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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.
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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 413
2. Nitric oxide and guanylate cyclase 414
3. NO forms reactive nitrogen species 416
4. NO activates ion channels 416
5. NO activates *mono*(ADP-ribosyl) transferase 419
6. Conclusions 421
Acknowledgements 421
References 421

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).

Therefore, NO-dependent, but GC-independent, mechanisms may also play an important role in synaptic functioning.

Behavioural studies have traditionally implicated either NO or cGMP in memory processing and have assumed a link between them. While the studies implicating NO in memory processing extend back to the early 1990s (Chapman et al., 1992) and have been numerous ever since, they do not confirm a role for cGMP in memory. However, it is more reasonable to suggest that those studies demonstrating a role for cGMP in memory processing also implicate NO.

Two approaches have been taken when studying the role of cGMP in memory processing. cGMP levels can be reduced via administration of GC antagonists, with any subsequent loss of retention reflecting a role for cGMP. Conversely, cGMP levels can be increased, with a role for cGMP implicated by improved retention. Whilst examples of the first type of study abound, including those discussed below, investigations which have sought to increase cGMP levels also deserve some explanation. For example, pharmaco-behavioural studies have sought to impair the action of phosphodiesterase type-5 (PDE5) which is primarily responsible for cGMP hydrolysis. Therefore, impairment of PDE5 increases cGMP concentrations. Prickaerts et al. (1997, 2002, 2005) and Rutten et al. (2005) have shown improved object recognition in rats and mice following PDE5 inhibition. Sildenafil given at, or prior to, the first exposure improved retention using 3 or 10 mg/kg po for rats (Prickaerts et al., 2002, 2005) or 1 mg/kg po for mice (Rutten et al., 2005). Administration of 0.3 mg/kg (po) vardenafil similarly improved retention when given immediately after the first trial (Prickaerts et al., 2002). Finally, 3 and 10 mg/kg zaprinast enhanced recognition 60 min after the first trial while 10 mg/kg facilitated object recognition 4 h after the first trial (Prickaerts et al., 1997).

More importantly, a number of behavioural studies have jointly implicated NO and GC in memory processing and in so doing clearly demonstrated a link between the two. For example, Kemenes et al. (2002) suggested that NO and GC were both involved in long-term memory for an appetitive single-trial associative conditioning task developed for the snail *Lymnaea stagnalis*. They noted the period of NO sensitivity appears to extend up to 5 h post-training when tested 24 h post-training. In addition, it was found that the specific inhibitor of GC, 1*H*-[1,2,4]oxadiazole[4,3-*a*]quinoxalin-1-one (ODQ), was effective in blocking retention 24 h post-training if administered 10 min post-training. However, no other times of administration were tested.

Although studies using invertebrates demonstrate the evolutionary significance of the NO/cGMP pathway, most work has been done in mammals and avians. For example, Chien et al. (2005) used the Morris water maze whereby rats were administered the GC agonist, 5-[1-(phenylmethyl)-1H-indazol-3-yl]-2-furanmethanol (YC-1), before trial 1 on each day of training. 1 mg/kg (ip) or 10 mg/kg (po) YC-1 resulted in persistent decreased escape latencies. In avoidance tasks 1 mg/kg (ip) or 10 mg/kg (po) YC-1 increased latencies for the passive task variant and decreased latencies for the active task variant. These findings suggest a role for cGMP in spatial learning. Importantly, Chien et al. (2005) subsequently explored the role of both NO and cGMP in memory processing. They first challenged the effects of YC-1 with the NOS antagonist *N*-nitro-L-arginine methyl ester (L-NAME; 1 μmol; icv) and then with the protein kinase G (PKG) antagonists KT5823 (0.2 nmol icv) and Rp-8-Br-PET-cGMPS (1 nmol; icv) given 10 min before YC-1 administration. Each drug was successful in challenging the effects of YC-1 thus implicating NO, cGMP and PKG in memory processing.

NO and cGMP have also been implicated in avoidance tasks by Bernabeu et al. (1995, 1996, 1997) and Izquierdo et al. (2000) who found that the NOS inhibitor nitroarginine (NO-Arg) effectively impaired retention for a single-trial step-down inhibitory avoidance task only when administered around the time of training. Importantly, 2.5 μg (icv; per hemisphere) of the GC inhibitor 6-anilino-5,8-quinolinedione (LY83583) was also effective only when administered at this time (Bernabeu et al., 1997; Izquierdo et al., 2000). Bernabeu et al. (1995, 1996) also determined that both NOS and GC activity increased immediately post-training. These findings provided convincing evidence for the role of NO-activated GC in avoidance learning using rats.

