Enhanced Cell Proliferation Induced by Nitric Oxide

Antonio Villalobo

ABSTRACT

Nitric oxide (NO) regulates multiple physiological functions including cell proliferation. The regulatory action of NO on cell proliferation is exerted in a bimodal mode, enhancing and inhibiting the progression of the proliferative process depending on the actual concentration of NO encountered by the cell. Although not all details are understood, the cytostatic action of NO, when attained at high concentrations, has been studied in more depth. However, the stimulatory action of minute quantities of NO on cell proliferation has received less attention, although its potential physiological importance is already apparent. Knowledge on the molecular mechanisms and signalling events responsible for the enhancement of cell proliferation induced by NO are still very limited, although new findings have started to uncover some of their details. In this review I shall describe the progress done in the last few years on this respect, and explore the physiological relevance of the enhancement exerted by NO on the proliferation of cells relevant for the regulation of normal organism growth and development. The action of NO stimulating the proliferation of tumour cells has become also an important pathophysiological issue and it will be outlined. The studies concerning the action of NO on cancerous cells could be significant to better understand the molecular mechanisms underlying this pathological process and its possible therapeutic control.

Keywords: Cell cycle, growth factors, nitric oxide synthase, tumour growth.

INTRODUCTION

Nitric oxide (NO) is a highly reactive free radical gas that is biologically generated by organisms ranging from bacteria to humans. Its synthesis in mammalian cells during the transformation of the substrate L-arginine to L-citrulline with the concourse of O2 is catalysed by three isoforms of the enzyme nitric oxide synthase (NOS), using the reducing power of the electron donor NADPH. The NOS family is composed of the so-called neuronal (nNOS; NOS-I), inducible (iNOS; NOS-II) and endothelial (eNOS; NOS-III) isoforms of the enzyme. The constitutive NOS and eNOS isoforms are regulated by the Ca2+/calmodulin (CaM) complex, which is formed upon rise of the cytosolic free Ca2+ concentration ([Ca2+]cyt) induced by multiple extracellular stimuli, while CaM is an intrinsic subunit of NOS.

NO exerts multiple biological actions working as an intracellular and extracellular messenger encompassing the regulation of the functionality of the vascular system, neurological functions, and the control of some aspects of the immune response, among other emerging roles of great physiological significance.

Not surprisingly, among the new uncovered roles of NO the regulation of cell proliferation stands out. As many reports attest, the major effect exerted by NO on cell proliferation in many normal and tumour cell types appears to be the arrest of cell cycle progression and the subsequent inhibition of the proliferative process (see for review Villalobo 2006). There are, however, a significant number of reports describing the stimulatory action of NO on cell proliferation. The reason for this biphasic phenomenon is not yet well understood in great detail, although recent findings...

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suggest that the actual concentration of NO is a critical factor for this dual behaviour. Thus, increasing proliferation at low concentrations (i.e. using NO donors in the mmolar or sub-mmolar ranges in most cases) inhibiting proliferation when its concentration rises (i.e. using NO donors in the mmolar range). In what follows, I shall describe a number of observations related to the stimulatory effect of NO on the proliferation of normal and tumour cells, some of the molecular mechanisms that underlie this process, and the physiological significance of this puzzling phenomena.

NO as a stimulator of cell proliferation

The analysis of the impact of suppression of endogenous NO production and/or the impairment of its availability to the cell could provide a good indication of whether NO has a positive action on cell proliferation, or not. Thus, it has been demonstrated that in lung epithelial and pleural mesothelial cells the depletion of endogenous NO by carbonyl-PTIO, an NO scavenger compound, stops cell proliferation by arresting the cell cycle at the late S or G2/M phases, events that are mediated by a CGMP-dependent pathway (Janssen et al. 1998).

