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Review

# Redox mechanisms at the glutamate synapse and their significance: a review

John Smythies *

*Institute of Neurology, Queen Square, WC1N 3BG London, UK*
*Division of Neurochemistry, Brain and Perception Laboratory, Center for Brain and Cognition, UCSD, La Jolla, CA 92093-0109, USA*

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**Abstract**

This paper reviews what is currently known about the redox state of the glutamate synapse and its possible role in modulating synaptic plasticity and thus learning and neurocomputation. The hypothesis is presented that the growth or pruning of the synaptic spine is controlled in part by the balance in the synapse between neurodestructive pro-oxidants (e.g., nitric acid radical and hydrogen peroxide) and neuroprotective antioxidants (e.g., ascorbate and carnosine). In addition, there may be a role for catecholamines, in particular dopamine, related to its role in reinforcement signalling. Activation of the dopamine $D_2$ receptor induces the synthesis of an antioxidant enzyme, possibly catalase. Dopamine may also affect the redox balance in the glutamate synapse directly by diffusion from the adjacent dopaminergic *bouton-en-passage*. Catecholamines are powerful antioxidants, scavengers of free radicals and iron chelators. Catecholamine–iron complexes are potent dismuters of superoxide ions. Additional agents participating in spine pruning may be neurotoxic catecholamine *o*-quinones present in the brain. This system may be at fault in schizophrenia and Parkinson's disease. Experiments to test the hypothesis are suggested. 

*Keywords:* Reactive oxygen species; Antioxidant; Glutamate synapse; Prostaglandin H synthase 2; Nitric oxide (NO); Catecholamine *o*-quinone

## 1. Introduction

Oxidative stress in a region occurs when the production of highly cytotoxic reactive oxygen species (such as the superoxide ion, the hydroxyl radical and hydrogen peroxide) is greater than what the antioxidant defenses can cope with. The major antioxidants in the brain are ascorbate, glutathione (mainly inside astrocytes) and vitamin E (in the lipid membrane). A redox mechanism is one involving a balanced interaction between oxidative reactions and antioxidative (reductive) defenses. Reactive oxygen species play a normal role in the brain as signalling molecules with a wide range of functions including modulation of gene expression (Suzuki et al., 1997) and in the mechanism of action of nerve growth factor (Dugan et al., 1997; Sampath and Perez-Polo, 1997).

## 2. Experimental and Discussion

There are several indications that redox mechanisms are important at the glutamate synapse (Fig. 1).

(1) Several enzymes in the postsynaptic cascade following activation of the *N*-methyl-D-aspartate (NMDA) receptor, produce reactive oxygen species during their enzymatic action. These include the cyclo-oxygenase portion of prostaglandin H synthase II and nitric oxide (NO) synthase. Cyclo-oxygenase II is widely distributed in the brain especially in layer 2 of the cerebral cortex and in limbic areas. In the higher brain, it is particularly located in areas that deal with polysensory integration (Breder et al., 1995). In the cortex, NO synthase is located densely in the spines of cortical spiny neurones (Aoki et al., 1997) as well as in some GABAergic interneurons (Yan and Garey, 1997).

Other enzymes in the neuron that produce reactive oxygen species include monoamine oxidase and various mitochondrial enzymes. There are very few mitochondria in spines but many in dendrites. Superoxide production is increased inside hippocampal neurons in tissue slice and

* Division of Neurochemistry, Brain and Perception Laboratory, Center for Brain and Cognition, UCSD, La Jolla, CA 92093-0109, USA. Fax: +1-619-534-7190; E-mail: smythies@psy.ucsd.edu

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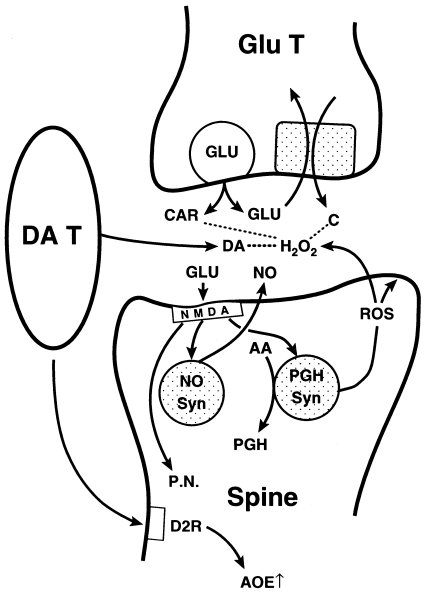