In contrast, an association between NO and GC has only recently been suggested for day-old chicks trained on a single-trial passive avoidance discrimination task. Initially, Hölscher and Rose (1992, 1993) and Rickard et al. (1998) noted a persistent loss of retention from about 40 min post-training following the administration of various NOS inhibitors. However, following bilateral intracranial administration of 100 μM ODQ immediately post-training, Edwards et al. (2002) noted two transient retention losses centred at 40 and 120 min post-training. While the transient retention loss at 40 min post-training was consistent with the time of retention loss onset following NOS inhibition (Hölscher and Rose, 1992, 1993; Rickard et al., 1998), the transient nature of this loss was nevertheless inconsistent with NO activation of GC. That is, while the persistent retention loss suggests that NO is involved in memory formation processes, temporary retention losses are more readily interpreted as deficits in retrieval (see Allweis et al., 1984).

However, Campbell and Edwards (2006) recently challenged this singular role of cGMP. Using a weakly reinforced variant of the passive avoidance task which typically does not allow the consolidation of long-term memory, they noted that when 100 μM (ic) of the PDE5 inhibitor zaprinast was given immediately post-training, memory consolidation did occur. This finding implicated cGMP in memory formation and was consistent with the action of L-NAME at 40 min post-training.

Nevertheless, Cutajar et al. (2005) used the same task and species with an inhibitor of haem oxygenase, zinc deuteroporphyrin IX 2,4 bis glycol (ZnBG), and noted two transient retention deficits centred around 40 and 130 min post-training which were consistent with the transient retention losses observed following GC inhibition (Edwards et al., 2002). Further, the inhibitory effects of 5 μM ZnBG was successfully challenged by 100 μM hemin acting as a haem oxygenase agonist. Taken together, the work of Campbell and Edwards (2006) and Cutajar et al. (2005) suggest a complex relationship between NO, endogenous carbon monoxide and cGMP in the day-old chick.

NO and GC have also been implicated in memory formation for other discrimination tasks. For example, Kendrick et al. (1997) used an olfactory discrimination task for *post-partum* ewes. It was found that 500 μM NO-Arg or 200 μM ODQ impaired recognition of the ewe's own lamb. Not only were NO and cGMP levels maximal around the time of birth but, in both instances, once a memory had formed, inhibition of either molecule was ineffective in preventing recall. Kendrick et al. (1997) therefore surmised that NO most likely activated GC to yield retention.

Finally, when measuring spontaneous alteration behaviour of mice in a Y-maze task, Yamada et al. (1996) noted that the NMDA receptor antagonist, dizocilpine, along with the NOS inhibitors L-NAME and 7-nitroindazole (7-NI), dose-dependently impaired such behaviour. They also noted that icv administration of the cGMP analogue 8-Br-cGMP overcame the effects of dizocilpine and L-NAME. Although challenge studies can be problematic to interpret as the challenge drug may have a number of effects, the authors rightly suggest their findings to be clear evidence that NO-induced GC activation underpinned spatial working memory in mice. To further clarify the role of NO-dependent mechanisms in spontaneous alternation behaviour, NOS activity and cGMP production were measured and found to be reduced in the cortex, hippocampus and cerebellum following L-NAME or 7-NI administration, while dizocilpine reduced cGMP levels only in the cerebellum. The authors interpreted this latter finding to suggest a specific role for the cerebellum in spontaneous alternation behaviour.

Taken together, a large number of studies now exist showing both a role for NO and cGMP in a wide variety of tasks and across a large number of species. However, NO is a highly reactive molecule which may affect memory processing by other means. These alternative mechanisms, although only recently recognised, provide important insights into the complex way in which NO acts to permit learning and memory.

3. NO forms reactive nitrogen species

Davis et al. (2001) reviewed, in great detail, the variety of reactions in which NO takes part. They argued that NO directly binds transition metals, and interacts with molecular oxygen and superoxide to form various reactive nitrogen species. The authors asserted the likelihood of these NO-derived reactive nitrogen species accounting for a range of other NO-dependent reactions including: *S*-nitrosylation of cysteine residues; tyrosine nitration; DNA oxidation, nitration and deamination; and oxidation and nitration of lipids.

