Evidence for the Role of Endogenous Carbon Monoxide in Memory Processing

M. C. Cutajar and T. M. Edwards

Abstract

■ For a decade and a half, nitric oxide (NO) has been implicated in memory processing across a wide variety of tasks and species. Comparatively, endogenously produced carbon monoxide (CO) has lagged behind as a target for research into the pharmacological processes underlying memory formation. This is surprising given that CO is formed in memory-associated brain regions, is structurally similar to NO, and along with NO can activate guanylate cyclase, which is an enzyme well characterized in memory processing. Nevertheless, a limited number of electrophysiological investigations have concluded that endogenous CO is involved in long-term potentiation. Although not evidence for a role in memory per se, these studies did point to the possible importance of CO in memory processing. In addition, there is now evidence to suggest that endogenous CO is important in avoidance learning and possible for other tasks. This review therefore seeks to promote endogenous CO as a potentially important target for memory research. ■

INTRODUCTION

Carbon monoxide (CO) is traditionally thought of as an air pollutant. Indeed, inhalation of environmental CO in sufficient quantities may lead to intoxication through the production of carbonmonoxyhemoglobin, which results in decreased oxygen storage and transport in the bloodstream. CO intoxication is manifest through signs such as headaches, dizziness, weakness, nausea, vomiting, and confusion (reviewed by Wu & Wang, 2005). Persistent CO poisoning can lead to permanent neurological change such as generalized brain atrophy (Gale & Hopkins, 2004). At worst, CO poisoning can be fatal.

Nevertheless, endogenous CO production occurring at comparatively low concentrations is thought to have a number of useful biological roles (reviewed by Wu & Wang, 2005). One suggested role for endogenous CO is at the synapse ultimately leading to behavioral change. In part, this view initially came from detailed research on the structurally similar molecule nitric oxide (NO). Not only was NO implicated in long-term potentiation (LTP), but also in memory processing for a host of different species and tasks. However, there remains only limited evidence implicating endogenous CO in memory processing. That CO may have an important role is possible given the structural similarities of both CO and NO and that either molecule can activate guanylate cyclase (Stone & Marletta, 1994; Marks, Brien, Nakatsu, & McLaughlin, 1991), an enzyme well understood to be important in memory processing (Kemenes, Kemenes, Andrew, Benjamin, & O'Shea, 2002; Izquierdo et al., 2000; Bernabeu et al., 1997; Kendrick et al., 1997). By detailing the evidence for CO production in the hippocampus, its role in synaptic plasticity and those few behavioral studies implicating CO in memory consolidation, it is argued that CO is a potentially important target in understanding the molecular basis of memory processing.

Memory-specific Localization of Heme Oxygenase

Endogenous CO is synthesized by the enzyme heme oxygenase (HO) from the metabolism of heme. HO in conjunction with NADPH-cytochrome P450 reductase catalyzes a mixed oxidation–reduction reaction, cleaving the porphyrin ring of the heme molecule to derive biliverdin, which is then rapidly converted to bilirubin (reviewed in Baranano, Ferris, & Snyder, 2001). This process is accompanied by the release of the chelated ferrous iron and the production of CO (reviewed in Baranano et al., 2001; Maines, 1997).

There exist three reported isoforms of HO: the inducible HO-1 and the constitutive isoforms HO-2 (Maines, Trakshel, & Kutty, 1986) and HO-3 (McCoubrey, Huang, & Maines, 1997). Overall, HO is expressed in a variety of tissues; however, the relative distribution of the three isoforms varies greatly between organs and tissues and with age (Maines, 1997). Even within a single organ, the rat brain, studies have shown regional differences in the expression of HO-1, HO-2, and HO-3 (Scapagnini et al., 2002; Maines, 1997).