Moreover, the knockout of the nNOS gene results in decreased proliferation of neural precursors with the subsequent depletion of immature neurones in the olfactory epithelium of new-born mice, and altered organisation of glo- merular cell layers in the adult olfactory bulb, suggesting a positive action of NO on early postnatal development (Chen et al. 2004). This latter assertion appears to be corroborated in other regions of the central nervous system using a different experimental approach. Thus, it has been demonstrated that proliferation of granule cell precursors in the adult dentate gyrus, induced by generalised clonic sei-
desmobilized by an nNOS inhibitor (Jiang et al. 1999), pancreatic tumours (Hajri et al. 1998), myo-
blasts (Ulibarri et al. 1999), keratinocytes (Krischel et al. 1998; Frank et al. 2000), ven endothelial cells (Luczak et al. 2004), and pheochromocytoma PC12 cells (Bal-Price et al. 2006), among others.

The proliferation of kidney glomelular endothelial cells mediated by VEGF is also under the control of NO as the treatment of experimental animals with L-NIL, an iNOS inhib-
itor, decreases its proliferation, while no effect of the inhibi-
or was detected in non-endothelial cells in the same tissue preparations (Ostendorf et al. 2004). Furthermore, in human umbilical vein endothelial cells the NOS inhibitor L-
NAME blocks VEGF-induced proliferation (Hood and Granger 1998).

A supplement of L-arginine increases nNOS expression in retinal cells concomitant with increased proliferation (Kim et al. 2002). This suggests that NO may also have a proliferative action in these cells. Nevertheless, reports describing the inhibitory action of NO on retinal cells have been published (Goureau et al. 1993; Yilmaz et al. 2000), suggesting again that the actual concentration of NO att-
tained in different experimental conditions may be a deci-

tive factor to explain this apparent disagreement. Pro/feration of the exocrine pancreas appears to be regulated also in a bimodal manner by endogenous NO. In this case, during cholestocystokin-in-8 (CCK-8)-induced hyperplasia, NO induces proliferative arrest in acinar cells but increases proliferation in ductal cells, while enhancing cell proliferation in basal non CCK-8-stimulated conditions (Trulsson et al. 2002). Moreover, during CCK-8-induced hyperplasia, exogenous NO enhances acinar cell turnover, suppress apoptosis, and favours cell regeneration increasing both proliferation and cell death via a non-apoptotic path-
way (Trulsson et al. 2004).

Table 1 summarizes some examples in which NO has been shown to stimulate the proliferation of different normal and tumour cell types in vitro upon the addition of NO donors of various chemical structures. The NO donors used in each instance and the concentration range at which en-
hanced proliferation was observed are indicated.

Implication of NO in tumour cells growth

The action of NO on tumour development and progression, its positive role in the induction of tumour-associated an-
giogenesis and its dual activating and inhibiting roles in tumour cell proliferation has been studied in detail (see for example Fukumura et al. 2006). In this section, therefore, I shall give a few examples on the stimulatory role of NO on the proliferation of different tumour cells.

Exogenous NO enhances the proliferation of human chorioncarcinoma JEG-3 cells and prevents the differenti-
ation of cytotrophoblasts to syncytial cells, processes that could be mediated by the expression of nNOS (San
yal et al. 2000). The NO-mediated increased proliferation of chorio-
carcinoma cells is not universal, however, as endogenous and exogenous NO inhibits the proliferation of the tropho-
blast-like chorioncarcinoma BeWo cell line (Cha et al. 2001). Ovarian carcinoma cell proliferation is negatively regulated by high concentrations of 17β-oestradiol, and negatively or positively regulated by progesterone depending on its concentra-
tion. These effects appear to be controlled by a posi-
tive action of NO on cell proliferation as lower growth cor-
related with decreased iNOS expression and vice versa (Bec
tel and Bonavida 2001). In human A375 malignant melanoma cells the proliferative response to VEGF appears to be mediated by endogenously produced NO because the enhanced proliferation of cells transfected with VEGF is accompanied by iNOS overexpression, and the NOS inhibi-
tor L-NAME, restrains its proliferation (Tao et al. 2005). Moreover, although NO has been implicated in the prolif-

erative arrest of normal T lymphocytes, its implication in the sustained proliferation of the T lymphoma BW5147 cell
line was demonstrated, a process that appears to be mediated by iNOS overexpression in the proliferating but not the arrested tumour cells (Barreiro-Arcos et al. 2003).