An important reactive nitrogen species formed from the reaction of NO with superoxide is peroxynitrite (Carreras et al., 1994). Trabace and Kendrick (2000) utilised *in vivo* microdialysis to determine whether NO modulated striatal neurotransmitter release in the rat. In addition to clarifying the role of GC, they also sought to determine a role for peroxynitrite. When a peroxynitrite scavenger was co-perfused with NO donors, glutamate and GABA concentrations increased. In contrast, perfusion of peroxynitrite decreased dopamine, dihydroxyphenylacetic acid and 5-hydroxyindoleacetic acid levels.

Peroxynitrite has also been implicated in memory processing. Levin et al. (1998) genetically disrupted superoxide production and by implication peroxynitrite production. Mice engineered to either over-express or under-express superoxide performed very poorly on a spatial memory task, suggesting that certain levels of superoxide are critical for learning and memory. However, these findings remain equivocal with regard to peroxynitrite as superoxide may itself be active in memory processing or at the very least act as an amnestic when produced in high concentrations.

A more convincing role for peroxynitrite in memory processing has been demonstrated in the pharmaco-behavioural studies of Edwards and Rickard (2005). Using a single-trial passive avoidance task developed for the day-old chick, intracranial administration of either 300 or 800 μM of the peroxynitrite scavenger Trolox® immediately post-training resulted in a loss of retention from 40 min post-training. The retention function following administration of Trolox is thus identical to that following NOS inhibition (Hölscher and Rose, 1992, 1993; Rickard et al., 1998). These data are therefore consistent with peroxynitrite's role as a reactive nitrogen species produced from NO. In addition, the effective times of drug administration for both Trolox and the NOS inhibitors used by Hölscher and Rose (1992, 1993) and Rickard et al. (1998) were comparable. This provided additional evidence that the role of NOS activation and peroxynitrite production were related for this task.

4. NO activates ion channels

NO can act upon ion channels through indirect means, such as the activation of GC leading to PKG activity, or through direct *S*-nitrosylation of cysteine residues. For example, PKG is known to act upon channels including the ryanodine receptor calcium release (RyR) channel (Clementi et al., 1996; Lu and Hawkins, 2002; Takasago et al., 1991), and in some circumstances the large conductance calcium-activated potassium (BK_{Ca}) channel (Fukao et al.,

1999; Lin et al., 2005). Similarly, by definition NO-induced cGMP activates cyclic nucleotide-gated (CNG) channels. However, *S*-nitrosylation of cysteine residues has come to prominence as being of significant biological relevance in non-pathological systems. Broadly, NO has been observed to nitrosylate the NMDA receptor (Manzoni and Bockaert, 1993), p21^{RAS} (Teng et al., 1999), seven different caspases (Li et al., 1997) and glyceraldehyde 3-phosphate dehydrogenase (Molina y Vedia et al., 1992) (see Table 3). In regards to ion channels, NO is known to nitrosylate RyR channels (Sun et al., 2001; Xu et al., 1998), BK_{Ca} channels (Lang et al., 2003) and CNG channels (Broillet, 2000; Broillet and Firestein, 1996, 1997, 1999) (see Table 3). Mutation studies have provided insight into the exact mechanisms used. For instance, NO affects the RyR1 channel isoform through nitrosylation of the Cys-3635 residue (Sun et al., 2001) and the rat olfactory rCNG2 (alpha) subunit through the Cys-460 residue (Broillet, 2000).

However, *S*-nitrosylation inhibits NMDA receptor function (Mazoni and Bockaert, 1993) and as such cannot account for the GC-independent actions of NO in promoting memory consolidation (Riedel et al., 2003). Four proteins are however known to be activated through *S*-nitrosylation: p21^{RAS} (Lander et al., 1995); CNG channels (Ahmad et al., 1994; Broillet, 2000; Broillet and Firestein, 1996, 1997, 1999); BK_{Ca} channels (Ahern et al., 1999; Lang et al., 2003); and RyR channels (Aghdasi et al., 1997; Hart and Dulhunty, 2000; Xu et al., 1998). While p21^{RAS} has not yet been directly implicated in memory, the MAPK signal transduction pathway through which it acts has been (Adams and Sweatt, 2002). Similarly, the evidence for the role of CNG channels and BK_{Ca} channels in memory formation remains peripheral. In contrast, RyR channels have been extensively implicated in memory formation across a number of species and tasks.

CNG channels: The role of CNG channels in memory processing is, perhaps, the least understood of those channels activated by *S*-nitrosylation. CNG channels have been widely reported in the central nervous system including memory-related regions such as the hippocampus (Kingston et al., 1996) and cerebellum (Zufall et al., 1997).