Fig. 1. Simplified diagram of the glutamate synapse. AA, arachidonic acid; AOE, antioxidant enzymes synthesis by nucleus; C, ascorbate; CAR, carnosine; DA, dopamine; D2R, dopamine $D_2$ receptor; GLU, glutamate; NMDA, *N*-methyl-D-aspartate glutamate receptor; NO syn nitric acid synthase; P.N., proteases and nucleases; PGHsyn, prostaglandin H synthase II; T, terminal.

culture on addition of NMDA. The major source of this superoxide is thought to be the mitochondria (Bindokas et al., 1996). Another of these reactive oxygen species is hydrogen peroxide ($H_2O_2$), which is freely diffusible and can thus act as a messenger to other neuronal regions including the synaptic cleft (Edelman and Gally, 1992; Zoccarato et al., 1995). Hoyt et al. (1997) state that hydrogen peroxide is a powerful and effective neurotoxin that produces oxidative stress, leading to DNA strand breaks, lowered glutathione levels and raised intracellular calcium. Hydrogen peroxide is much more cytotoxic than NO (Wink and Mitchell, 1998). There is evidence that the neurotoxicity of β-amyloid protein (Zhang et al., 1997) and methamphetamine (Hom et al., 1997) is mediated in part by hydrogen peroxide.

(2) When the glutamate transporter protein takes up glutamate from the synaptic cleft it does so in exchange for ascorbate (vitamin C) (Grünewald, 1993; Rebec and Pierce, 1994), which is the principle antioxidant in the extracellular fluid (and thus in the synaptic cleft) in the brain.

(3) The NMDA receptor protein has a redox sensitive site consisting of two adjacent sulphydryl groups that can be oxidized to form a disulphide bond. This oxidation results in the downregulation of the receptor (Aizenman et al., 1989). Redox agents that act at this site can modulate activity of the NMDA receptor by up to 50% (Quesada et al., 1996). NO also acts on this site as an oxidant to down regulate the receptor (Bains and Ferguson, 1997). Thus, this reaction could be a neuroprotective negative feedback mechanism cutting off a major source of reactive oxygen species and reactive nitrogen species following excess NMDA receptor activation.

(4) The antioxidant dipeptide carnosine is co-localized with glutamate in the presynaptic terminal and may be released with it (Boldyrev et al., 1997).

(5) NO has two redox forms—the pro-oxidant nitric acid radical and the nitrosium ion. In most circumstances the former is predominant (Grasbon-Frodl and Brundin, 1997). In fact, doubts have been expressed if the nitrosium ion exists in vivo (Koppenol, 1998). NO can also form reactive nitrogen species such as nitrogen dioxide and, by interaction with the superoxide ion, the powerful oxidant peroxynitrite. Thus, the major sources of oxidative stress in the glutamate synapse are $H_2O_2$ and the nitric acid radical. The major antioxidant defenses are ascorbate, carnosine and possibly glutathione (Cuénod et al., 1997).

Glutamate neurotoxicity is mediated in part via reactive oxygen species and reactive nitrogen species produced in the postsynaptic cascade (Dykens et al., 1987; Coyle and Puttfarcken, 1993; Favit et al., 1993; Lafon-Cazal et al., 1993; Rothman and Olney, 1995; Dawson and Dawson, 1996; Patel et al., 1996; and see Maeda et al., 1997). Most glutamate receptors are carried on dendritic spines. These spines are highly dynamic structures and are constantly being formed and deleted or pruned (Quartz and Sejnowski, 1997). The $Ca^{2+}$ inflow through the NMDA receptor controlled channel activates neurodestructive nucleases and proteases. Metabotropic receptors are largely neuroprotective via their activation of protein phosphatases that result in spine growth and differentiation (Harris and Kater, 1994; Bruno et al., 1996). Earlier reports that activation of type I metabotropic glutamate (mGlu) receptors resulted in neurodestructive cascades have been criticized by Sagara and Schubert (1998) on the grounds that excessive doses of agonists were used. They state that, at physiological doses, agonists at the type I mGlu receptor result in a neuroprotective cascade involving raised glutathione levels.

