Partial agonism in the picture

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One of the first pharmacologists to address the concept of partial agonism on G protein-coupled receptors was Evert Ariëns (1918-2002). In his typical way of phrasing he used to compare a partial agonist with a pianist having one hand bound, somehow suggesting that partial agonism is troublesome. A first realization is that partial agonism is not only compound- but also context-dependent. As an example, an adenosine A_1 receptor agonist may be a partial agonist in heart tissue but emerge as a full agonist when studied on fat pad lipolysis, as a consequence of differences in receptor densities. Secondly, with an evolving understanding of cellular pharmacology it is now also appreciated that even within a cell a ligand may act as a full agonist for certain cellular pathways, e.g. G protein activation, while in others it is only partially so, e.g. in beta-arrestin modulation. This biased behavior may offer opportunities for drug discovery, but it seems that most pharmaceutical companies, keeping Ariëns's metaphor in mind, are hesitant to spend time and other resources on the phenomena of both partial and biased agonism.

Over the years my team together with colleagues over the world has studied partial agonism on the four subtypes of adenosine receptors, aspects of which I will integrate into this lecture. Our joint efforts have recently culminated in elucidating the structure of the adenosine A_{2A} receptor in the presence of a partial agonist. This detailed 3D architecture provides atomic resolution of the principle of partial agonism with clear hints for future drug discovery.