Table 3
Effect of NO on the activity of *S*-nitrosylated proteins

Protein	Activity following *S*-nitrosylation
BK_{Ca} channels	Increased[1]
Caspases 1–4, 6–8	Decreased[2]
CNG channels	Increased[3,4]
glyceraldehyde 3-phosphate dehydrogenase	Decreased[5]
NMDA receptor	Decreased[6]
p21^{RAS}	Increased[7]
RyR channel	Increased[8–10]/ decreased[8,9]

Superior numbers refer to: [1]—Lang et al. (2003); [2]—Li et al. (1997); [3]—Broillet (2000); [4]—Broillet and Firestein (1996); [5]—Molina y Vedia et al. (1992); [6]—Manzoni and Bockaert (1993); [7]—Lander et al. (1995); [8]—Aghdasi et al. (1997); [9]—Hart and Dulhunty (2000); [10]—Xu et al. (1998).

Olfactory CNG channels have also been implicated in both synaptic processes and memory processing although the evidence remains limited at present. Attenuation of LTP in the CA1 hippocampal region has been shown to occur following the application of LY83583, a potent inhibitor of the olfactory CNG channels. However, LY83583 also blocks the action of GC (Zhuo et al., 1994a, b) which confounds such findings. More convincingly, Parent et al. (1998) found that CNG channels contribute to the induction of LTP in the presence of weak stimulation by using mice with a genetically disrupted olfactory type-I CNG channel α-subunit. While measures of basal synaptic transmission were unaltered in the α-subunit-deficient mice, a theta-burst stimulation protocol (15 bursts of 4 pulses at 100 Hz, 200 ms burst interval, 5 sets at 0.1 Hz) caused the mutant mice to demonstrate a decreased initial amplitude of LTP and potentiation decayed faster.

There is as yet little direct evidence suggesting a role for these channels in memory formation *per se*. Indirect evidence includes the fact that *Drosophila eag* mutants display learning difficulties (Finn et al., 1996; Griffith et al., 1994; Schmidt et al., 1993) and that there is considerable homology between *eag* and genes coding for CNG channels (Guy et al., 1991).

Nevertheless, Matsumoto et al. (2006) specifically explored the role of CNG channels in memory formation using crickets administered either L-*cis* diltiazem (L-DIL) or 3,4,-dechlorobenzamil (DCB) in conjunction with odour conditioning. By using two pharmacological agents and noting any convergent findings, the impact of confounds associated with secondary actions of either drug were reduced. Administration of 1 mM L-DIL or 1mM DCB before multi-trial conditioning did not impair retention 30 min later, but was effective 24-h post-training. This implicates CNG channels in the consolidation of long-term memory. However the process was found to be cGMP-dependent as the action of the cGMP analogue 8-Br-cGMP (200 μM) was blocked by the administration of L-DIL (1 mM).

In vertebrates those few behavioural studies which have shed light on the role of this cation channel have typically done so by accident. That is, while several investigators have used the drug verapamil as an L-type Ca^{2+} channel antagonist, this drug preferentially blocks CNG channels. For example, in studying the role of calcium channels in anxiety Jankowska et al. (1991) used the elevated plus maze and observed arm entries for both isolated and group-housed rats. Along with diltiazem, verapamil was observed to alter the number of arm entries for isolated rats. More relevant, however, were the studies of Quartermain et al. (2001) who noted that verapamil also facilitated retention for a linear maze task.

