contrast agents. Here we show protection from warm ischemia/reperfusion (I/R) injury in mouse kidneys using a new CB2 selective and orally bioavailable agonist RO6839328.

Methods: RO6839328 was applied once by gavage 1h before warm I/R, whereby kidney blood flow was interrupted for 25min at 37°C with nontraumatic microvascular clamps. After 24h parameters of kidney function were assessed (plasma creatinine and urea). But also plasma biomarkers of kidney injury (KIM1, NGAL, Osteopontin) were assessed.

Results: RO6839328 is a CB2 agonist with a 139 fold selectivity against CB1 based on Ki (mCB2 Ki = 115nM; hCB2=72nM) and 1500 fold based on cAMP (EC50 mCB2=75nM; hCB2=66nM) as measured in CHO cells transfected with mouse and human CB1/2 receptors respectively. Plasma levels were determined after oral application suggesting to reach plasma concentrations in the range of the EC 50 determined in vitro. Plasma creatinine levels were increased in in vehicle treated animals to 1.3 ±0.15 mg/dl. Treatment with RO6839328 inhibited creatinine levels by 28% at 10mg/kg and 23% at 1mg/kg oral dosing. (Plasma urea was reduced by 22% and 26% respectively). Moreover plasma biomarkers indicative for kidney injury namely KIM1, Osteopontin and NGAL were inhibited by

	1mg/kg dose	10mg/kg dose
KIM1	90%	96%
Osteopontin	58%	76%
NGAL	50%	60%

In contrast scavengers of reactive oxygen species (n-acetyl cysteine=NAC or Tempol) or dopamine agonist Fenoldopam fail reproducibly to reduce induction of plasma biomarkers of kidney injury while being able to improve plasma creatinine by up to 50%.

Conclusions: CB2 agonist RO6839328 is able to protect mouse kidneys from warm ischemia reperfusion injury beyond classical efficacy markers like plasma creatinine and urea. In contrast to drugs used in clinics (NAC, Fenoldopam) the CB2 agonist could reduce biomarkers of kidney injury indicative or kidney organ protection. These data suggest a potential for CB2 agonists to protect kidneys from acute kidney injury.