Monash University, Australia

Scapagnini et al. (2002) used real-time reverse transcription PCR to gain what is arguably the most comprehensive understanding of HO distribution in the rat brain. Surveying the frontal, parietal, temporal, and occipital cortices; hippocampus; cerebellum; striatum; bulb; and pons; they noted as a general finding that the concentration of HO-2 in the various regions was greater than that of HO-1, which was in turn greater than that of HO-3. Generally, there were noticeable regional differences in overall levels. However, HO-2 was abundantly expressed in brain regions implicated in memory and learning. For example, the cerebellum had the greatest concentration of each HO isoform, and the hippocampus ranked second. Furthermore, hippocampal HO-2 transcript levels were more than four times greater than those for HO-1 and more than seven and a half times greater than HO-3 transcript levels. This distribution is in keeping with past studies (McCoubrey et al., 1997; Ewing & Maines, 1992; Maines, 1988). From this finding it may be suggested that along with HO-2, HO-1 is likely to be important in hippocampal activity, although the concentration of HO-3 may be too low to provide a significant contribution. Nevertheless, in situ hybridization demonstrated greatest expression of HO-3 in the hippocampus, cerebellum, and some specific cortical areas, with hippocampal distribution greatest in the CA1, CA3, and dentate gyrus.

Scapagnini et al. (2002) also used primary cortical cultures to note the cellular distributions of each HO isoform. HO-3 was found in astrocytic cultures, whereas HO-2 was found in neuronal cultures, and HO-1 is expressed in both neuronal and astrocytic cultures. This is in keeping with past studies that have also looked at the cellular distribution of HO isoforms. For example HO-2 was found to be highly expressed in hippocampal granule cells and pyramidal neurons of the CA1 and CA3 regions (Verma, Hirsch, Glatt, Ronnett, & Snyder, 1993).

Taken together, these findings suggest that the distribution of HO is appropriate to suggest a role for endogenous CO in memory processing. In addition, that the hippocampus demonstrates particularly high levels of expression for HO-2 and HO-1 provides further evidence linking endogenous CO with memory processing.

Role of Carbon Monoxide in Synaptic Plasticity

A number of studies have supported a role for CO in LTP. At a general level, Shinomura, Nakao, and Mori (1994), using a fluorometric system, investigated the effects of CO on the release of glutamate from synaptosomes. An inhibitor of HO, zinc protoporphyrin IX (ZnPP; 10 μM), was found to reduce the calcium-dependent release of glutamate consistent with a role for CO in LTP. However, Zhuo, Small, Kandel, and Hawkins (1993) provided direct evidence demonstrating the perfusion of exogenous CO paired with weak titanic stimulation increased excitatory postsynaptic potentials (EPSPs) for at least 1 hr. Stevens and Wang (1993) were one of the first to show that ZnPP (5–15 μM) and an alternate HO antagonist, zinc deuteroporphyrin IX 2,4-bis-ethylene glycol (ZnBG; 10 μM), blocked the induction of LTP and attenuated preexisting LTP in rodent CA1 slices. Interestingly, these drugs had no effect on long-term depression (LTD). Zhuo et al. (1993) and Zhuo, Laitinen, Li, and Hawkins (1999) similarly demonstrated that ZnPP attenuated LTP in a dose-dependent manner, with 10 μM being the most effective concentration, and that a similar agent, tin protoporphyrin IX (SnPP; 10 μM), was also effective. Importantly, Zhuo et al. (1999) also excluded the possibility that the observed attenuation of LTP was the result of an HO antagonist acting on NO synthase (NOS).

Nevertheless, these findings have been challenged by two studies. Meffert, Haley, Schuman, Schulman, and Madison (1994) used a number of HO inhibitors, but found no clear evidence to support a role for CO in LTP using a tetanus of 100 Hz for 1 sec, given four times with an interval of 30 sec between each burst. Instead, they suggested that the efficacy of 15 μM chromium mesoporphyrin IX and 15 μM ZnPP in attenuating LTP may have been due to a secondary action on NOS. In contrast, 15 μM tin mesoporphyrin IX and 15 μM ZnBG did not affect NOS activity, nor did they attenuate LTP. In addition, all drugs tested failed to attenuate previously established LTP. These anomalous findings may, in part, relate to the concentration of drugs used. Previous studies have sought to use drug concentrations no greater than 10 μM, whereas Appleton et al. (1999) recommend concentrations no greater than 5 μM for many HO antagonists. As Meffert et al. used concentrations of 15 μM for each inhibitor, this may go some way to explain their findings.

