8. Functional Selectivity / Biased Agonism

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Taking advantage of the publication of two reviews on this topic by two of our colleagues from the SBFTE (Costa-Neto et al., 2016; Pupo et al., 2016), we felt it timely to revisit the concept of **functional selectivity (biased agonism)**.

The phenomenon whereby different agonists acting at the same receptor selectively activate distinct cellular signaling pathways has been referred to by different names, with the term **"functional selectivity"**, first proposed by the group of Richard Mailman in 1994, being the most commonly used (Kenakin and Miller, 2010). In a conceptual and consensus article published in 2007, several leading investigators proposed that ligands induce different receptor conformations, unique and ligand-specific, which often result in differential activation of the signaling transduction pathways associated with that receptor (Urban et al., 2007). For 7TM receptors (GPCRs), coupling may occur not only with G proteins (the canonical pathway) but also with other cytosolic proteins, among which arrestins are the best characterized.

> *Note on terminology. The term **"functional selectivity"** has the advantage of being descriptive and mechanistically neutral (Urban et al., 2007). By contrast, the term **"biased agonism"** could be criticized because the word bias may carry a pejorative connotation, as when used to indicate experimental or statistical bias (or even a personal preference).*

This new concept is triggering a tsunami in classical pharmacology, generating new challenges, as outlined below:

- Challenge 1 (and discomfort): Functional selectivity forces us to revisit the concept of intrinsic efficacy and drug nomenclature. Classically (Furchgott, 1966, cited in Kenakin, 2013), intrinsic efficacy is a measure of the stimulus produced by receptor occupancy and is considered a system-independent parameter, that is, constant for a given ligand at a given receptor regardless of where that receptor is expressed. Thus, agonists are classically defined as substances capable of activating receptors, whereas antagonists have no intrinsic effect other than blocking agonist-mediated receptor activation. We now know that certain receptor ligands can act as antagonists for one signaling pathway while simultaneously acting as agonists for another pathway linked to the same receptor. A now classic example of such "Janus-faced" drugs is propranolol and carvedilol, which block the increase in cAMP levels mediated by activation of the β_2-adrenergic receptor while simultaneously activating the ERK pathway via β-arrestin (Kenakin and Miller, 2010).

- Challenge 2 (and opportunity): The possibility of designing ligands with selectivity for a specific signaling pathway may lead us to the discovery of truly innovative drugs, by enabling the separation of beneficial effects from adverse effects that were previously considered intrinsically linked because they depended on activation or inhibition of the same receptor. The potential is such that, in 2007, a company (Trevena®) was created focusing exclusively on the discovery and development of ligands with functional

selectivity for G protein-coupled receptors. Oliceridine (TRV130) is a new "biased" ligand of the μ-opioid receptor that activates Gi protein-mediated signaling (responsible for analgesia) with minimal recruitment of β-arrestin (responsible for gastrointestinal and respiratory adverse effects) (Kingwell, 2015), and it successfully completed a phase IIb clinical study in May 2016.

CONCLUSION

This new paradigm is already affecting the way pharmacology should be conceived, taught, and applied to the process of new drug discovery.

References

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