A few examples of enhanced cell proliferation attained in vitro upon addition of a variety of NO donors on tumour cells, and the concentration range at which the effect was observed, are also collected at the end of Table 1.

**Mechanistic insights on NO-induced proliferation**

Information on the action of NO activating the cell cycle machinery is rather scanty. Thus, there is a single report in which it has been shown that an ill-defined gaseous mixture of nitrogen oxides, possibly containing NO, increases the proliferation of lung fibroblasts, a process mediated by enhanced production of the cyclin-dependent kinases 2 and 4 (Cdk2 and Cdk4); enhanced phosphorylation of the retinoblastoma protein (pRb), and decreased expression of the cyclin-dependent kinase inhibitors p27Kip1 and p16Ink4a, while no effect was detected on p21Cip/Waf1 expression (Chen et al. 2003). Nevertheless, the actual nature of the agent(s) inducing those effects on the cell cycle remains to be established as the complexity of the gaseous mixture used prevents the identification of NO as the direct intervening agent.

In coronary venular endothelial cells, exogenous and endogenous NO both induce a proliferative response by a mechanism implicating basic fibroblast growth factor (bFGF), as an anti-bFGF antibody blocks NO-mediated proliferation (Ziche et al. 1997). In addition, the proliferative action of exogenous NO, via activation of the mitogen-activated protein kinase (MAPK) pathway, was also demonstrated in foetalplacental artery endothelial cells (Zheng et al. 2006), suggesting a positive role of NO in angiogenesis. Moreover, in endothelial cells and cardiomyocytes, VEGF not only upregulates the expression of eNOS but activates this enzyme either by increasing the [Ca**2+**]cyt, and subsequent formation of the Ca**2+**/CaM complex, by activation of the phosphatidylinositol-3-kinase (PI3K)/Akt pathway and/or by recruitment of heat-shock protein 90 (Hsp90) (Duda et al. 2004; Lepic et al. 2006). VEGF-mediated proliferation of umbilical vein endothelial cells and activation of Raf-1, the first kinase of the MAPK cascade, are NO-dependent processes controlled by cGMP and its target protein kinase G (PKG) (Hood and Granger 1998). This was demonstrated because of the formation of a Raf-1/PKG complex detected by immunoprecipitation, and because PKG inhibitors prevent both VEGF-induced proliferation and Raf-1 phosphorylation (Hood and Granger 1998). Consistent with the proliferative action of NO mediated by the activation of the MAPK pathway is also the observation that this agent activates its upstream regulator Ras promoting the GDP/GTP exchange because of the S-nitrosylation of its cysteine 118 (Lander et al. 1995, 1996).

The proliferation and differentiation of osteoblasts induced by 17β-oestradiol is also mediated by the enhanced expression of eNOS (O’Shaughnessy et al. 2000). In agreement with this observation, exogenous NO, supplied as an NO donor, also has a proliferative effect on osteoblasts, a process that is independent of cGMP (Kanamaru et al. 2001). In addition, osteoblasts proliferation, induced by a pulsed electromagnetic field, was prevented by a NOS inhibitor (Diniz et al. 2002). However, 17β-oestradiol has been shown to increase NO production by vascular smooth muscle cells, which is accompanied by decreased proliferation concomitant with decreased c-fos expression (Yang et al. 2002), suggesting that the mechanism of action of the 17β-oestradiol/NO system is not universal, and could well depend on the actual concentration of NO generated and/or available in the system.

Mechanistically, the NO-mediated enhanced proliferation of vein endothelial cells appears to require the secondary production of reactive oxygen species (ROS) because superoxide dismutase and catalase in part suppress the stimulatory effect (Luczak et al. 2004). Moreover, the stimulatory effect of NO on aortic endothelial cells was the consequence of eNOS activation by the Ca**2+**/CaM complex. This complex is formed upon rise of the Ca**2+**/CaM, induced by activation of CD44v10, a hyaluronan receptor, after interacting with its extracellular ligand, and recruitment and activation of inositol-1,4,5-trisphosphate receptors (IP3R) in the endoplasmic reticulum via the cytoskeleton adaptor ankyrin (Singleton and Bourguignon 2004).