It used to be thought that learning was mediated largely by changing synaptic weights at more or less permanent hard-wired synapses. Now, however, it is known that much learning is mediated by growing new synapses and removing old ones (Sossin, 1996; Quartz and Sejnowski, 1997). It is also known that much learning is mediated by reinforcement in which system dopamine plays a prominent role (Rebec et al., 1997). A stimulus correlated with the receipt by the organism of positive reinforcement is accompanied with increased release of dopamine widely in the brain (Schultz, 1997). This release is very diffuse and capable of influencing 'vast neuronal assemblies' (Beaudet and Descarries, 1978). It has been estimated that 95% of catecholamine terminals in the brain are non-synaptic, and that every neuron in the brain may lie within a distance of less than 30 μm from a norepinephrine bouton (Dismukes, 1977). A similar relationship may apply in the case of dopamine boutons. It is therefore of interest to note than

many glutamate synapses in the cortex and striatum have closely attached on one side a non-synaptic dopamine terminal or *bouton-en-passage* (Kötter, 1994). This could release dopamine directly into the glutamate synaptic cleft. Dopamine can diffuse widely through extracellular space and bind to distant receptors (Pickel et al., 1997). This possibility is supported by the observation that dopamine neurotoxicity is mediated by the action of its quinone metabolites acting, not on dopamine receptors, but on NMDA receptors (Michel and Hefti, 1990; Cadet and Kahler, 1994; Ben-Shachar et al., 1995; Lieb et al., 1995). Therefore, presumably dopamine metabolites are capable of entering the glutamate synaptic cleft. There is evidence to suggest that glutamate itself released by a terminal on one spine may 'spill over' to activate receptors on adjacent spines (Kullmann et al., 1996). Sesack and Pickel (1990) have found that glutamate and dopamine can interact by non-synaptic mechanisms 'perhaps following diffusion from synaptic sites of release.' In a similar fashion, VanderWende and Johnson (1970a,b) have described direct chemical interactions between serotonin and dopamine, in which serotonin inhibited dopamine auto-oxidation to quinones, which they considered to have functional significance.

The possible entry of dopamine into the glutamate synapse may be important because of the finding reported by Liu and Mori (1994) that, in brain homogenates, mitochondria and microsome preparations, catecholamines are potent antioxidants and scavengers of free radicals, in particular the hydroxyl radical. These authors propose that catecholamines and their metabolites are a group of endogenous antioxidants in the brain. In other in vitro systems, dopamine was found to inhibit the oxidation of polyunsaturated fatty acids by free radicals (Sam and Verbeke, 1995) and to inhibit the oxidation of linoleic acid with a potency equal to vitamin E and to show, in addition, potent scavenging effects on superoxide anions and hydroxyl radicals (Yen and Hsieh, 1997). The oxidation of β-phycoerythrin is completely prevented by dopamine (Kang et al., 1998). In none of these systems are specific dopamine receptors involved. Moreover, it has also been recently reported (Sawada et al., 1998) that activation of dopamine $D_2$ receptors induces the synthesis of new antioxidant protein, possibly superoxide dismutase, that scavenges free radicals. A similar dual system of action via both a redox mechanism and dopamine $D_1$ receptors has been proposed to explain the action of methamphetamine in activating Zif268 production in brain (Hirata et al., 1998). Another location where reactive oxygen species are involved in tissue deletion is during luteal regression in the ovary (Kolodecik et al., 1998).

In view of this evidence, the hypothesis has been suggested (Smythies, 1997a) that learning is in part mediated by the antioxidant action of dopamine, either by direct molecular action in the glutamate synapse and/or by $D_2$ receptor-mediated increased synthesis of antioxidant proteins. This would tilt the redox state of the glutamate synapse in the neuroprotective antioxidant direction leading to spine growth and differentiation. The latter would be mediated in part by the unopposed action of mGlu receptors. Whereas low levels of dopamine (signalling lack of reinforcement) could lead to spine deletion by the now insufficiently opposed action of toxic reactive oxygen species and reactive nitrogen species.

