Abstract Our knowledge of nitric oxide (NO) as a crucial endogenous signalling molecule continues to expand. Many, but not all, of the actions of NO are mediated by activation of soluble guanylyl cyclase (sGC) in target tissues. The aim of this chapter is to encapsulate the functions of NO in mammalian biology, tied to...
the chemistry of this unusual signalling entity. The experimental usefulness and therapeutic potential of the most widely utilised NO donor drugs is reviewed, with special consideration given to the importance of choosing the correct NO donor for any given experiment, in vitro, in vivo or in clinical studies.

Keywords: Nitric oxide · Measurement · NO donors · Organic nitrates · NONOates · Nitrosothiols · NO hybrids

1 Introduction

Nitric oxide (NO) and its interaction with soluble guanylyl cyclase (sGC) has turned our understanding of endogenous signalling on its head: no longer is cell signalling the exclusive domain of large organic or peptide molecules that dock with specific receptors to trigger downstream events. For NO is a small, inorganic free radical that has a very short half-life in biological systems and, whilst sGC is generally regarded to be its primary target, its reactive nature facilitates a wide variety of chemical interactions, accounting for a range of cGMP-independent effects, particularly when generated in large amounts.

NO is now recognised to have crucial roles in the cardiovascular, nervous and immune systems and it is unsurprising that, since its identification as a key mediator in the 1980s, the interest in NO and its biological functions has mushroomed: each year since 1995, there have been >2000 papers that include “nitric oxide” in the title and many more that deal with some aspect of NO. In this chapter, we have concentrated on providing an overview of the different roles of NO as a precursor to discussing the use of NO donor drugs as sGC stimulators in pre-clinical and clinical studies, both as tools for investigating the role of NO and as potential therapeutics. There are now a wide range of NO donors available, each with its own specific properties: selection of the best-suited agent for the purposes of a specific experiment is a critical consideration that is easily overlooked and can have a significant bearing on the results that are obtained and their interpretation.

1.1 Functions of NO

NO is a powerful vasodilator but its actions, both within the cardiovascular system and elsewhere, range well beyond its ability to relax vascular smooth muscle (see Moncada et al. 1991 for comprehensive review). Remarkably, NO is now recognised to behave as a neurotransmitter, neuromodulator, anti-thrombotic agent, pro- or anti-inflammatory agent, modulator of cellular respiration and cytostatic and cytoxic agent, depending on the concentration of NO in the locality, together with its source (Fig. 1).