Nevertheless, most investigators have used avoidance tasks. While verapamil was without effect when mice were tested using a step-through inhibitory avoidance task (Quartermain et al., 2001), Lee and Lin (1991) found verapamil effectively blocked retention 24 h post-training for rats trained on a similar task. To more clearly ascertain the role of CNG channels in memory processing, Edwards et al. (in preparation) used a passive avoidance paradigm testing retention at a number of times up to 180 min post-training, well within long-term memory. Verapamil was initially chosen as the CNG channel blocker as previous studies using this task, and a related avoidance task, found no effect of L-type Ca^{2+} channel blockade (nifedipine 0.1–10 nmole/hemisphere ic or nimodipine 0.5 mg ip) when tested 30 min and 3 h post-training (Clements et al., 1995). Further, nifedipine (0.1–10 nmole/hemishere; ic), nimodipine (0.5 mg; ip) and amlodipine (0.5 mg; ip) did not affect retention for a weakly reinforced variant of the passive avoidance task when tested 24 h post-training. Therefore, it was suggested that any action of verapamil following passive avoidance training was likely to be due to an effect on CNG channels and not L-type Ca^{2+} channels. 900 μM verapamil resulted in a transient retention loss from 90 to 120 min post-training which is after the onset of the long-term memory stage as defined by Gibbs and Ng (1979). These findings were further supported by subsequent experiments noting that the specific L-type Ca^{2+} channel inhibitor nimodipine was without effect 120 min post-training and that the alternate CNG channel blocker dequalinium (1 μM; ic) replicated the retention loss first observed with verapamil. Although these findings lend support for the involvement of CNG channels in memory processing, it is of note that they are inconsistent with the earlier persistent retention loss observed following NOS inhibition (Hölscher and Rose, 1992, 1993; Rickard et al., 1998). Therefore, Edwards et al. concluded that the function of NO in memory for this task was *not* mediated by *S*-nitrosylation of CNG channels.

BK_{Ca} channels: Not only have BK_{Ca} channels been identified in memory-related brain regions such as the hippocampus (Shao et al., 1999), but they have also been implicated in memory processing. Schreurs et al. (1998) observed a strong relationship between the level of classical conditioning in rabbits and membrane excitability (as measured by the mean dendritic spike threshold) in Purkinje cells which persisted for at least 1 month. Interestingly, increases in membrane excitability related to conditioning could be mimicked in control rabbits by application of a variety of K^+ channel blockers including tetraethylammonium chloride and the BK_{Ca}-specific antagonist iberiotoxin (IbTX). These findings would suggest that classical conditioning is dependent upon the inhibition of K^+ channels. Further, these data are consistent with those of Alkon (1984), who demonstrated a persistent potassium current reduction for days following the acquisition of classical conditioning in the mollusc *Hermissenda crassicornis*. However, this may not be the case with all types of learning.

In a study of acquisition, Ghelardini et al. (1998) trained mice on a step-through passive avoidance task and tested retention 24 h later. Administration of a number of K^+ channel blockers 20 min before training, including the polypeptide BK_{Ca}-specific antagonist charybdotoxin (ChTX), prevented ATP-activated K^+ (K_{ATP}) channel agonist-induced amnesia. In contrast, recent investigations by Edwards and Rickard (2006) have shown a transient retention loss (40–70 min post-training) associated with the administration of 50nM IbTX immediately post-training. This is significant for two reasons. First, this transient retention loss is consistent with the transient retention loss brought about by 10 nM dantrolene, which impairs RyR channel activity, and may imply calcium-induced calcium release in memory processing (Edwards and Rickard, 2006). Second, that the onset of the transient retention loss brought about by 50 nM IbTX is consistent with the onset of the persistent retention loss following NOS inhibition (Hölscher and Rose, 1992, 1993; Rickard et al., 1998) is important. However, transient retention losses have traditionally been interpreted as an effect upon retrieval whereas persistent retention losses, pertain to formation pathways. Therefore there does not appear to be an obvious link between the action of NO and BK_{Ca} channels in the day-old chick. In addition, the finding that blockade of BK_{Ca} channels *impairs* memory in the chick would seem to be inconsistent with the findings of Ghelardini et al. (1998) who noted that retention was dependent upon inhibition of BK_{Ca} channels following ATP-activated K^+ (K_{ATP}) channel agonist-induced amnesia. However, the nature of the passive avoidance task used with the neonate chick allows a much greater number of training-test intervals to be explored, including those representing shorter-term memory stages. It is therefore possible that while longer-term memory (as tested 24 h after training by Ghelardini et al., 1998) is dependent on BK_{Ca} channel inhibition, recall of memory at earlier times (between 40 and 70 min post-training) as demonstrated by Edwards and Rickard (2006) requires BK_{Ca} channel activation. Clearly, this is an issue requiring further investigation.

