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Review Article

Redox Aspects of Signaling by Catecholamines and Their Metabolites

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ABSTRACT

This review covers certain novel aspects of catecholamine signaling in neurons that involve redox systems and synaptic plasticity. The redox hypothesis suggests that one important factor in neurocomputation is the formation of new synapses and the removal of old ones (synaptic plasticity), which is modulated in part by the redox balance at the synapse between reactive oxygen species (ROS) (such as hydrogen peroxide and the nitric oxide radical) and neuroprotective antioxidants (such as ascorbate, glutathione, and catecholamines). Catecholamines, in particular dopamine, which signals positive reinforcement, may play a key role in this activity. Dopamine has powerful antioxidant properties by several separate mechanisms—direct ROS scavenging, activation of the synthesis of antioxidant proteins, and possibly via dismuting complexes with iron inside endosomes or in catecholaminergic synaptic vesicles. This may contribute to synaptic growth and reinforcement-directed learning. On the other hand, catecholamines are easily oxidized to toxic quinones on the neuromelanin pathway. This might contribute under certain circumstances to synaptic deletion. Evidence is presented that abnormalities in this system may contribute to the pathogenesis of Parkinson's disease and schizophrenia. Antiox. Redox Signal. 2, 575–583.

INTRODUCTION

UNTIL RECENTLY, the standard model of neurotransmitter (NT) and neuromodulator (NM) signaling was a static one. The NT or NM molecule released from the axon terminal crosses the synaptic cleft and binds to its specific receptor in the post-synaptic membrane. This results in a conformational change in the receptor protein, which, in some cases opens an ion channel, or, in other cases, activates a G-protein link to a variety of cascade systems involving *inter alia* cyclic nucleotides, protein phosphorylation, lipid hydrolysis, *etc.* Following this activation, the NT/NM molecule was supposed to leave the receptor, which remained in the membrane awaiting the next NT/NM molecule to arrive, whereupon this process was repeated. It was recognized that the receptor protein was replaced by new synthesis, but this was thought to be a slow process. Catecholamines take a part in this process by activating a number of specific G-protein-linked receptors and then being metabolized by monoamine oxidase (MAO) and/or catecholamine-*O*-methyltransferase (COMT) to inactive products. No other mechanisms for catecholamine signaling were recognized.

Moreover, it was held until recently that synapses are more or less permanent structures and that neurocomputation depends on changing weights by a Hebbian mechanism at individual synapses organized into hard-wired semipermanent matrix-multiplying nerve nets

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(Churchland and Sejnowski, 1992). However, it is now apparent that this account is over-simplified and leaves out several important mechanisms.

SYNAPTIC PLASTICITY AND THE REDOX HYPOTHESIS

Over the last few years, abundant evidence has been obtained that the glutamate synapses on dendritic spines in the cortex, hippocampus, striatum, and elsewhere are in a constant state of flux (Quartz and Sejnowski, 1997). New spines and synapses are continually being formed and old ones removed. The biochemical mechanisms controlling this process are very complex and closely involve catecholamine signaling.

Simple activation of the glutamate synapse results in the up-regulation of more than 400 mRNAs and the down-regulation of more than 40 mRNAs in the postsynaptic neuron (Hevroni *et al.*, 1998). Many of these have been identified and include those for trophic factors, structural and related proteins, vesicle proteins, protease inhibitors, various types of receptors, phosphatases, kinases, neuromodulators (*e.g.*, neuropeptides), and enzymes synthesizing retrograde messenger molecules. It is certainly the case that much neurocomputation depends on the classical system whereby individual synapses become more or less efficient. This is characteristic of the primary sensory and motor cortex. But much neurocomputation depends on the creation of new synapses and removal of old ones so that the brain is continually rewiring itself. This is particularly so in the limbic system and association cortex. Moreover much learning does not depend merely on the Hebbian rule that synapses become more efficient if that synapse is fired at the same time that the post-synaptic membrane is already depolarized. Much 'higher' learning depends on reinforcement—both positive and negative—and thus on the biochemical mechanisms that underlie these.

Dopamine (DA) plays a major role in mediating signaling of positive reinforcement received by the organism. Widespread volume release of DA by the *boutons-en-passage* of the extensive network of fine axons in the cortex, particularly in the frontal lobe, signals the message "positive reinforcement received—so whatever you are doing go on doing it" (Rebec *et al.*, 1997; Dismukes, 1977; Schultz, 1997).

