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COMMENTARY

Role of Nitric Oxide and Its Intracellular Signalling Pathways in the Control of Ca^{2+} Homeostasis

*Emilio Clementi**

Department of Pharmacology, Faculty of Pharmacy CNR-IBAF, University of Reggio Calabria, Catanzaro; and Consiglio Nazionale delle Ricerche Cellular and Molecular Pharmacology Center, DIBIT-H San Raffaele Scientific Institute, 20132 Milano, Italy

ABSTRACT. Ca^{2+}, a primary regulator of physiological functions in all cells, is involved in a variety of intracellular signalling pathways; control of Ca^{2+} homeostasis is, therefore, a fundamental cell activity. To this end, cells have developed a variety of mechanisms to ensure the buffering of Ca^{2+}, its influx and extrusion from the plasma membrane, and its release/accumulation within specific intracellular storage compartments. Over the last few years, evidence gathered from a number of cell systems has indicated that one of the key messengers governing the overall control of Ca^{2+} homeostasis is nitric oxide (NO), which may be produced intracellularly or may originate from neighboring cells. The aim of the present commentary is to concentrate on the biochemical steps in Ca^{2+} homeostasis that are controlled by NO and to describe what is known thus far concerning the molecular mechanisms of its action. Particular attention will be given to the effects of NO on: (i) inositol 1,4,5-trisphosphate and cyclic ADP ribose generation; (ii) Ca^{2+} release from both inositol 1,4,5-trisphosphate-sensitive and ryanodine-sensitive Ca^{2+} stores; and (iii) Ca^{2+} influx via both store- and second messenger-operated Ca^{2+} channels. The evidence discussed here documents the complexity of the interactions between the Ca^{2+} and the NO signalling systems, which represent an extraordinary example of cross-talk operating at multiple sites and which are continuously active in the regulation of cytosolic Ca^{2+} (and NO) levels. BIOCHEM PHARMACOL **55**;6:713–718, 1998. © 1998 Elsevier Science Inc.

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As long ago as the late 1970s, pharmacological evidence indicated that NO†, cGMP, and Ca^{2+} were interconnected and played crucial roles in vascular cell physiology. The first discovery was that nitroglycerin and nitroprusside relax blood vessels by means of the generation of cGMP, and that NO is the active substance derived from these drugs [1]. This was followed by the recognition of the existence of an endothelial-derived substance that was responsible for the cGMP-dependent relaxation of smooth muscle cells [2, 3]. cGMP was soon demonstrated to be able to reduce $[Ca^{2+}]_i$, a critical step in the inhibition of the enzymes involved in smooth muscle cell contraction such as myosin light chain kinase [4], as well as in the inhibition of platelet aggregation [5]. After the discovery that the endothelial-derived relaxing factor was actually NO [6, 7], the role of NO in controlling Ca^{2+} homeostasis was investigated more thoroughly; this led to the discovery of various steps in which NO was active in the process, and partial elucidation of the mechanisms involved. This knowledge was subsequently extended beyond the vascular system, to hepatocytes, neurons, oocytes, lymphocytes, and pituitary cells. The purpose of this commentary is to give a concise description of our current understanding (and its implications for future pharmacological research) of the functions and molecular mechanisms underlying the physiological control of Ca^{2+} homeostasis by NO. We will concentrate on Ca^{2+} release from intracellular stores and its influx from the outside via the voltage-independent Ca^{2+} channels of the plasmalemma. The control of voltage-dependent Ca^{2+} channels and *N*-methyl-D-aspartate (NMDA) receptor activity, the activation of cGMP-gated channels, Ca^{2+}-ATPases, and Ne^{+}/Ca^{2+} exchanger have all been exhaustively reviewed elsewhere [8–10].