RyR channels: Findings from pharmacological and knock-out studies indicate that RyR channels have an important, but complex, role in LTP and LTD (Balschun et al., 1999; Futatsugi et al., 1999; Katchman and Hershkowitz, 1993; Kohda et al., 1995; Obenaus et al., 1989; Shimuta et al., 2001; Tekkök and Krnjević, 1996; Wang and Kelly, 1997). For example, O'Mara et al. (1995) used the common and specific RyR channel antagonist, dantrolene, to investigate the action of RyR channels in synaptic plasticity in the dentate gyrus. Low-frequency stimulation-induced LTD was blocked by application of dantrolene while high-frequency stimulation-induced LTP was enhanced by the drug. Using the RyR channel ligand ryanodine (threshold extracellular concentration of about

1 μM) to potentiate the action of RyR channels, Wang et al. (1996) found that ryanodine inhibited high-frequency stimulation-induced LTP in the dentate gyrus but facilitated low-frequency stimulation-induced LTP. In subsequent experiments, the action of ryanodine was overcome by the co-perfusion of a RyR channel blocker, ruthenium red, thereby demonstrating that at the concentration used ryanodine did up-regulate RyR channels. These findings are consistent with those of O'Mara et al. (1995) and demonstrate the importance of RyR channels to processes which alter synaptic efficacy.

Unlike CNG and BK_{Ca} channels, the role of RyR channels in memory formation has been studied more broadly in both clinical conditions associated with memory loss (Kelliher et al., 1990) and in the laboratory using animals subjected to various learning tasks. For example, using molecular techniques, Zhao et al. (2000) observed an increase in RyR2 mRNA and protein in the hippocampus of rats trained intensively using a water maze task compared with control rats allowed to swim in the water maze but not provided with an escape platform. However, most evidence for the role of RyR channels in memory processing comes from behavioural studies which have either blocked or disrupted the RyR channel and then measured the level of retention. Such studies include that by Blackwell and Alkon (1999) who demonstrated that the application of 50 μM dantrolene disrupted classical conditioning in *H. crassicornis*. In a related study, Kouzu et al. (2000) found that mutant mice lacking a functional RyR3 channel exhibited impairments in contextual fear conditioning. They also noted an impairment of passive avoidance and spatial memory. Balschun et al. (1999) tested RyR3-deficient mice in the Morris water maze, and further characterised the spatial memory deficit to situations when the location of a new platform had to be learnt. This suggests that the effect was upon the formation of new memories rather than the retrieval of information already stored.

Studies examining the role of RyR channels in passive avoidance learning have provided more consistent findings. For example, Ohnuki and Nomura (1996) blocked the action of the RyR channel in mice using dantrolene. When retention was tested using a step-through inhibitory avoidance task, 6 nmol dantrolene shortened the response latency. While 6 nmol dantrolene did not appear to affect acquisition, 10 nmol did so in addition to producing a shortened response latency at test. When mice were trained and tested using a radial arm maze 20 nmol dantrolene impaired maze-choice accuracy and increased error numbers.

Consistent with Ohnuki and Nomura (1996), Salinska et al. (2001) used a non-discrimination variant of the single-trial passive avoidance task for neonate chicks and found dantrolene impaired retention. Using two times of administration (either 30 min before training or 30 min after training), dantrolene was found to impair retention 3 h post-training. The findings of Salinska et al. (2001) were refined in the later studies of Edwards and Rickard (2006). Using a discrimination variant of the task they found two distinct concentration ranges of dantrolene impaired retention. Administration of 10 nM dantrolene resulted in a transient retention loss centred around 40 min post-training while 5 mM dantrolene resulted in a persistent retention loss from 40 min post-training. This persistent retention function was consistent with that previously determined following NOS inhibition (Hölscher and Rose, 1992, 1993; Rickard et al., 1998). In addition, the effective times of drug administration for both concentrations of dantrolene and the NOS inhibitors used by Hölscher and Rose (1992, 1993) and Rickard et al. (1998) were comparable. This suggested that NOS activity and RyR channel opening may temporally coincide. The authors conclude that consolidation of long-term memory for this task in the chick may depend on NO activation of RyR channels though *S*-nitrosylation.

5. NO activates *mono*(ADP-ribosyl) transferase

One non-metalloprotein which holds promise as being both directly activated by NO and involved in memory processing is mono(ADP-ribosyl) transferase. Although the mechanism by which NO activates this enzyme remains unclear, ADP ribosylation is a common biochemical process which involves transfer of an ADP-ribose group from NAD^+ to a protein.

Early work investigating the relationship between NO and *mono*(ADP-ribosyl) transferase pathway was performed by Brüne and Lapetina (1989) who administered the spontaneous NO donor SNP to a preparation of platelet cells. They observed ADP ribosylation of a 39 kDa protein. To determine whether ADP ribosylation was the result of GC activation, cGMP analogues were administered in place of SNP but were found to be without effect. Brüne and Lapetina (1989) also isolated the cytosolic fractions of a number of tissues, including brain, and again demonstrated ADP ribosylation of the 39 kDa protein.