Using mice for which the HO-2 gene had been disrupted, Poss, Thomas, Ebralidze, O'Dell, and Tonegawa (1995) noted that although brain HO activity was markedly reduced in HO-2-deficient mice compared with wild types, both groups demonstrated an equal ability for synaptic potentiation. Further, ZnPP (15 μM) was effective in attenuating LTP in both groups. Therefore, the authors acknowledged that this concentration of ZnPP may have acted on enzymes other than HO. That LTP was not adversely affected by disrupting the HO-2 gene suggested two alternatives: Either CO does not play a significant role in LTP, or perhaps HO-1, and not HO-2, is important for synaptic potentiation.

More recent studies have sought not only to determine if CO is necessary in LTP, but what its role may be. Initially, evidence for the role of CO in LTP was informed by similar studies investigating NO as a retrograde transmitter (O'Dell, Hawkins, Kandel, & Arancio, 1991). The concept of a retrograde transmitter comes about through observations noting induction of LTP is *N*-methyl-D-aspartate (NMDA) receptor dependent (i.e., localized postsynaptically), whereas the maintenance of LTP, at least in part, is dependent on presynaptic mech-

anisms. As postsynaptic events have to lead to presynaptic changes, this necessitates retrograde messenger(s). Four retrograde messengers have been proposed: arachidonic acid (Williams, Errington, Lynch, & Bliss, 1989), platelet-activating factor (Wieraszko, Li, Korncki, Hogan, & Ehrlich, 1993), NO (O'Dell et al., 1991), and CO (Shinomura et al., 1994; Stevens & Wang, 1993; Zhuo et al., 1993).

Evidence for CO as a retrograde messenger came first from Stevens and Wang (1993) and Zhuo et al. (1993). Whereas Stevens and Wang noted that HO inhibitors blocked preexisting LTP, suggesting an effect on presynaptic maintenance, Zhuo et al. tested a number of aspects of the retrograde transmitted hypothesis. Initially, application of CO (or NO) was observed to rapidly bring about synaptic potentiation when paired with weak tetanic stimulation. They also observed that this potentiation was spatially restricted to synapses with activated presynaptic fibers. NO and CO were also co-perfused with 50 μM of the NMDA receptor antagonist DL-2-amino-5-phosphonovaleric acid (APV) and with APV + 10 μM 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid dimethyl ester (nifedipine), which blocks voltage-dependent calcium influx. In this way the role of NMDA receptor-dependent and -independent forms of LTP could be assessed with respect to NO and CO. In both instances, potentiation was still observed, and with specific reference to CO, EPSPs were enhanced for over an hour in the presence of APV and nifedipine. This suggested that both NO and CO acted downstream of postsynaptic induction. Consistent with this finding, Shinomura et al. (1994) also suggested a presynaptic site of action for CO, noting 10 μM ZnPP reduced the calcium-dependent release of glutamate.

However, a more sophisticated role for CO was put forward by Zhuo et al. (1999). More importantly, this role seemed to differ from that of NO. They demonstrated that 100 μM of the NOS inhibitor L-NG-nitro arginine (L-NOArg) blocked LTP induction derived from a one-train tetanus and significantly impeded induction when a two-train tetanus was provided. However, L-NOArg only slightly reduced potentiation when a four-train tetanus was used. In contrast, the HO inhibitors SnPP (10 μM) and ZnBG (10 μM) effectively attenuated any potentiation brought about by a two-train tetanus, whereas both ZnBG (10 μM) and ZnPP (10 μM) were similarly effective in blocking potentiation from a four-train tetanus. The authors inferred from these findings that although NO and CO are required for LTP they may have different roles. Interestingly, Zhuo et al. go on to suggest that NO has a signaling role in LTP, whereas constitutive CO production provides a background level of stimulation required for potentiation.

