Peptide YY (PYY) and pancreatic polypeptide (PP) promote satiety and alter intestinal functions in response to food ingestion by activating Y2 and Y4 receptors, respectively. These satiety hormones have generated considerable interest recently in the pursuit of novel anti-obesity drugs. Our collaborators, 7TM Pharma, have developed novel dual Y2/Y4 agonists (TM48560 and TM48563) that have been lipidated and pegylated to gain increased stability, potency and longevity of responses compared to existing dual and single receptor agonists (TM30338, a Y2/Y4 dual agonist and TM30339, a Y4 receptor agonist only), as potential anti-obesity treatments.

Here we investigated the antisecretory effects of Y2/Y4 agonism on human (h) epithelial monolayers (Col-24) that constitutively express the Y4 receptor (Cox et al., 2001). Confluent monolayers were mounted in Ussing chambers and short-circuit current (Isc) recorded (Cox et al., 2001). Monolayers were prestimulated with vasoactive intestinal polypeptide (VIP, 30nM) and 20 min later a Y4 agonist was added (to the basolateral surface throughout). The time dependence of epithelial Isc responses was recorded for up to 60 min and compared with reductions in Isc to hPP. A final addition of hPP (10 nM) was made to determine the degree of Y4 receptor desensitization. Concentration-response curves were non-cumulative and EC50 values were determined using GraphPad Prism (V.501). Multiple comparisons were calculated using one-way ANOVA with a Dunnett’s post-test comparing all groups with control hPP (10nM) responses (P < 0.05 being significant).

Responses to single additions of TM30338 (100nM) reduced Isc with a peak response within 10 min (maximal response of -1.3 ± 0.17µA.cm⁻²; n=3). Similarly, additions of TM30339 reduced Isc with a peak response within 10 min (maximal response of -1.0 ± 0.21µA.cm⁻²; n=5). This transient Isc response was comparable to 10nM hPP (maximal response of -2.7 ± 0.32µA.cm⁻²; n=12). Single concentrations of the novel dual agonists (TM48560 and TM48563, 100nM) resulted in an increase in the longevity of the Isc response compared with their predecessors, with maxima being achieved after 40 min.

Concentration-response curves showed an increased potency with TM30339 (EC50 = 4.8nM) compared with TM30338 (EC50 = 36.0nM). Initial data indicates that the potencies of TM48560 and TM48563 have not been altered by their chemical modifications.

Basolateral additions of a maximally effective concentration of hPP (10nM) significantly attenuated the response to a second application of hPP (10nM) 20 min later (P<0.001). Responses to hPP were also reduced following TM30338 (1nM-3uM, P<0.05) and TM30339 (1-300nM, P<0.05) in a concentration-dependent manner. Both modified dual agonists also caused desensitisation to subsequent hPP responses and this effect was more significant with TM48560 (0.3- 1000nM, P<0.01).

In conclusion our data provides the first functional evidence that the modified new Y2/Y4 receptor agonists have prolonged antisecretory effects in comparison to their non lipidated predecessors. With such prolonged activity at the Y4 receptor, these modified dual agonists may act as potential anti-obesity treatments.

Cox et al., 2001. BJP 132, 345 -353

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