However, there is a further mechanism that may mediate, in part, spine deletion. Catecholamines are easily oxidized, either spontaneously in a low antioxidant environment, or enzymatically by an oxygenase, to form *o*-quinones including the highly neurotoxic *o*-semiquinones which are free radicals. It was once thought that these reactions occurred only in vitro and that these catecholamine *o*-quinones do not occur in vivo. However, they must occur in vivo as they are necessary metabolic precursors of neuromelanin as well as of 5-cysteinyl dopamine, both of which certainly occur in the brain (see Smythies, 1996). The highly unstable and short lived *o*-semiquinone, as well as the hydroquinone have now been detected in vitro by advanced and definitive mass spectrographic methods (Costa et al., 1992). Furthermore, Fornstedt and Carlsson (1991) have shown that vitamin C deficiency leads to raised levels of 5-cysteinyl dopamine in the striatum, presumably a result of the increased oxidation of dopamine along the oxidative pathway. Hirsch et al. (1998) have found that dopamine in the dendrites of neurons in the substantia nigra pars compacta is not contained in synaptosomes, where it would be protected by ascorbate from auto-oxidation, but is free in the oxidative environment of the cytoplasm, where it is liable to form dopamine *o*-quinones. Hirsch et al. (1998) suggest that the dopamine in the dendrite is released and taken up by surrounding glia where it can be metabolized by monoamine oxidase to form harmless metabolites. Thus, the glutamate synaptic cleft may contain a mixture of dopamine, ascorbate and other antioxidants, as well as the pro-oxidants hydrogen peroxide and NO, which interact in complex ways.

In the absence of sufficient antioxidant cover, reactive nitrogen species will oxidize dopamine to form the toxic free radical dopamine *o*-semiquinone (Cook et al., 1996). Thus, if the dopamine influx is insufficient to maintain sufficient antioxidant cover, but yet is sufficient to be oxidized in this way to enough of its highly toxic *o*-semiquinone metabolite, then the latter could contribute powerfully to spine deletion. This may be part of the normal action of these *o*-quinones (since spine deletion is a normal process). Abnormalities in this system may be associated with certain diseases such as Parkinson's disease and schizophrenia. For example, dopamine *o*-quinone synthesis is greatly increased ($p = 0.001$) in the striatum in Parkinson's disease (Mattammal et al., 1995) (and see Smythies, 1997b for details).

However, there is one aspect of this proposed mechanism that needs further attention. In the case of most

physiological antioxidants like vitamin E and ascorbate, the oxidized form that results from interaction with the free radical is not itself a highly toxic molecule, and, moreover, it is converted back into the active form by additional mechanisms involving a chain of antioxidants—e.g., glutathione, α-lipoic acid, caretenoids, and NADH, as well as vitamin E and ascorbate for each other (Chan, 1993; Böhm et al., 1997). In the case for dopamine as an antioxidant, at first sight it might appear to be an unsatisfactory candidate for the role, since dopamine oxidation leads eventually to the production of the highly toxic free radical *o*-semiquinone, which cannot be converted back into dopamine, as well as large amounts of new reactive oxygen species. However, if we examine the details of dopamine oxidation, the following facts emerge. The first stage is the conversion of dopamine to the uncyclized dopamine quinone (Fig. 2b). This stage is fully reversible by ambient antioxidants such as ascorbate and glutathione. Dopamine quinone may then be further metabolized by three routes:

(i) 5-Cysteinylization. 5-Cysteinyldopamine is also an antioxidant and chelator of ferric ions (Napolitano et al., 1996),

(ii) 5-Glutathionylization (Cuénod et al., 1997; Baez et al., 1997),

(iii) Irreversible ring closure to form dopaminochrome (Fig. 2c).

Dopaminochrome may then be metabolized in either of two routes. The first is by the enzyme DT-diaphorase to form the relatively non-toxic dopamine *o*-hydroquinone (Fig. 2e), which is then converted into *O*-methylated or sulphated products which are excreted. The second route is by the enzyme NADPH cytochrome *P*450 reductase to form dopamine *o*-semiquinone (Fig. 2d). Both the hydroquinone and the semiquinone are then converted to 5,6-dihydroxyindole (Fig. 2f), which polymerizes to form neuromelanin.