Endogenous Carbon Monoxide and Memory

Although studies implicating endogenous CO in synaptic plasticity are suggestive of a role for CO in memory, they are of themselves not conclusive. What is required are behavioral studies that manipulate endogenous CO levels and observe any consequences on retention. To date, there are only a handful of studies seeking to understand the role of endogenous CO in memory processing. Not only have these studies been confined to either spatial or avoidance tasks, but some probably suffer from limitations brought about by the use of relatively nonspecific HO antagonists.

Two studies that have attempted to ascertain the role of CO in spatial memory are those of Toyoda, Saito, and Matsuki (1996) and Bing, Grundemar, Ny, Moller, and Heilig (1995). Toyoda et al. used mice trained on the Morris water maze. A 40-nmol intracerebroventricular (icv) dose of the NOS inhibitor L-NOArg produced an impairment in spatial memory. However, the HO antagonist ZnPP was generally without effect. This being said, 10 nmol but not 20 nmol ZnPP icv resulted in a slight impairment of retention as measured by a reduction in the number of crossings made of the water maze quadrant that previously contained the platform. Nevertheless, mice administered 10 nmol ZnPP still crossed this quadrant more often than they did the other three quadrants when searching for the platform. These results may suggest some minor impairment of spatial memory, although Toyoda et al. are hesitant to conclude this.

A second study using the Morris water maze was conducted by Bing et al. (1995). They administered the potent HO inhibitor SnPP (25 mg kg^{-1} ip) to male Wistar rats 6–9 hr prior to training sessions. They noted a decreased latency to find the hidden platform (~60%) compared with controls and therefore concluded that SnPP actually improved acquisition. The authors also noted that whereas a single administration of SnPP (25 mg kg^{-1} ip) reduced brain HO activity by 70% at the time of sacrifice 6 hr postadministration, administration of SnPP daily for 4 days overcame the initial inhibition of HO activity. In light of these biochemical findings, the authors provided three possible explanations for the counterintuitive effect of SnPP on spatial memory, the first explanation being that a "learning effect" exists from Day 1 of training. However, the authors also noted that the SnPP-treated rats performed progressively better than did controls on each successive day of training. Their second speculation is that after 4 days of SnPP administration HO-1 is up-regulated as a redundant mechanism to overcome the effect of SnPP on HO-2. Finally, they speculated that the HO-1 isoform could have a memory-potentiating role. However, there is a fourth explanation that is perhaps the most parsimonious. SnPP has been reported to activate guanylate cyclase at concentrations equal to or higher than 25 μM (Serfass & Burstyn, 1998). Behavioral studies that have either sought to activate guanylate cyclase or administer a cyclic GMP (cGMP) analogue in combination with the Morris water maze have shown a similar improvement

in learning (Smith, Dringenberg, Bennett, Thatcher, & Reynolds, 2000).

In contrast to spatial studies, avoidance studies more consistently suggest a role for CO in memory processing. Toyoda et al. (1996) demonstrated that 10 nmol ZnPP, but not 20 nmol, significantly increased the number of errors made by mice using a single-trial step-down avoidance task. However, in a later experiment comparing the effect of 10 and 100 nmol ZnPP on retention, they were unable to observe any impairment. This was in contrast to the NOS inhibitor L-NOArg, which dose-dependently impaired retention. The authors therefore concluded that whereas NO affected avoidance learning, any action of CO remained unclear.

The studies of Bernabeu et al. (1995), Fin et al. (1994), and Cutajar, Edwards, and Ng (2005) are more definite in their findings. Bernabeu et al. used a single-trial step-down inhibitory avoidance task to investigate the role of endogenous CO in memory processing. Immediately following training rats demonstrated a 76% increase in hippocampal HO activity, and this was not apparent 60 min later. Furthermore, this increase in HO activity was not apparent in the cerebral cortex or cerebellum at either time of sacrifice. The temporal and spatial restriction of HO activity to the hippocampus around the time of learning is indicative of a role for HO, and thus CO, in memory processing. Consistent with these findings are those of Bernabeu et al. (1997), who sought to investigate changes in the activity levels of hippocampal guanylate cyclase following avoidance learning. Guanylate cyclase is considered to be a main target for both CO and NO. More importantly, hippocampal guanylate cyclase activity increased immediately posttraining, but by 60 min posttraining, activity had subsided to the level of controls.

