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Melatonin receptors: Molecular and functional considerations

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Melatonin is a neurohormone mainly synthesized by the pineal gland at night. It is the main endocrine output of the circadian master clock in the way that it relays the succession of nights and days to central and peripheral organs. Melatonin acts through 3 main reported proteins: The seven trans-membrane domain G-coupled receptors, MT1 and MT2; and the MT3 binding site, identical to the cytosolic enzyme quinone reductase 2. The exact characteristics of the binding of the ligands at MT1 and MT2 receptors is poorly documented, as often in the GPCR area, because purification of a functional receptor and its crystallization are difficult, at best. We succeeded in assessing a protocol leading to an active MT1 receptor in milligram amounts, with binding characteristics similar to those of the membrane MT1 receptor. We are using this material to reconstitute a functional MT1 in nanodiscs. Depending on the nature of the signaling pathways measured, more and more is reported concerning the biased nature of receptor ligands, particularly the agonists. We report here the molecular pharmacology of both recombinant human MT1 and MT2 receptors with a set of 24 molecules and 5 signalization pathways (GTPγS, cAMP, cellular dielectric spectroscopy, receptor internalisation, β-arrestin) as well as their binding affinities. These studies clearly show that depending on the chemical nature of the ligands, the pathway by which the signal is transmitted is different and the nature of the GPCR/ligand might vary from very partial agonist (almost antagonist) to pure agonist. These data will help the scientists in the field to build better compounds purer in their actions, and probably more specific.

Biography

Jean A Boutin has completed his PhD from the Faculty of Nancy (France) in 1983 on Phase II Drug Metabolism enzymes and Postdoctoral studies from Johns Hopkins University School of Medicine (Baltimore, MD) and Karolinska Institutet (Stockholm, Sweden). He is the Director of the early drug discovery platform of the French Pharma Laboratoires Servier. He has published more than 200 papers in peered journals. His main interests, beside melatonin, are N-myristoyltransferase and quinone reductase 2, as well as a series of peptide-based research programs aiming at both the assessment of new research tools and the discovery of new drug candidates.

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