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New vistas on NO-cGMP signalling

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Recognition that a biochemically familiar enzyme called (in homogenate terms) soluble guanylyl cyclase (GC), serves as the major physiological receptor for NO immediately raises a host of questions concerning how this receptor transduces NO signals in the many different cells in which it is found. Simply calling it a receptor (which it is) is helpful in bringing into play a wealth of theoretical and practical knowledge built up over decades to describe and understand the principles of biological signalling mechanisms. Viewed in this context, much of the most basic information about the operation of GC-coupled NO receptors was missing or incoherent. During the last few years, we and others have tried to rectify this situation. Devising methods for supplying NO in known, constant concentrations [1,2] was a prerequisite for carrying out meaningful experiments. Measurement of the potency of NO for activating GC and of the rates of activation and deactivation has now permitted the introduction of a simple but realistic kinetic model [3]. The receptors in cells can detect very brief NO signals (millisecond range) because they activate and deactivate with subsecond kinetics, and they can also detect very low NO concentrations (subnanomolar) There are, however, a number of important differences in the way that the receptors behave in cells versus cell-free preparations. For example, in homogenates or with the purified protein, NO is about 10-fold more potent as an agonist than it is in intact cells and, unlike in cells, NO-evoked GC activity does not desensitize. The possible role of a number of endogenous factors in shaping NO-evoked GC activity in cells will be discussed.

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References

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