Fin et al. (1994) and Bernabeu et al. (1995) used bilateral intrahippocampal infusion of ZnPP (2 μg per hemisphere) administered variously at 10 min before training, immediately after training, and 30, 60, or 100 min after training. Adult rats were subjected to the same single-trial step-down inhibitory avoidance task as above. When tested 24 hr posttraining, a significant retention loss was observed, but only when the drug was given 10 min before, or immediately after training. Not only was a clear impairment of retention observed, but the effective times of administration were consistent with the biochemical investigations of Bernabeu et al.

Although promising, the retention data of both Fin et al. (1994) and Bernabeu et al. (1995) should be interpreted with caution. This comes about because high concentrations of ZnPP have a number of secondary actions (Appleton et al., 1999; Grundemar & Ny, 1997). For example, 10 to 15 μM ZnPP has been shown in vitro to inhibit both guanylate cyclase (Luo & Vincent, 1994) and NOS (Meffert et al., 1994) along with HO. Therefore, the loss of retention observed 24 hr posttraining could be the result of ZnPP blocking cGMP production either directly or through NOS inhibition without any effect on HO. Although it is likely that Fin et al. and Bernabeu et al. did observe an effect of ZnPP on HO, this is nevertheless difficult to unequivocally conclude.

To clearly ascertain a role for endogenous CO in memory processing, a number of methodological aspects must be taken into account. For example, a sufficiently low concentration of an HO antagonist must be used to avoid secondary actions that may confound the interpretation of any retention loss. Antagonist specificity to HO can further be assured by challenging its action with an agonist of HO. Finally, use of a detailed retention function following antagonist administration may also help clarify the temporal parameters of HO inhibition as distinct from NOS inhibition.

Using neonate chicks trained on a single-trial passive avoidance task (Gibbs & Ng, 1977), Cutajar et al. (2005) sought to determine if HO inhibition would impair retention. In addition, by use of a detailed retention function they hoped to determine if the temporal characteristics of any retention loss matched those previously observed following the inhibition of guanylyl cyclase (Edwards, Rickard, & Ng, 2002). Aware of the potential for many HO antagonists to be less than specific, they used the HO inhibitor ZnBG. ZnBG is regarded as one of the most potent (Appleton et al., 1999; Chernick, Martasek, Levere, Margreiter, & Abraham, 1989) and selective (Appleton et al., 1999) inhibitors of HO. Specifically, in vitro studies have revealed that 5 μM ZnBG provided 80% to 89% inhibition of HO activity without affecting either NOS or basal guanylate cyclase activity (Appleton et al., 1999).

A dose–response study determined that 5 μM ZnBG was the minimum concentration able to significantly impair retention. This concentration was also thought low enough not to affect other enzymes including NOS (Appleton et al., 1999; Meffert et al., 1994). When retention was tested at a range of times posttraining, there resulted two transient retention losses occurring at around 40 and 130 min posttraining. More importantly, the timing of these transient retention losses was similar to those observed following inhibition of guanylate cyclase (Edwards et al., 2002) but not NOS (Rickard, Gibbs, & Ng, 1998; Hölscher & Rose, 1992, 1993). This suggested 5 μM ZnBG did not inhibit NOS and that the likely target of endogenous CO was guanylate cyclase. Although 5 μM ZnBG did not inhibit guanylate cyclase in vitro (Appleton et al., 1999) there was nevertheless a small chance that the two retention functions were similar due to an action of ZnBG on guanylate cyclase. To test if ZnBG was specific to HO it was necessary to challenge its effects with the HO agonist hemin. If hemin was ineffective in restoring retention following the administration of ZnBG then this would suggest the action of ZnBG to be downstream of HO, most likely inhibiting guanylate cyclase. Conversely, if hemin restored retention following ZnBG administration then it could be

concluded that ZnBG was specifically inhibiting CO production. More importantly, hemin did challenge the action of 5 μM ZnBG restoring retention to normal levels at all times of test. This supported ZnBG as a specific inhibitor of HO. As the inhibition of HO and guanylate cyclase resulted in similar retention functions, this challenge also supported the notion that the molecular target of endogenous CO is guanylate cyclase.