Although an early report suggested that proliferation of mesangial cells was not affected by exogenously added or endogenously produced NO (Mohaupt et al. 1994), a more recent report demonstrates that NO expression in mesangial kidney cells induced by LPS plus IFNγ treatment re-

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**Table 1** Stimulatory action of exogenous NO on the proliferation of cultured cells.

<table>
<thead>
<tr>
<th>Cells</th>
<th>NO donor</th>
<th>Concentration (μM)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary venule endothelial cells (bovine)</td>
<td>SNAP</td>
<td>1-100</td>
<td>Ziche et al. 1997</td>
</tr>
<tr>
<td>Umbilical vein endothelial cells (human)</td>
<td>SNAP</td>
<td>1</td>
<td>Luczek et al. 2004</td>
</tr>
<tr>
<td></td>
<td>GSNO</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SIN-1*</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Fetoplacental artery endothelial cells (sheep)</td>
<td>SNAP</td>
<td>1</td>
<td>Zheng et al. 2006</td>
</tr>
<tr>
<td>Cardiomyocytes (mouse)</td>
<td>DETANO</td>
<td>2</td>
<td>Lepic et al. 2006</td>
</tr>
<tr>
<td>Myoblasts (turkey)</td>
<td>SNAP</td>
<td>1-10</td>
<td>Ulbarri et al. 1999</td>
</tr>
<tr>
<td></td>
<td>SNAP</td>
<td>5-10</td>
<td></td>
</tr>
<tr>
<td>Mesangial MES-13 cells (murine)</td>
<td>SNAP</td>
<td>100-200</td>
<td>Sheu et al. 2005</td>
</tr>
<tr>
<td></td>
<td>SNAP</td>
<td>100-500</td>
<td></td>
</tr>
<tr>
<td>Keratinocytes (human)</td>
<td>DETANO</td>
<td>50-250</td>
<td>Krischel et al. 1998</td>
</tr>
<tr>
<td></td>
<td>SNAP</td>
<td>50-500</td>
<td></td>
</tr>
<tr>
<td>HaCaT keratinocytes (human)</td>
<td>GSNO</td>
<td>100</td>
<td>Frank et al. 2000</td>
</tr>
<tr>
<td></td>
<td>DETANO</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>MC3T3-E1 osteoblasts (mouse)</td>
<td>SNAP</td>
<td>10-100</td>
<td>Kanamaru et al. 2001</td>
</tr>
<tr>
<td>BALB/c 3T3 fibroblasts (mouse)</td>
<td>SNAP</td>
<td>5-20</td>
<td>Du et al. 1997</td>
</tr>
<tr>
<td></td>
<td>GSNO</td>
<td>25-50</td>
<td></td>
</tr>
<tr>
<td>W138 fibroblasts** (human)</td>
<td>SNAP</td>
<td>1000</td>
<td>Gansauge et al. 1997</td>
</tr>
<tr>
<td></td>
<td>SNAP</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>Pancreatic tumour HA-hpc2 cells (human)</td>
<td>SNAP</td>
<td>250-1000</td>
<td>Hajri et al. 1998</td>
</tr>
<tr>
<td>Ovarian carcinoma HOC-7 cells (human)</td>
<td>SNAP</td>
<td>10</td>
<td>Bechtel and Bonavida 2001</td>
</tr>
<tr>
<td>Choriocarcinoma JEG-3 cells (human)</td>
<td>SNAP</td>
<td>5-40</td>
<td>Sanyal et al. 2000</td>
</tr>
<tr>
<td>Phaeochromocytoma PC12 cells (rat)</td>
<td>DETANO</td>
<td>25-50</td>
<td>Bal-Prieto et al. 2006</td>
</tr>
</tbody>
</table>