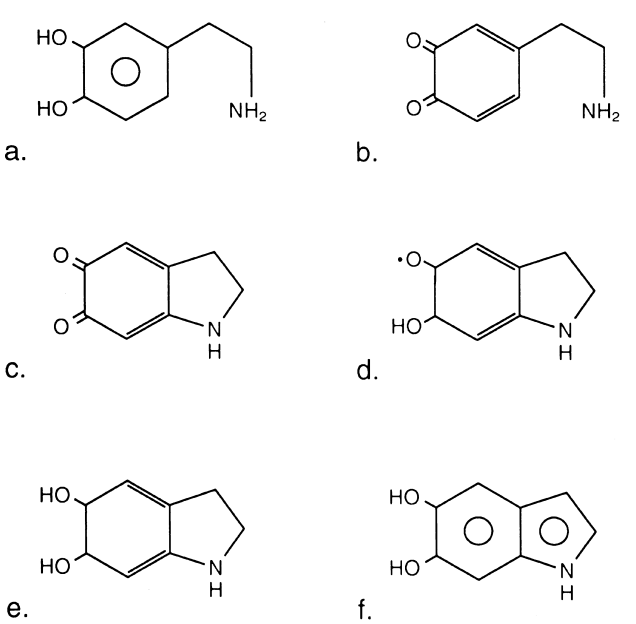


Fig. 2. (a) Dopamine. (b) Dopamine quinone. (c) Dopaminochrome. (d) Dopamine *o*-semiquinone. (e) Dopamine *o*-hydroquinone. (f) 5,6,-dihydroxyindole.

Thus, in an environment with sufficient ambient antioxidants, we have a situation in which dopamine could act as an antioxidant by reducing a reactive oxygen species and being converted into dopamine *o*-quinone in the process. The ambient antioxidants then convert the dopamine *o*-quinone back to dopamine, thus providing the necessary redox recycling mechanism. Support for this hypothesis is provided by the observation that dopamine oxidizes to its *o*-quinone more rapidly, and dopamine *o*-quinone cyclizes more slowly to its aminochrome, than do other catecholamines (Hawley et al., 1967; Graham, 1979). The production of the toxic *o*-semiquinone and additional reactive oxygen species production is thus avoided. It has also been suggested that 5-cysteinylization and 5-glutathionylization form the major routes of metabolism of dopamine quinone and that ring closure, leading to the production of toxic *o*-semiquinones and further reactive oxygen species terminating in neuromelanin formation, occurs only when supplies of cysteine and glutathione are exhausted (Carstam et al., 1991; Odh et al., 1994; Cheng et al., 1996). This would aid the antioxidant redox cycling of dopamine. This redox cycling mechanism between dopamine and dopamine quinone would provide for modulation of the redox state of the glutamate synapse resulting in spine growth or deletion parallel to the reinforcement status of incoming stimuli as signalled by volume dopamine release. The other synaptic antioxidants by themselves could not respond in this manner.

Another possible way in which the antioxidant effect of dopamine might be significant at the glutamate synapse is suggested by the recent report by Zhao et al. (1998) that catechol–iron complexes are much more potent scavengers of superoxide anions than is the catechol alone due to the redox cycle set-up. Since dopamine is very active in this way (O'Brien, personal communication), then dopamine might interact with iron in the synapse to set up this neuroprotective redox cycle. Chelatable iron has been detected in cerebrospinal fluid (Gutteridge, 1992). Moreover, dopamine releases iron from stores (Double et al., 1998). An alternative site for the production of antioxidant catecholamine–iron complexes is suggested by the following facts. When the dopamine $D_1$ receptor binds a molecule of dopamine, the receptor–transmitter complex is rapidly endocytosed in a clathrin-coated vesicle and delivered to the same endosome system of the postsynaptic cell to which the iron carrier protein transferrin is delivered after it binds a molecule of iron at the cell membrane and is itself endocytosed (Koenig and Edwardson, 1997; Dumartin et al., 1998). In the acidic environment of the late endosome, both the iron and dopamine molecules will be released

from their receptor proteins in close proximity. The dopamine $D_2$ receptor is also endocytosed upon binding dopamine but clathrin is not involved and the endosome targeted does not also process the transferrin–iron complex (Vickery et al., 1998). It is, thus, possible that the dopamine–iron complex may play a role in the trafficking of the toxic iron molecule to its targets, which are the iron dependent enzymes of the neurone that include tyrosine hydroxylase as well as mitochondrial enzymes that are potent sources of reactive oxygen species formation. This mechanism would thus be located appropriately at the microanatomical level to scavenge by dismutation the superoxide ions produced by adjacent mitochondria. Thus, it is possible that dopamine may play an additional antioxidant role in the postsynaptic cell via this mechanism. However, this has to be established by direct experiment as there is at present no direct evidence for or against this hypothesis.