Conclusion

Whereas NO has been extensively recognized as a key molecule underlying memory processing, the structurally similar molecule CO has not. Indeed CO is, more often than not, thought of as an environmental toxin that impairs cognition. Nevertheless, as both diatomic radicals are produced in the hippocampus, and both activate guanylate cyclase, an enzyme widely implicated in memory processing, it would seem that the importance of endogenous CO in memory processing is yet to be completely realized.

Nevertheless, there exist a number of studies hinting at the importance of CO in both synaptic plasticity and in memory processing. For example, CO has been implicated in LTP by Stevens and Wang (1993), among others. Zhuo et al. (1993) have even prescribed to it a role as a retrograde messenger, something more often associated with NO. Zhuo et al. (1999) further refined this role, suggesting that CO may act in a constitutive fashion unlike NO, which may be induced by specific synaptic events. Behavioral studies have also begun to recognize the importance of CO in memory processing. Fin et al. (1994) and Bernabeu et al. (1995) both make strong arguments in favor of CO in avoidance learning, and this was further supported by Cutajar et al. (2005).

Although initial findings positively assert the importance of CO in memory processing, a number of questions still remain. For example, CO appears to affect LTP but not its functional opposite, LTD (Stevens & Wang, 1993). More than just retrograde messengers, NO and CO have begun to demonstrate potentially separate roles in LTP (Zhuo et al., 1999). In regard to behavioral studies implicating CO in memory processing, there presently exists only a handful, and these are limited to either tasks of spatial or avoidance learning. Future investigations must utilize a greater range of tasks to determine if endogenous CO is as important as NO in memory processing. Furthermore, the role of endogenous CO in memory processing in higher mammals remains unclear. Therefore, CO provides an exciting target for future studies that seek to understand the molecular basis of memory processing.

Acknowledgments

The authors gratefully acknowledge the assistance of Emeritus Professor Kim Ng in the development of this manuscript.

Reprint requests should be sent to T. M. Edwards, Department of Psychology, School of Psychology, Psychiatry and Psychological Medicine, Monash University—Clayton, Wellington Road, Clayton, 3800 Victoria, Australia, or via e-mail: tom.edwards@med.monash.edu.au.

REFERENCES

Appleton, S. D., Chretien, M. L., McLaughlin, B. E., Vreman, H. J., Stevenson, J. F., Brien, J. F., et al. (1999). Selective inhibition of heme oxygenase, without inhibition of nitric oxide synthase or soluble guanylyl cyclase, by metalloporphyrins at low concentrations. *Drug Metabolism and Disposition, 27,* 1214–1219.

Baranano, D. E., Ferris, C. D., & Snyder, S. H. (2001). Atypical neural messengers. *Trends in Neuroscience, 24,* 99–106.

Bernabeu, R., Princ, F., de Stein, M. L., Fin, C., Juknat, A. A., Batile, A., et al. (1995). Evidence for the involvement of hippocampal CO production in the acquisition and consolidation of inhibitory avoidance learning. *NeuroReport, 6,* 516–518.

Bernabeu, R., Schroder, N., Quevedi, J., Cammarota, M., Ixquierdo, I., & Medina, J. H. (1997). Further evidence for the involvement of hippocampal cGMP/cGMP-dependent protein kinase cascade in memory consolidation. *NeuroReport, 8,* 2221–2223.

Bing, O., Grundemar, L., Ny, L., Möller, C., & Heilig, M. (1995). Modulation of carbon monoxide production and enhanced spatial learning by tin protoporphyrin. *NeuroReport, 6,* 1369–1372.

Chernick, R. J., Martasek, P., Levere, R. D., Margreiter, R., & Abraham, N. G. (1989). Sensitivity of human tissue heme oxygenase to a new synthetic metalloporphyrin. *Hepatology, 10,* 365–369.

