FUNCTIONAL HETEROGENEITY OF HISTAMINERGIC NEURONS SUGGEST INTERESTING APPLICATIONS OF GSK189254, A NOVEL H_3 RECEPTOR ANTAGONIST

Patrizia Giannoni[1], M.Beatrice Passani[1], Daniele Nosi[2], Andrew D. Medhurst[3], Paul Chazot[4], Fiona Shenton[4] and Patrizio Blandina[1]

[1]Dipartimento di Farmacologia Preclinica and Clinica, [2]Dipartimento di Anatomy Universita' di Firenze Italy, [3]Neurology Centre of Excellence for Drug Discovery,GlaxoSmithKline,Essex CM19 5AW, UK, [4]Centre for Integrative Neuroscience, School of Biological and Biomedical Sciences, Durham University, UK

Neuronal histamine (HA) is released from axon varicosities innervating the entire brain. The only source of HA fibers is the tuberomammillary nucleus (TMN) in the posterior hypothalamus. Several receptors control HA neurons activity. To learn whether functional differences exist among HA neurons projecting to different brain areas, SD rats were implanted with one probe in the TMN, and one in the nucleus basalis magnocellularis (NBM), nucleus accumbens (NAc), dorsal striatum (DS) or prefrontal cortex (PFC). HA output from the two probes perfused with Ringer at 2-µl/min, was measured in 15-min samples by HPLC-fluorometric detection.The H_3 receptor (H_3R) antagonist thioperamide (300nM), or the $GABA_A$ receptor atagonist bicuculline (10 µM) were infused for 60 min into the TMN, where HA cell bodies are localized. Both drugs increased HA release from the TMN and PFC, but not from the DS. Thioperamide, but not bicuculline increased HA release from the NBM. Conversely, bicuculline and not thioperamide increased HA release from the NAc. Effects similar to those obtained with thioperamide were observed with a novel H_3 receptor antagonist, GSK189254. Spontaneous HA release from all regions was stable, ranging between 0.05-0.08 pmol/15min (N=18). GSK189254 (1µM), infused for 60 min into the TMN, increased HA release from the TMN and PFC, but not from the DS, nor the NAc. These results demonstrate that H_3R blockade does not activate all HA neurons. Significant effects were determined by ANOVA/Fisher's test. To add strength to this observation, we examined H_3R distribution on HA neurons. Hypothalamic slices were labelled with anti-H_3R and anti-histidine decarboxylase (HDC)-antibodies. Confocal analysis showed HDC-positive cell bodies or dendrites strongly immunopositive for H_3R, and HDC-positive cell bodies or dendrites weakly immunolabelled for H_3R, thus suggesting the existence HA neurons with different densities of H_3R. H_3R ligands may be important in the treatment of cognitive deficits, sleep disorders and obesity. Recruitment of HA subpopulations may achieve more selective actions, and reduce collateral effects.