* The indicated concentrations of NO donors represent the range at which increased cell proliferation was observed. Higher concentrations of NO donors may inhibit cell proliferation (for review see Villalobo 2006). * SIN-1 is an NO· plus O2·- donor. ** Senescent fibroblasts. See text for additional details and the abbreviations list for the full name of the NO donors used.
The implication of NO\textsuperscript{·} in the control of cell proliferation is an area of great research interest as its study could provide a better understanding of major physiological processes such as tissue remodelling during development and adulthood, and mechanisms of repair after tissue injury. Moreover, the study of the consequences of the dysregulation of NO\textsuperscript{·}-mediated control mechanisms implicated in different pathologies characterized by cell hyperproliferation, such as cancer, could give new insights on the genesis and progression of these pathological processes. However, to better establish the physiological significance of NO\textsuperscript{·} as an inducer of cell proliferation, further studies should be done to clarify the molecular mechanisms of action of this agent, particularly to identify the target molecules and signalling pathways affected during this process, and posttranslational modifications that protein targets suffer upon exposure to NO\textsuperscript{·}, such as S-nitrosylation and/or tyrosine nitration, and to determine whether additional mechanisms related to the activation of the soluble guanylyl cyclase and the subsequent increase in cGMP are implicated. Another point of interest in this area of research is to establish the concentration threshold required for NO\textsuperscript{·} in vivo to shift its action from being an enhancer of cell proliferation to be an antiproliferative agent, and to determine the cellular mechanisms required to attain this adaptation.

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Fig. 1 Extracellular signalling systems responsible for the cellular production of NO, and some mechanisms implicated in NO-induced cell proliferation. The activation of a series of plasma membrane-bound receptors, such as vascular endothelial growth factor receptors (VEGFR), tumour necrosis factor-α receptors (TNF-αR), interferon-γ receptors (IFN-γR), interleukin-1β receptors (IL-1βR), and lipopolysaccharide receptors (LPSR) by their cognate extracellular ligands results in the expression of the inducible nitric oxide synthase (iNOS) isoform. On the other hand, the 17β-oestradiol receptor (17β-OestrR) controls the expression of the endothelial nitric oxide synthase (eNOS) isoform. Some tyrosine kinase receptors such as VEGFR and the fibroblast growth factor receptor (FGFR), and some non-related receptors such as CD44v10, activated by their extracellular ligands: VEGF, the basic FGF and hyaluraron, respectively, also control NO production. Activation of the latter plasma membrane-bound receptors induce an increase of the cytosolic concentration of free Ca\textsuperscript{2+} ([Ca\textsuperscript{2+}]\textsubscript{cyto}) because production of inositol-1,4,5-trisphosphate by phospholipase C\textsubscript{γ} (PLC\textsubscript{γ}) and Ca\textsuperscript{2+} released from the endoplasmic reticulum mediate by the subsequent activation of Ca\textsuperscript{2+} channels such as inositol-1,4,5-trisphosphate receptors (IP3R). The ensuing Ca\textsuperscript{2+} rise results in the formation of the Ca\textsuperscript{2+}/calmodulin (Ca\textsuperscript{2+}/CaM) complex and the subsequent activation of cNOS and nNOS. NO also activates the cytosolic guanylyl cyclase inducing the production of cGMP. This cyclic nucleotide activates protein kinase G (PKG) which phosphorylates some target proteins such as the kinase Raf-1 (not shown) to initiate the activation of the mitogen activated protein kinase (MAPK) pathway. Among the few mechanisms already suggested to be implicated in NO-mediated stimulation of cell proliferation are: i) the activation of the Raf/MAPK pathway; ii) the upregulation of cyclooxygenase-2 (COX-2) via the phosphatidylinositol-3-kinase (PI3K)/Akt pathway; and iii) the secondary production of reactive oxygen species (ROS) such as anion superoxide (O\textsuperscript{2-}) and oxygen peroxide (H\textsubscript{2}O\textsubscript{2}). See text for additional details.
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