Cutajar, M. C., Edwards, T. M., & Ng, K. T. (2005). Inhibition of endogenous carbon monoxide production induces transient retention losses in the day-old chick when trained using a single trial passive avoidance learning task. *Neurobiology of Learning and Memory, 83,* 243–250.

Edwards, T. M., Rickard, N. S., & Ng, K. T. (2002). Inhibition of guanylate cyclase and protein kinase G impairs retention for the passive avoidance task in the day-old chick. *Neurobiology of Learning and Memory, 77,* 313–326.

Ewing, J. F., & Maines, M. D. (1992). In situ hybridisation and immunohistochemical localization of heme-oxygenase-2 mRNA and protein in normal rat brain: Differential distribution of isozyme 1 and 2. *Molecular and Cellular Neuroscience, 3,* 381–384.

Fin, C., Schmitz, P. K., Da Silva, R. C., Bernabeu, R., Medina, J., & Izquierdo, I. (1994). Intrahippocampal, but not intra-amygdala, infusion of an inhibitor of heme oxygenase causes retrograde amnesia in the rat. *European Journal of Pharmacology, 271,* 227–229.

Gale, S. D., & Hopkins, R. O. (2004). Effects of hypoxia on the brain: Neuroimagining and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. *Journal of the International neuropsychological society, 10,* 60–71.

Gibbs, M. E., & Ng, K. T. (1977). Psychobiology of memory: Towards a model of memory formation. *Biobehavioural Reviews, 1,* 113–136.

Grundemar, L., & Ny, L. (1997). Pitfalls using metalloporphyrins in carbon monoxide research. *Trends in Pharmacological Sciences, 18,* 193–195.

Hölscher, C., & Rose, S. P. (1992). An inhibitor of nitric oxide synthesis prevents memory formation in the chick. *Neuroscience Letters, 145,* 165–167.