Following the work of Brüne and Lapetina (1989), Williams et al. (1992) prepared homogenates from rat cerebellum, striatum, thalamus, cerebral cortex and hippocampus. ADP ribosylation of three proteins, including a 39 kDa protein, was observed in each sample after administration of SNP. Later studies by Huang and Lee (1995) and Sullivan et al. (1997) identified several proteins within hippocampal synaptosomes which were subject to NO-dependent ADP ribosylation. While the identities of these proteins remain unknown, their molecular masses were determined to be 42, 48, 51, 54, 74 kDa, respectively. The 54 and 74 kDa proteins were found to be brain-specific, while the 42 and 51 kDa proteins were more widespread in their localisation.

With regard to the role of ADP ribosylation in synaptic plasticity, Zhang et al. (2006) were unable to demonstrate a role for *mono*(ADP-ribosyl) transferase in spinal LTP. Nevertheless, there is growing evidence for its role in

hippocampal LTP. Schuman et al. (1992) found that N-[2-(methylamino)ethyl]-5-isoquinoline-sulfonamide (H-8), an inhibitor of the GC-activated kinase PKG, failed to block LTP following strong tetanic stimuli. In contrast, three different inhibitors of *mono*(ADP-ribosyl) transferase did inhibit LTP. These data therefore provided evidence for a GC-independent, but ADP-ribosyl transferase-dependent, LTP. In support Schuman et al. (1994) who demonstrated that cGMP analogues and PKG inhibitors were without effect upon CA1-localised LTP in the rat, while inhibitors of ADP ribosylation were effective. Similarly, Kleppisch et al. (1999) found that LTP in the CA1 region of the hippocampus was not impaired in PKG knock-out mice, nor in wild-type mice administered the specific GC inhibitor ODQ. These findings provide support for a GC- and PKG-independent form of LTP. NO was still found to be necessary for this form of LTP since inhibitors of NOS blocked LTP induction. Finally, application of the *mono* (ADP-ribosyl) transferase inhibitor nicotinamide to the hippocampal slice prevented induction of LTP. More recently, Barcellos et al. (2000) have demonstrated that synaptic transmission in the intermediate medial mesopallium (IMM; formerly the intermediate medial hyperstriatum ventrale IMHV; Reiner et al., 2004) of the chick, an area implicated in memory formation (Rose and Csillag, 1985), was both NO-dependent and *mono*(ADP-ribosyl) transferase-dependent. Nevertheless, while *mono*(ADP-ribosyl) transferase has been shown to be involved in PKG-independent LTP, this does not negate a role for PKG in all circumstances. Other studies have shown LTP to be PKG-dependent. For example, PKG antagonists have been observed to block the induction of LTP (Son et al., 1998; Zhuo et al., 1994a, b) while injection of PKG agonists (Zhuo et al., 1994a, b), and even the alpha isozyme of PKG type 1 (Arancio et al., 2001), produce activity-dependent long-lasting enhancement. Similarly, LTP in the CA1 region of the rat has been shown to be dependent upon a GC-PKG-phosphodiesterase pathway (Monfort et al., 2002, 2004).

In contrast, Blond et al. (1997) found that the post-synaptic effect of NO in hippocampal LTD was not dependent upon ADP ribosylation. This was further supported by Gage et al. (1997) who found that ODQ blocked low-frequency stimulated LTD in the hippocampus, but that the ADP ribosylation inhibitor nicotinamide did not. These data suggest that the NO/GC pathway is the primary pathway in LTD. Taken together, ADP ribosylation appears to be an important alternative mechanism