EFFECTS OF NO ON Ca^{2+} RELEASE FROM INTRACELLULAR STORES

The storage of Ca^{2+} inside the cells occurs in specialized compartments of the endoplasmic reticulum that are endowed with the intracellular Ca^{2+} channels responsible for the release of the cation into the cytosol. Two of these have been known for many years: IP_3Rs and RyRs. The first are

* Correspondence: Dr. Emilio Clementi, Dip. Farmacologia, DIBIT-H San Raffaele Scientific Institute, Via Olgettina 58, 20132 Milano, Italy. Tel. 39-2-2643-4814; FAX 39-2-2643-4813; E-mail: clemene@dibit.hsr.it

† *Abbreviations:* NO, nitric oxide; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; IP_3 and IP_3R, inositol 1,4,5-trisphosphate and its receptor; RyR, ryanodine receptor; PLC, phospholipase C; G kinase, cGMP-dependent protein kinase I; cADP ribose, cyclic ADP ribose; SOCC and SMOC, store-operated and second messenger-operated Ca^{2+} channels; and cGMP, cyclic GMP.

opened following the activation of membrane receptors coupled with phosphatidylinositol 4,5-bisphosphate hydrolysis by means of the G protein-PLCβ signalling cascade or the tyrosine phosphorylation and activation of the PLCs of the γ family. The second are operated by Ca^{2+} itself, and are responsible for the Ca^{2+}-induced Ca^{2+}-release process in all cell systems, as well as for excitation–contraction coupling in skeletal muscle. Ca^{2+} release may also be triggered by means of sphingolipid metabolism via the opening of a newly characterized intracellular Ca^{2+} channel [11]. The role of NO in the control of Ca^{2+} release from IP_3-sensitive and ryanodine-sensitive stores has been clearly ascertained and will be extensively discussed here; mention will also be made of recent evidence suggesting that sphingolipid Ca^{2+} signalling may also be modulated by NO (see concluding remarks).

IP_3-Sensitive Ca^{2+} Stores

The inhibition of Ca^{2+} release from IP_3-sensitive stores, which is induced by agonists coupled with phosphatidylinositol 4,5-bisphosphate hydrolysis via G proteins and the activation of PLCβ, is a well established function of NO in various cell systems, including smooth muscle cells [12–14], platelets [15], fibroblasts [16], neurosecretory PC12 cells [17], and neuronal cells [18, 19]. These studies have shown that the physiological modulation of Ca^{2+} release may be due not only to the diffusion of NO from the outside but also to the NO generated inside the cells by the constitutive Ca^{2+}-dependent NO synthases. Endogenous NO, therefore, appears to work as a sensor for $[Ca^{2+}]_i$: an increase in cytosolic Ca^{2+} levels leads to increased NO synthase activity and NO generation, followed by a negative modulation of intracellular Ca^{2+} release that contributes towards reducing $[Ca^{2+}]_i$.

The effect of NO appears to be mediated via increased cGMP levels and the ensuing activation of cytosolic G kinase, whose involvement has been demonstrated in muscle [12, 14], platelets [20], PC12 cells [17], NIH-3T3 fibroblasts [16], and CHO cells [21]. A major contribution to the characterization of the role of G kinase in NO signalling has come from the use of various G kinase inhibitors, the most frequently used of which have been cGMP analogues, such as the Rp compounds Rp-8-Br guanosine-3,5 monophosphorothioate and Rp 8-(4-chlorophenylthio)-guanosine-3,5 monophosphorothioate, or *Nocardiopsis sp*. derivatives, such as KT5823 [17, 20, 22–25]. Although more selective for G kinase, none of these compounds is G kinase specific; nevertheless, their use in combination with more selective inhibitors of other kinases (protein kinases A and C) has provided convincing evidence that G kinase plays a crucial role in mediating the inhibitory effects of NO on Ca^{2+} release.

The major effect of G kinase is to reduce IP_3 generation, an effect that accounts for the long-known ability of NO to inhibit inositol phosphate accumulation, which was first reported in aortic strips and platelets [26, 27], and subsequently confirmed by studies of many other cell systems. However, the biochemical steps downstream of G kinase that are responsible for the reduction in IP_3 generation have not been completely clarified. Since NO and G kinase inhibit the Ca^{2+} release elicited by a variety of different agonists in different cell systems, their effects are probably exerted downstream of membrane receptor activation. Inhibition of G proteins via G kinase-dependent phosphorylation has in fact, been proposed as a possible mechanism in both smooth muscle [28, 29] and platelets [15]. In neurosecretory PC12 cells and fibroblasts, it has been suggested that the site of G kinase action may be both β and γ PLCs [16, 17]. However, the main problem facing these studies is the current lack of drugs capable of selectively activating the different types of PLCs/G proteins. As far as G proteins are concerned, evidence has been obtained using aluminum/sodium fluoride or GTPγS, which are non-specific direct stimulants of all of them; in the case of PLCs, enzyme activity could be triggered only by an even less specific stimulus, i.e. increased $[Ca^{2+}]_i$. A further element of complexity arises from the fact that, although investigated, no direct phosphorylation of either G proteins or PLCs has ever been documented, which suggests the possible existence of as yet unidentified regulatory proteins that may be the direct target of G kinase. An attractive candidate that has been proposed as bridging this gap in platelets is the actin-binding protein, VASP, whose phosphorylation by G kinase correlates well with the inhibition of PLC activity [30], although its mechanism of action is still unexplained. Whether VASP is active in other cell systems is still uncertain.

A clearer picture is beginning to emerge from the other site at which NO exerts its inhibitory action on Ca^{2+} release: G kinase-mediated phosphorylation of IP_3R. This effect has been well documented in smooth muscle, in which direct phosphorylation has also been demonstrated to occur with the purified receptor and enzyme [25, 31], as well as in platelets, in which the functional link between Ca^{2+} release and IP_3R phosphorylation has been clearly established [32]. However, IP_3R phosphorylation does not occur in all cells: for instance, the transfection of G kinase into CHO cells did not lead to any receptor phosphorylation [33]. Such discrepancies among cell systems are possibly due to the heterogeneity of the IP_3Rs, which are large tetramers composed of three types of subunits that are differently expressed in different cell types.

Although widespread, the inhibition of IP_3-induced Ca^{2+} release is not a ubiquitous physiological function of NO. In hepatocytes, G kinase phosphorylation of IP_3R enhances its sensitivity to IP_3, leading to increased Ca^{2+} release, which is an important mechanism for sustaining Ca^{2+} oscillations in these cells [34, 35]. Furthermore, in endothelial cells, NO appears to have no effect at all on Ca^{2+} homeostasis *per se* [36, 37], although its reaction with superoxide anions may lead to the formation of peroxynitrite, which is ultimately responsible for the depletion of intracellular Ca^{2+} stores [36].

Ryanodine-Sensitive Ca^{2+} Stores

The discovery that NO plays a key role in controlling Ca^{2+} release from ryanodine-sensitive stores is quite recent, originating from the first report by Galione *et al.* [38] that a metabolite of NAD^+, cADP ribose, triggers RyR opening in sea urchin oocytes. The involvement of cGMP in the synthesis of this messenger was demonstrated first [39, 40]; then two independent lines of work converged in defining NO as the physiological modulator of cADP ribose levels, and thus of the functioning of ryanodine channels in sea urchin oocytes [41] and PC12 cells [42]. G kinase activation was found to be a crucial step in both systems, but the precise physiological role of the NO/cGMP/cADP ribose cascade is only beginning to be elucidated, and a number of questions still remain. In particular, it is not clear whether cADP ribose acts as a direct triggering molecule for RyR-mediated Ca^{2+} release (as suggested in sea urchin oocytes, in which high levels of cADP ribose are produced after NO stimulation), or as a modulatory factor (as in PC12 cells, in which the levels of the cyclic nucleotide are only doubled). In the latter case, however, small increases in cADP ribose levels are enough to potentiate Ca^{2+}-induced Ca^{2+} release activated by other mechanisms (i.e. caffeine) in a dramatic manner, with an effect that is similar to that observed in sea urchin oocytes [43]. A second open question is whether NO is able to activate all RyR subtypes in all cell systems. Although the activation of RyR 2 is beyond any reasonable doubt, and its sensitivity to cADP ribose is unquestioned [44], no data yet exist concerning the skeletal (type 1) and the type 3 RyRs. RyR 1 activation by cADP ribose is still debated, and has been shown to occur *in vitro* only under specific ionic conditions [for a review, see Ref. 44]; there are no data at all concerning type 3.

Activation of the cGMP/G kinase/cADP ribose signalling cascade is not the only pathway that NO can use to activate RyR. It recently was reported that it can directly activate RyR by means of the nitrosylation of regulatory thiols: in this case, both skeletal (type 1) and cardiac (type 2) RyRs are activated [45].

EFFECTS OF NO ON VOLTAGE-INDEPENDENT Ca^{2+} CHANNELS

Unlike the voltage-operated channels, that predominate in excitable cells, voltage-independent Ca^{2+} channels are a widespread heterogeneous family of channels that are responsible for the influx of Ca^{2+} into all cell systems and implicated in the regulation of cell growth and differentiation processes [46, 47]. The best characterized channels so far are those responsible for the capacitative influx, which are known to be active whenever intracellular Ca^{2+} stores are depleted and are responsible for their refilling (called store-operated Ca^{2+} channels, SOCC). Other Ca^{2+} channels that are independent of the status of the stores are directly opened after membrane receptor activation via the generation of various second messengers and for this reason have been collectively termed second messenger-operated channels (SMOC). Many of the functional characteristics of these channels have been elucidated [46, 47], revealing a high degree of heterogeneity among them, but none has yet been identified with certainty.

Most studies of NO effects on SOCCs have been carried out in pancreatic acinar cells, the activity of whose channels is finely tuned by NO via the generation of cGMP. In particular, low cGMP levels have a stimulatory effect [48–50], which becomes inhibitory as the concentration increases [50]. A similar dual control by NO/cGMP has also been found to be active in colonic epithelial cells [51]. Interestingly, in most of the experimental systems, NO originates from increased activity of the constitutive Ca^{2+}-dependent NO synthases activated by increased Ca^{2+} influx, suggesting that NO is involved in a positive-feedback loop responsible for activation of these channels. The molecular mechanisms underlying the NO/cGMP activation of SOCCs still remain to be investigated.

Like the other functions of NO described above, SOCC control is not a ubiquitous mechanism. Jurkat T lymphocytes appear to be insensitive to NO [52]; only inhibition was observed in platelets [23, 53]. Interestingly, the action of NO in the latter cells seems to be due to the attenuation of tyrosine phosphorylation, a process that may have an important facilitating effect on SOCC opening in various cell systems, including platelets [54]. NO thus appears to be part of an on/off switch mechanism devoted to fine tuning of the opening of SOCCs. Further studies are needed to define more clearly the molecular pathways operated by NO, and clarify whether this specific function is restricted to platelets or is more widespread.

The effects of NO on the modulation of SMOC activity have been investigated in only a few cases, yielding a largely incomplete picture. Heterogeneity in this family of channels may well explain the variety of NO effects observed. A definite role for NO appears to emerge only in the case of SMOCs coupled with muscarinic receptors, in which NO/cGMP is the second messenger responsible for their opening [48, 55, 56]. Clear stimulatory activity has also been demonstrated for SMOCs coupled with growth factor receptors, in which the likely mechanism of NO action is via G kinase activation [24, 33]. However, under other circumstances, the NO/G kinase pathway has been found to have no effect [23], or even to be inhibitory [57]. Progress in this field is currently unpredictable and will largely depend on a better understanding of the molecular structure and pharmacological properties of SMOC channels.

CONCLUDING REMARKS

The interactions between the Ca^{2+} and the NO/cGMP signalling systems represent an extraordinary example of cross-talk operating at multiple sites and continuously active in the regulation of $[Ca^{2+}]_i$. Almost all of the molecules and regulatory mechanisms involved in the control of Ca^{2+} homeostasis seem to be modulated by NO,

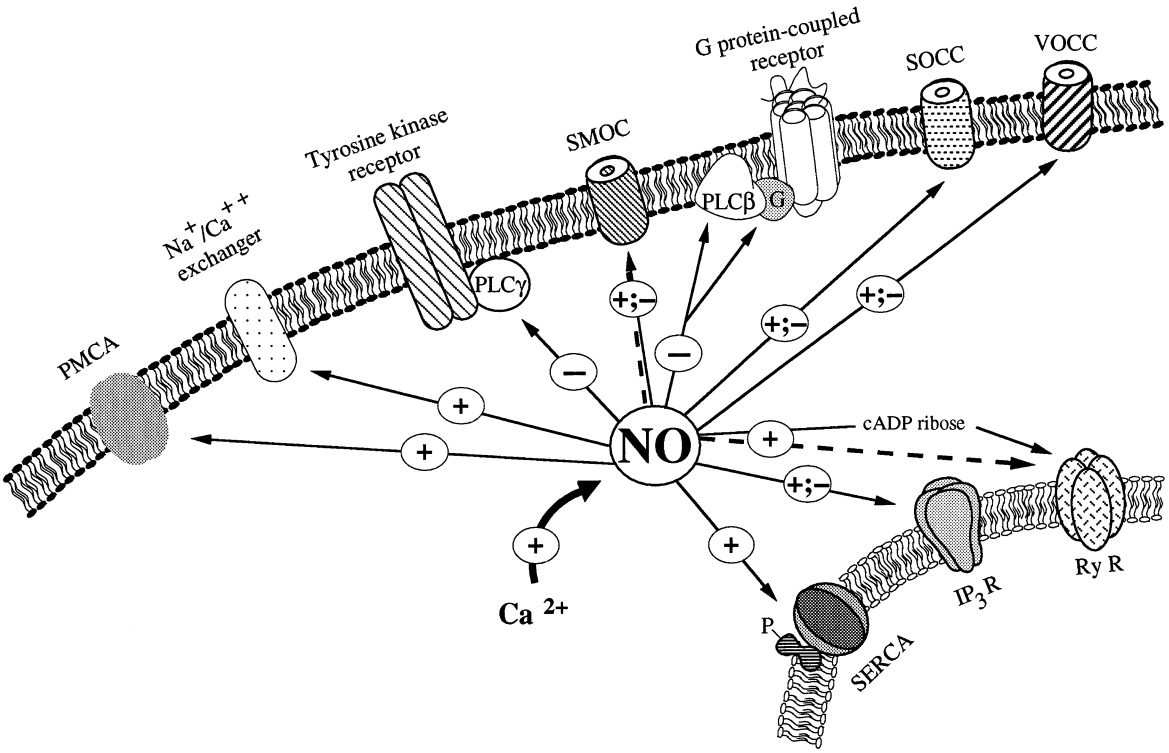

FIG. 1. Molecular targets and mechanisms of NO modulatory actions on Ca^{2+} homeostasis. The diagram shows in a schematic way a portion of plasmalemmal and endo/sarcoplasmic reticulum membranes that are endowed with those components of the Ca^{2+} homeostasis machinery whose function is modulated by NO. Arrows refer to the effects of NO, which are mediated via either cGMP/G kinase-dependent (solid line) or -independent (dashed line) pathways. The signs + and − refer to stimulation or inhibition, respectively. When both signs are present, the effect may be either stimulatory or inhibitory, depending on the cell type investigated (see text for details). The acronyms that have not already been described in the text are as follows: G, heterotrimeric G protein; VOCC, voltage-operated Ca^{2+} channels, and PMCA and SERCA, plasma membrane and sarcoplasmic-endoplasmic reticulum Ca^{2+} ATPases. The stimulatory action of NO on SERCA may be mediated via phospholamban, which is depicted near the enzyme [8].

from the plasma membrane to the endoplasmic reticulum (Fig. 1). Recent evidence from our laboratory suggests that NO also controls the Ca^{2+} release induced by sphingosine-1P, a metabolite of the sphingolipid/ceramide signalling cascade [58, 59], which is involved in such relevant biological processes as the apoptosis triggered by members of the TNFα/CD95 membrane receptor family [60, 61], and signalling via the high-affinity IgE receptor [62]. The effect of NO at this level appears to be inhibitory and essentially due to a reduction in intracellular ceramide levels (Sciorati C, Manfredi A and Clementi E, unpublished results).

The interference of NO with Ca^{2+} homeostasis seems to be cell specific in many cases, with opposite effects appearing even under apparently similar experimental conditions. Explanations for these differences are still elusive, because of the current state of our knowledge, which is largely phenomenological and restricted to the effectors immediately downstream of NO, such as G kinase. In particular, the phosphorylated targets of G kinase remain to be identified and their functions clarified. Deeper insight into the molecules involved in NO signalling will not only permit the detailed characterization of all of the biochemical steps involved in NO control of the Ca^{2+} signalling system, but also will allow us to understand the physiological significance of the heterogeneous behaviour of NO. Furthermore, it is to be hoped that these studies will contribute towards the identification of new targets for drug development, at a time when alterations in NO control of Ca^{2+} homeostasis are beginning to be recognized as important events in the context of specific diseases, including hypertension and schizophrenia [63, 64].

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