ABSTRACTS

P1.1
MODULATION OF EXTRASYNAPITIC GABAA RECEPTORS BY G-PROTEIN-COUPLED RECEPTORS

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$GABA_A$ receptors ($GABA_ARs$), the main inhibitory neurotransmitter-gated ion channels in the central nervous system, are finely tuned by other neurotransmitters and endogenous ligands. The regulation of synaptic $GABA_ARs$ ($sGABA_ARs$) by G protein-coupled receptors (GPCRs) has been well characterized and is known to occur either through the conventional activation of second-messenger signalling cascades by G proteins or directly by protein-protein coupling. In contrast, research on the modulation of extrasynaptic $GABA_AR$ (eGABAARs) is still in its infancy and it remains to be determined whether both of the above mechanisms are capable of controlling $eGABA_AR$ function. In this talk, I will summarize the available literature on $eGABA_AR$ modulation by GPCRs, including $GABA_B$, dopamine (DA) and serotonin (5-HT) 2A/2C (5–$HT_{2A/2C}$). Although at present these GPCRs−$eGABA_ARs$ cross-talks have been investigated in a limited number of brain areas (i.e. thalamus, cerebellum, hippocampus, striatum), it is already evident that $eGABA_ARs$ show nucleus and neuronal type-selective regulation by $GPCR_s$ that differs from that of $sGABA_ARs$. This distinct regulation of $eGABA_ARs$ versus $sGABA_ARs$ by GPCRs provides mechanisms for receptor adaptation in response to a variety of physiological stimuli and under different pathophysiological conditions. Further research will advance our understanding of $eGABA_ARs$ and GPCR signalling and offer novel targets for the treatment of many neurological and neuropsychiatric disorders where abnormalities in $eGABA_ARs$ have been suggested to exist.

KEY WORDS: Absence epilepsy, metabotropic receptors, monoamines, phosphorylation, tonic $GABA_A$ inhibition.

P1.2
GPCR LIGANDS PROBING STRUCTURE AND CONTROLLING FUNCTION

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GPCRs constitute a large superfamily of target proteins (nearly 800 different human genes encode for GPCRs) and each of them can adopt functionally distinct conformations. The first X-ray crystal structures of druggable GPCRs in complex with ligands provide a basis for the investigation of molecular determinants responsible for affinity and selectivity of ligands. Moreover, the structures of different activity states of GPCRs allow us to identify molecular interactions discriminating between inverse agonists, antagonists and agonists. These fundamental results also contribute to the rational discovery of drugs selectively binding to particular conformational states. Thus, there is growing evidence that homo- and heterodimers effect and diversify G-protein coupling. Besides this, the concept of functional selectivity (biased signaling) owing to ligand-specific GPCR conformations has been corroborated. Although GPCR-binding drugs could be evolved for a number of target GPCRs, the rational development of drugs with beneficial selectivity patterns between structurally related GPCRs and functionally relevant GPCR conformations, controlling intrinsic activity profiles, requires a better understanding for GPCR ligand interactions. We have developed GPCR ligands as molecular probes for structural investigations and structure-function relationship studies. Probing the molecular determinants of GPCR function, we designed functionally selective dopamine D2 receptor agonists that are able to differentiate between the activation of two relevant G-proteins, G_o and G_i.

KEY WORDS: GPCR, molecular probe, functional selectivity.

P1.3
FROM MAGIC BULLET TO SCATTERGUN: IS THERE A VIABLE ALTERNATIVE?

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It is over 100 years since the Ehrlich concept of the magic bullet, but, leaving aside monoclonal antibodies,