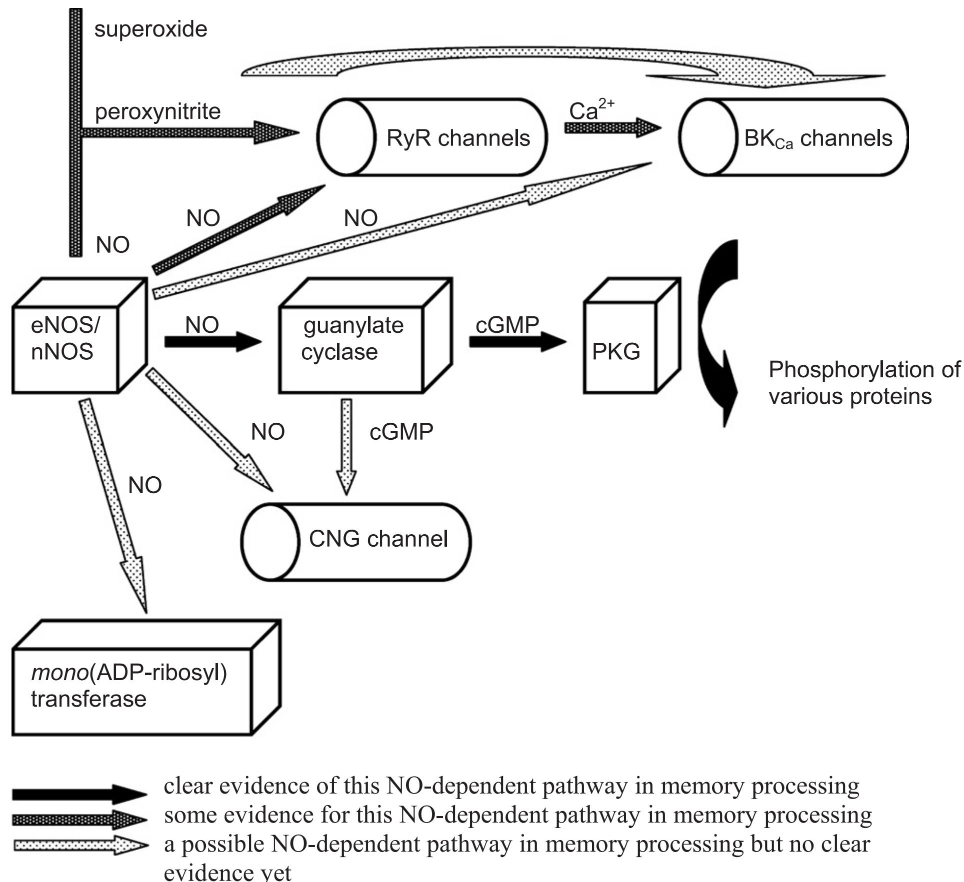

Fig. 1. NO may bring about memory processing by acting on a number of enzymes and ion channels. Each of the above enzymes and channels have been implicated in memory processing and are capable of being activated by NO, peroxynitrite and/or cGMP. The arrows denote likely relationships between NO and each enzyme and channel. The shading of each arrow provides an indication as to the quality of evidence linking NO to a particular mechanism.

through which NO acts during LTP but not in other synaptic processes such as LTD.

There are very few behavioural studies investigating the role of ADP ribosylation as an NO-dependent mechanism required for memory consolidation in the literature. Edwards and Rickard (2002) administered the mono (ADP-ribosyl) transferase inhibitors menadione bisulphate (vitamin K_3) and novobiocin to day-old chicks trained on a single-trial passive avoidance task. As previously noted, inhibition of NOS results in a persistent retention loss from about 40 min post-training within this paradigm (Hölscher and Rose, 1992, 1993; Rickard et al., 1998). In contrast, inhibition of *mono*(ADP-ribosyl) transferase produced a persistent retention loss from 120 min post-training, the onset of which is well into the long-term memory stage. The role of *mono*(ADP-ribosyl) transferase in memory formation for this task is therefore inconsistent with that observed for NO, although the authors could not exclude the possibility that NO plays a second, later function in memory formation that also involves mono(ADP-ribosyl) transferase.

6. Conclusions

While NO has traditionally been thought to affect memory processing by activating GC, the current review of the literature indicates that this should no longer be considered the only mechanism. There now exists ample evidence supporting the role of NO in a wide array of biochemical reactions (Fig. 1).

One reaction which is gaining prominence is the *S*-nitrosylation of various proteins. Depending upon the protein species, *S*-nitrosylation can either inhibit or up-regulate activity. Three cation channels opened by *S*-nitrosylation are CNG, BK_{Ca} and RyR channels. While there is some support for the role of each channel in memory processing, pharmaco-behavioural studies have been critical in determining whether these mechanisms are also NO-activated following learning. Using a single-trial passive avoidance task developed for the day-old chick, RyR channel inhibition yielded the only retention profile that was consistent with that observed following NOS inhibition. Here we suggest that this represents an example of an NO-activated, but GC-independent, process necessary for memory consolidation. In addition, the passive avoidance paradigm has also been beneficial in identifying a role for peroxynitrite in memory formation. The authors speculate that it is possible that NO is responsible for RyR channel activation through peroxynitrite activation.

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