It might also be argued that the dopamine content of the cortex is too low to support such purely chemical reactions suggested by this hypothesis. However, the overall level is not what is important. What is important is the level at each glutamate synapse. Since many of these have a dopamine *bouton-en-passage* immediately adjacent (Kötter, 1994), this might provide the quantity of dopamine required.

This proposed mechanism is only meant to cover one aspect of learning. Long-term potentiation induced in the hippocampus results in the induction of a large number of genes and the activation of a most complex series of cellular mechanisms (Hevroni et al., 1998). Furthermore, dopamine clearly modulates learning by effects mediated by its own specific receptors via postsynaptic cascades involving cyclic nucleotides modulating biochemical events inside the neurone. The redox hypothesis presented here is meant to complement this not replace it.

## 3. Conclusion

To summarize, the redox hypothesis of neurocomputation and learning comes in several parts. The major part suggests that the redox mechanisms described are concerned in the growth and deletion of synapses that may underlie much of neurocomputation and learning. One such factor is the action of dopamine at $D_2$ receptors on the synthesis of an antioxidant protein. Other secondary parts of the redox hypothesis suggest that one of these redox factors acting at the glutamate synapse may be the direct antioxidant properties of the dopamine molecule, redox cycling between dopamine and dopamine quinone and a possible role for antioxidant catecholamine–iron complexes. Another secondary part suggests that neurotoxic catecholamine *o*-semiquinones may contribute to spine pruning.

This hypothesis suggests the following experimental programs.

(1) An investigation of the action of these various catecholamine quinones on neurons growing in tissue culture, especially on the mechanisms of spine formation and deletion.

(2) Investigations of their effect on the electroencephalogram. Would, for example, they cause electroencephalographic abnormalities similar to those reported by Lutzenberger et al. (1995) in schizophrenia as evidence in favor of the theory of Hoffman and McGlashan (1993)? The Hoffman and McGlashan hypothesis links the development of parasitic foci in the non-linear networks of the brain to the excessive spine pruning reported in schizophrenia by Garey et al. (1995, 1998), Glantz and Lewis (1995) and Roberts et al. (1995).

(3) Does prostaglandin H synthase convert dopamine to dopamine quinone in vivo as well as in vitro?

(4) What does prostaglandin H synthase use as a co-factor when no dopamine is available?

(5) An intensive study is suggested of the physiology and pharmacology of the intermediate metabolites of the neuromelanin synthetic pathway—including the *O*-methylated dihydroxy indoles found in urine, in health and in various diseases, such as Parkinson's disease and schizophrenia.

(6) Can we obtain direct evidence that dopamine does enter the glutamate synapse in the manner suggested? For example, dopamine *o*-semiquinone will form covalent links with sulphydryl groups on proteins. Can this adduct be detected in the glutamate synapse?

(7) Do dopamine–iron complexes form in the endosome system of the postsynaptic cell and play a role there in the dismutation of superoxide, as they do in vitro?

(8) Several other experimental approaches suggested by the theory have been detailed elsewhere (Smythies, 1997a,b, 1998).

It has almost been universally accepted in neuropharmacology that the biological action of catecholamines is confined to their own specific receptors via classical second messengers. One such action relevant to the redox theory has been reported at the $D_2$ receptor that leads to redox modulation by promoting the synthesis of antioxidant proteins. However, the diffuse non-synaptic nature of much of dopamine (and norepinephrine) axonal distribution, and the evidence listed above, supports the theory that some of their actions at least may be mediated by their potent antioxidant direct chemical properties at other adjacent synapses, such as the glutamate synapse, as well as by possible dismuting catecholamine–iron complexes.

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