Hölscher, C., & Rose, S. P. (1993). Inhibiting the synthesis of the putative retrograde messenger nitric oxide results in amnesia in a passive avoidance task in the chick. *Brain Research, 619,* 189–194.
Izquierdo, L. A., Vianna, M., Barros, D. M., Mello e Souza, T., Ardenghi, P., Sant' Anna, M. K., et al. (2000). Short- and long-term memory are differentially affected by metabolic inhibitors given into hippocampus and entorhinal cortex. *Neurobiology of Learning & Memory, 73,* 141–149.
Kemenes, I., Kemenes, G., Andrew, R. J., Benjamin, P. R., & O'Shea, M. (2002). Critical time-window for NO-cGMP-dependent long-term memory formation after one-trial appetitive conditioning. *Journal of Neuroscience, 22,* 1414–1425.
Kendrick, K. M., Guevara-Guzman, R., Zorrilla, J., Hinton, M. R., Broad, K. D., Mimmack, M., & Ohkura S. (1997). Formation of olfactory memories mediated by nitric oxide. *Nature, 388,* 670–674.
Luo, D., & Vincent, S. R. (1994). Metalloporphyrins inhibit nitric oxide-dependent cGMP formation in vivo. *European Journal of Pharmacology, 267,* 263–267.
Maines, M. D. (1988). Heme oxygenase: Function, multiplicity, regulatory mechanisms, and clinical applications. *The Federation of American Society for Experimental Biology Journal, 2,* 2557–2568.
Maines, M. D. (1997). The heme oxygenase system: A regulator of second messenger gases. *Annual Review of Pharmacology and Toxicology, 37,* 517–554.
Maines, M. D., Trakshel, G. M., & Kutty, R. K. (1986). Characterization of two constitutive forms of rat liver microsomal heme oxygenase. Only one molecular species of the enzyme is inducible. *Journal of Biological Chemistry, 261,* 411–419.
Marks, G. S., Brien, J. F., Nakatsu, K., & McLaughlin, B. E. (1991). Does carbon monoxide have a physiological function? *Trends in Pharmacological Sciences, 12,* 185–188.
McCoubrey, W. K., Huang, T. J., & Maines, M. D. (1997). Isolation and characterization of a cDNA from the rat brain that encodes hemoprotein heme oxygenase-3. *European Journal of Biochemistry, 247,* 725–732.
Meffert, M. K., Haley, J. E., Schuman, E. M., Schulman, H., & Madison, D. V. (1994). Inhibition of hippocampal heme oxygenase, nitric oxide synthase, and long-term potentiation by metalloporphyrins. *Neuron, 13,* 1225–1233.
O'Dell, T. J., Hawkins, R. D., Kandel, E. R., & Arancio, O. (1991). Tests of the roles of two diffusible substances in long-term potentiation: Evidence for nitric oxide as a possible early retrograde messenger. *Proceedings of the National Academy of Science, U.S.A., 88,* 11285–11289.
Poss, K. D., Thomas, M. J., Ebralidze, A. K., O'Dell, T. J., & Tonegawa, S. (1995). Hippocampal long-term potentiation is normal in heme oxygenase-2 mutant mice. *Neuron, 15,* 867–873.
Rickard, N. S., Ng, K. T., & Gibbs, M. E. (1998). Further support for nitric oxide-dependent memory processing in the day-old chick. *Neurobiology of Learning and Memory, 69,* 79–86.
Scapagnini, G., D'Agata, V., Calabrese, V., Pascale, A., Colombrita, C., & Alkon, D., et al. (2002). Gene expression profiles of heme oxygenase isoforms in the rat brain. *Brain Research, 954,* 51–59.
Serfass, L., & Burstyn, J. N. (1998). Effect of heme oxygenase inhibitors on soluble guanylyl cyclase activity. *Archives of Biochemistry and Biophysics, 359,* 8–16.
Shinomura, T., Nakao, S., & Mori, K. (1994). Reduction of depolarization-induced glutamate release by heme oxygenase inhibitor: Possible role of carbon monoxide in synaptic transmission. *Neuroscience Letters, 166,* 131–134.
Smith, S., Dringenberg, H. C., Bennett, B. M., Thatcher, G. R., & Reynolds, J. N. (2000). A novel nitrate ester reverses the cognitive impairment caused by scopolamine in the Morris water maze. *NeuroReport, 11,* 3883–3886.
Stevens, C. F., & Wang, Y. (1993). Reversal of long-term potentiation by inhibitors of haem oxygenase. *Nature, 364,* 147–149.
Stone, J. R., & Marletta, M. A. (1994). Soluble guanylate cyclase from bovine lung: Activation with nitric oxide and carbon monoxide and spectral characterization of the ferrous and ferric states. *Biochemistry, 33,* 5636–5640.
Toyoda, M., Saito, H., & Matsuki, N. (1996). Nitric oxide but not carbon monoxide is involved in spatial learning of mice. *Japanese Journal of Pharmacology, 71,* 205–211.
Verma, A., Hirsch, D. J., Glatt, C. E., Ronnett, G. V., & Snyder, S. H. (1993). Carbon monoxide: A putative neural messenger. *Science, 259,* 381–384.
Wieraszko, A., Li, G., Kornecki, E., Hogan, M. V., & Ehrlich, Y. H. (1993). Long-term potentiation in the hippocampus induced by platelet-activating factor. *Neuron, 10,* 553–557.
Williams, J. H., Errington, M. L., Lynch, M. A., & Bliss, T. V. (1989). Arachidonic acid induces a long-term activity-dependent enhancement of synaptic transmission in the hippocampus. *Nature, 341,* 739–742.
Wu, L., & Wang, R. (2005). Carbon monoxide: Endogenous production, physiological functions and pharmacological applications. *Pharmacological Reviews, 57,* 585–630.
Zhuo, M., Laitinen, J. T., Li, X. C., & Hawkins, R. D. (1999). On the respective roles of nitric oxide and carbon monoxide in long-term potentiation in the hippocampus. *Learning and Memory, 6,* 63–76.
Zhuo, M., Small, S. A., Kandel, E. R., & Hawkins, R. D. (1993). Nitric oxide and carbon monoxide produce activity-dependent long-term synaptic enhancement in hippocampus. *Science, 260,* 1946–1950.