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Erratum

Airways pharmacology of DNK333A, a dual NK1/NK2 neurokinin receptor antagonist

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The British Pharmacological Society wish to apologise that in the above Supplement the correct abstract for 69P was omitted.

Abstract 69P appears below.

AIRWAYS PHARMACOLOGY OF DNK333A, A DUAL NK_1/NK_2 NEUROKININ RECEPTOR ANTAGONIST.

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The tachykinins, substance P (SP) and neurokinin A (NKA) produce their biological effects through NK_1 and/or NK_2 receptors and have been implicated in respiratory disease (Joos et al., 2000). We here describe the airways pharmacology of DNK333A [((1R,3R,2E)-N-[3,4-dichlorobenzyl)]-4-[(hexahydro-2-oxo-1H-azepin-3-yl)amino]-N-methyl-3,5-bis(trifluoromethyl)benzamide], a novel dual NK_1/NK_2 receptor antagonist.

Affinities to cloned human NK_1, NK_2 and NK_3 receptors expressed in CHO cells were measured in radioligand binding assays using ^{3}H-Sar^{9}SP, ^{125}I-NKA and ^{125}I-MePhe^{7}NKB, respectively. Tracheal rings from male Dunkin Hartley (DH) guinea pigs were set up for recording isotonic tension changes. DNK333A was incubated with the tissues for 15 min prior to Sar^{9},Met$(O_2)^{11}$-SP or (βAla^{8})-NKA(4-10) being applied cumulatively. Male DH guinea pigs (400-550g) were anaesthetised (phenobarbitone 100 mgkg^{-1} and pentobarbitone 30 mgkg^{-1} i.p.), ventilated and airway resistance was measured. Bronchoconstrictor dose-response curves were constructed to Sar^{9}SP or (Ala^{5},β-Ala^{8})-α-NKA(4-10) given i.v. In other experiments, the nasopharynx was perfused (0.25 mlmin^{-1}) with saline or SP (10^{-4}M 10 min) and the concentration of Evans blue dye, injected i.v. 10 min prior to SP challenge measured, in the perfusate by spectrophotometry.

Female squirrel monkeys (500-800g) were anaesthetised (Saffan™ 3.6 mgkg^{-1} and 0.6 mgkg^{-1} valium™ i.m.), intubated, but spontaneously breathing and airways resistance measured before and after aerosolised (β-ala^{8})-NKA (1 mM for 5 min). Mean values ± s.e. mean are presented and significance is defined by p values < 0.05 (Mann Whitney Rank sum test).

DNK333A bound with high and similar affinities to human NK_1 (pKi, 7.90 ± 0.12, n=3) and NK_2 (pKi, 8.02 ± 0.02, n=4) receptors and showed selectivity over NK_3 (pKi, 6.87 ± 0.05, n=3). In guinea pig trachea *in vitro*, DNK333A induced concentration-dependent, surmountable blockade of constrictor responses induced by selective NK_1 (pKB, 7.93 ± 0.1, n=3) and NK_2 (pKB, 7.27 ± 0.1, n=4) agonists. In guinea pigs, DNK333A (-2h, p.o., n=4-5) significantly shifted the bronchoconstrictor dose-response curve by 21.8- (3 mgkg^{-1}) and 6.8-fold (10 mgkg^{-1}) for the NK_1 and NK_2 receptor agonists, respectively and had a duration of action of up to 12 h (10 mgkg^{-1} p.o.). Also in guinea pigs, DNK333A (0.3-0.75 mgkg^{-1}, p.o., -2 h, n=10) suppressed NK_1 receptor mediated nasal extravasation induced by SP (ED_{50}, 0.07 mgkg^{-1}) and showed a duration of action of > 8 h following 1 mgkg^{-1} p.o. In squirrel monkeys, DNK333A (1-10 mgkg^{-1} p.o., -2 h, n=12) inhibited dose-dependently the bronchoconstrictor response to aerosolised (β-ala^{8})-NKA (ED_{50}, 1 mgkg^{-1}).

These data establish DNK333A as a potent, dual NK_1/NK_2 receptor antagonist *in vitro* and *in vivo*. The potency and long duration of action renders DNK333A particularly suitable for exploring the role of tachykinins in respiratory disease.

Joos G.F. et al. (2000) *Allergy* 55 (4) 321-337