A simplified diagram of the relevant aspects of the glutamate synapse is shown in Fig. 1. Two enzymes of the post-*N*-methyl-D-aspartate (NMDA) receptor cascade—prostaglandin H synthase and nitric oxide synthase (NOS)—produce large amounts of reactive oxygen species (ROS) as by-products of their reactions. These ROS include hydrogen peroxide (H_2O_2), which is freely diffusible and can therefore diffuse back into the synaptic cleft. NO produced by NOS is also a freely diffusible pro-oxidant via its dominant NO radical form. The production of these pro-oxidants at the glutamate synapse requires the presence of protective antioxidants to avoid excessive oxidative stress and the resultant oxidative damage to protein,

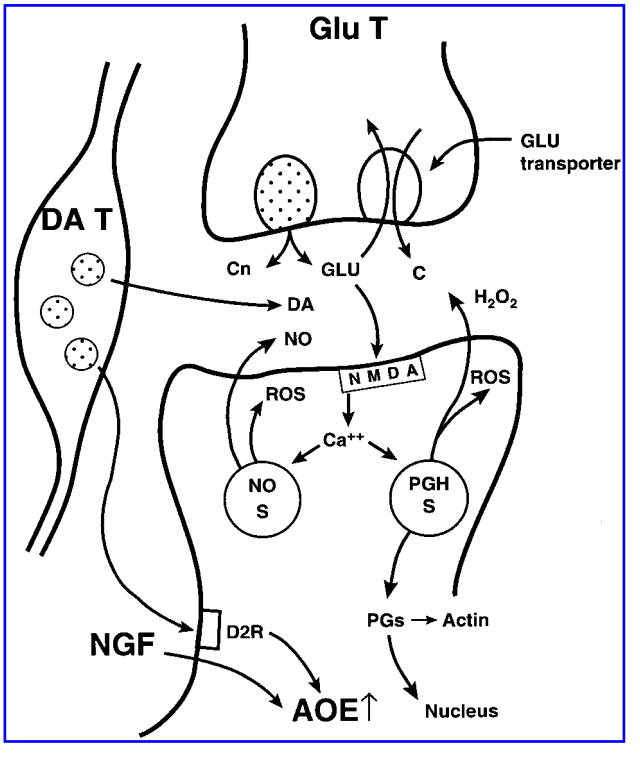

FIG. 1. A diagram of the glutamate synapse. AOE, Antioxidant enzyme; C, ascorbate; Cn, carnosine; DA, dopamine; Glu, glutamate; PGHS, prostaglandin H synthase; PGs, prostaglandins; NO, nitric oxide; NOS, nitric oxide synthase; NGF, nerve growth factor; T, terminal.

lipids and nucleic acids. The antioxidants present in the glutamate synapse are shown in Fig. 1. When the glutamate transporter terminates the action of released glutamate by reuptake, it also releases ascorbate into the synaptic cleft (Grünewald, 1993; Rebec and Pierce, 1994). Ascorbate is the premier extracellular antioxidant in brain. Other antioxidants of importance at the synapse are carnosine (co-packaged with glutamate in synaptic vesicles and released with it) and glutathione (GSH) (released by astrocytes).

CATECHOLAMINES

Some 35% of glutamate synapses in the cortex and striatum have closely attached to one side a DA *bouton-en-passage* (Kötter, 1994). The DA released could therefore diffuse across into the glutamate synaptic cleft. In 1994, Liu and Mori showed that DA has potent antioxidant properties and can directly scavenge ROS. Its antioxidant properties depend on recycling between DA and DA quinone. This is supported by the report that DA prevents cell death in tissue culture by a direct antioxidant mechanism that does not involve DA receptors (Iacovitti *et al.*, 1999). This direct chemical property of DA involving scavenging ROS has been confirmed by Yen and Hsieh (1997). A second antioxidant mechanisms for DA is provided by the fact that activation of D2 receptors induces the synthesis of new antioxidant protein, possibly superoxide dismutase (Sawada *et al.*, 1998; Iida *et al.*, 1999). I will detail two further possible antioxidant mechanisms for DA below.

The redox hypothesis of synaptic plasticity (Smythies, 1997, 1999a,b,c) suggests that one factor, out of many, that modulates synaptic plasticity is the redox balance at the glutamate synapse between pro-oxidants and antioxidants. The hypothesis also suggests that when DA (signaling "positive reinforcement received") is released into the glutamate synapse it tilts this balance in the antioxidant direction and thus promotes growth of spines and synapses. Lack of DA would lead to loss of spines and synapses.

This modulation could be effected by the direct oxidative attack by ROS on the proteins and lipids of the spine membrane and, thus, its removal. However, it seems more likely that more subtle methods are used. ROS play a role in a wide range of signaling mechanisms. For example, they play a modulatory role in the control of intracellular calcium by an effect on a variety of regulators such as Na^+/H^+ and Na^+/Ca^{2+} exchangers. Na^+/K^+ ATPase, and Ca^{2+} ATPase (Chakraborti *et al.*, 1998). They also play roles in: (i) the secretion and action of cytokines, growth factors, and hormones, (ii) ion transport; (iii) control of transcription factors such as NF-κB; and (iv) neuromodulation (Lander, 1997). The role of superoxide in cell signal transduction has been reviewed by Irani and Goldschmidt-Clermont (1998). Recently, it has been shown that H_2O_2 inhibits the endocytosis of epidermal growth factor (de Wit, 2000). Some or any of these could mediate the redox modulation of synaptic plasticity. Atkins and Sweath (1999) stress that nonsynaptic signaling is important in brain, in particular in connection with neurogenesis and synaptic plasticity.

A third possible antioxidant mechanism for catecholamines is suggested by the following data. In 1998, Zhao *et al.* reported that catechols form a complex with iron that acts as a powerful dismuter of superoxide anions. DA is a very effective catechol in this system (P. O'Brien, personal communication, 2000). The mechanism depends on complicated recycling between ferrous and ferric iron bound variously to DA and DA quinone. This process effectively converts 5 molecules of superoxide to 2 molecules of oxygen and 3 of H_2O_2. The question then naturally arises of whether this mechanism operates *in vivo* or only *in vitro*? And, if it does operate *in vivo*, the question then arises where does it do so? Where could iron, DA, and superoxide come into physical microanatomical contact for this chemical reaction to take place? Free iron levels in tissues are normally extremely low because almost all the iron is securely bound to iron storage proteins such as ferritin or iron transport proteins such as transferrin. However, there are two locations where such a reaction could theoretically take place.

The first is the early endosome. To explain this requires an account of recent work in cell biology on the endocytosis of receptors. In the

old static model, receptors remained in the membrane in between activations. Now it has been found in many cases that this is not so. Upon binding a molecule of a NT/NM a G-protein-linked receptor molecule is rapidly taken up into the body of the post-synaptic neuron, which is endocytosed, and is then trafficked to the endosome system. This is a series of tubes and vesicles in the interior of the cell concerned in processing protein and other molecules (Koenig and Edwardson, 1997; Dumartin *et al.*, 1998). In some cases, such as neuropeptides, it is known that the NM neuropeptide molecule is carried along with its receptor into the endosome. In the case of smaller NT/NMs such as catecholamines, it is not known whether they too are endocytosed or not (Koenig and Edwardson, 1997; Dumartin *et al.*, 1998). At present this remains purely hypothetical.

In the acid environment of the early endosome, the protein receptor molecule and the NM/NT molecule part company. A small proportion of the receptor molecule is then trafficked to the endosome for proteolytic breakdown. The rest is recycled back to the surface membrane for reuse. Neuropeptide NMs are trafficked to the nucleus where they modulate transcription. The function of this process may be: (i) to modulate the sensitivity of the synapse by removing and replacing its receptors; (ii) to redistribute membrane to areas of new growth of membrane such as growing dendrites and new spines (Hu *et al.*, 1993); (iii) to dephosphorylate membrane proteins (many phosphorylated desensitized receptors, and other proteins, cannot be dephosphorylated *in situ* in the membrane; this has to be done in the endosome; Ferguson and Caron, 1998); (iv) to capture the NT/NM molecule for further use by the post-synaptic neuron; and (v) possibly to repair oxidatively damaged membrane proteins and lipids (Smythies, 1999c).

In this context, it may be significant that the transferrin receptor in the external membrane, upon binding a molecule of iron, is also endocytosed together with its cargo and is trafficked to the same endosome to which the DA D1 receptor is trafficked. Inside, the endosome free iron is released from the complex. So, if DA is also endocytosed together with its D1 receptor, it too would be released inside the endosome, and free iron and DA could come into physical contact. The source of the superoxide could be the nearby mitochondria, which convert 5% of the oxygen they consume into superoxide. Therefore, it is microanatomically possible, but still only theoretically, that a DA–iron complex may play an important dismuting antioxidant role inside the neuron. Further research is needed to determine if such complexes do indeed occur *in vivo*.

The second location where dismuting iron–DA complexes could occur is inside the catecholamine synaptic vesicle in the axon terminal. Colburn and Maas (1965) have presented evidence that catecholamines are stored in these vesicles in the form of a complex with a heavy metal (iron or copper) and ATP. So in this case we already have evidence of an iron–DA complex *in vivo*, but it is not known if this has dismuting properties, especially in the presence of ATP also in the complex.

In 1985, