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Review

New perspectives on the mechanisms through which nitric oxide may affect learning and memory processes

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Abstract

Nitric oxide (NO) has been well established as a molecule necessary for memory consolidation. Interestingly, the majority of research has focused on only a single mechanism through which NO acts, namely the up-regulation of guanylate cyclase (GC). However, since NO and NO-derived reactive nitrogen species are capable of interacting with a broad array of enzymes, ion channels and receptors, a singular focus on GC appears short-sighted. Although NO inhibits the action of a number of molecules there are four, in addition to GC, which are up-regulated by the direct presence of NO, or NO-derived radicals, and implicated in memory processing. They are: cyclic nucleotide-gated channels; large conductance calcium-activated potassium channels; ryanodine receptor calcium release (RyR) channels; and the enzyme *mono*(ADP-ribosyl) transferase. This review presents evidence that not only are these four molecules worthy of investigation as GC-independent mechanisms through which NO may act, but that behavioural evidence already exists suggesting a relationship between NO and the RyR channel.

Keywords: Nitric oxide; Guanylate cyclase; ADP ribosylation; Cyclic nucleotide-gated ion channels; Large conductance calcium-activated potassium channels; Ryanodine receptor calcium release channel; Peroxynitrite

Contents

1. Introduction

Nitric oxide (NO) is well established as a molecule necessary for memory processing across a wide variety of tasks and species, from odour discrimination in honey bees (Muller, 1996) to delayed recall in primates (Prendergast et al., 1997). Studies such as these have most often used inhibitors of nitric oxide synthase (NOS) (Bernabeu et al., 1995), or its constitutive isoforms (eNOS or nNOS) (Rickard and Gibbs, 2003), but some have also used spontaneous NO donors such as sodium nitroprusside (SNP) (Rickard et al., 1994). Researchers have also attempted to identify the mechanism(s) through which

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NO acts. However, most studies have focused on only one mechanism, namely the activation of guanylate cyclase (GC). In doing so they have neglected the fact that NO is a highly reactive radical. Indeed, there are many reports detailing a diverse range of effects on metalloproteins, enzymes, cation channels, transcription factors, nucleic acids and lipids for both NO and NO-derived reactive nitrogen species (Davis et al., 2001). In fact, the plethora of biochemical interactions possible for NO makes the role of GC as the only means through which NO affects memory appear unlikely.

2. Nitric oxide and guanylate cyclase

NO can affect the action of metalloproteins by directly binding the transition metal complex (Davis et al., 2001). Such metalloproteins most often contain an iron, copper or iron–sulphur moiety (Cooper, 1999; McCleverty, 2004) but may also include zinc in the form of a zinc-finger motif (Kronke and Carlberg, 2000). Even a brief survey of the metalloproteins known to interact with NO illustrates the diversity of cellular processes regulated by this diatomic radical (refer Table 1). In addition, it is interesting to note that, of the many enzymes which are metalloproteins, the overwhelming action of NO is to inhibit their catalytic functions (refer Table 2). However, as the metalloprotein GC is both activated by NO and initiates cellular processes through the production of the second messenger guanosine 3′,5′-cyclic monophosphate (cGMP), it has received much attention as being the likely mechanism through which NO brings about physiological changes including memory consolidation.

Table 1
A sample of metalloproteins affected by NO

Haem iron-containing metalloproteins
Catalase[1]
Cyclooxygenase[2]
Cytochrome *c*[3]
Cytochrome *P*450[4]
Guanylate cyclase[5]
Haemoglobin[6]
Myoglobin[7]
Non-haem iron-containing metalloproteins
Ferritin[8]
Lipooxygenase[9]
Iron/copper-containing metalloproteins
Cytochrome oxidase[10]
Iron/sulphur-containing metalloproteins
Aconitase[11]
NADH dehydrogenase[12]
Zinc-containing metalloproteins
VDR-RXR zinc finger heterodimer[13]

Superior numbers refer to: [1]—Cooper (1999); [2]—Velardez et al. (2001); [3]—Ascenzi et al. (1994); [4]—Wink et al. (1993); [5]—Stone and Marletta (1994); [6]—Sharma et al. (1987); [7]—Sharma et al. (1983); [8]—Lee et al. (1994); [9]—Nelson (1987); [10]—Guiffre et al. (1996); [11]—Castro et al. (1998); [12]—Clementi et al. (1998); [13]—Kronke and Carlberg (2000).

Table 2
Effect of NO on the activity of transition metal-containing enzymes

Enzyme	Activity following NO binding
Haem iron-containing enzymes	
Catalase	Decreased[1]
Cyclooxygenase	Increased[2]
Cytochrome *P*450	Decreased[3]
guanylate cyclase	Increased[4]
Non-haem iron-containing enzymes	
Lipooxygenase	Decreased[2]
Iron/copper-containing enzymes	
Cytochrome oxidase	Decreased[5]
Iron/sulphur-containing enzymes	
Aconitase	Decreased[6]
NADH dehydrogenase	Decreased[7]

Superior numbers refer to: [1]—Brown (1995a); [2]—Velardez et al. (2001); [3]—Wink et al. (1993); [4]—Arnold et al. (1977); [5]—Brown (1995b); [6]—Gardner et al. (1997); [7]—Clementi et al. (1998).

The first direct evidence that GC was activated by NO came from the studies of Arnold et al. (1977) who bubbled NO gas through various tissue preparations, including brain. They showed that in all tissues tested cGMP concentrations were increased following exposure to NO gas. Indeed, brain preparations demonstrated large increases in cGMP following NO exposure indicating the potential importance of this pathway in brain functioning. The relationship between NO and GC was further investigated by Marsault and Frelin (1992) who used physiological concentrations of NO to elicit similar increases in cGMP levels in cerebral capillaries.

There is a variety of evidence suggesting the importance of the NO/GC pathway in synaptic processes underlying memory consolidation. One important synaptic process consistent with a role in memory processing is long-term potentiation (LTP). There is considerable evidence that hippocampal LTP is both NO- and GC-dependent (Arancio et al., 1995; Boulton et al., 1995; Chetkovich et al., 1993; East and Garthwaite, 1991; Monfort et al., 2002; Zhuo et al., 1994a, b). A role for NO and GC in long-term depression (LTD) has also been demonstrated in the hippocampus using low-frequency stimulation (Gage et al., 1997; Zhuo et al., 1994a, b). Consistent with this, Daniel et al. (1992) showed exogenous cGMP to be effective in initiating cerebellar LTD and these results have since been confirmed by a number of researchers (Boxall and Garthwaite, 1996; Hartell, 1994, 1996; Wu et al., 1998). Even so, there is growing evidence that NO can act independently of GC during LTP (Barcellos et al., 2000; Jacoby et al., 2001; Kleppisch et al., 1999; Schuman et al., 1992, 1994; Selig et al., 1996; Zhang et al., 2006).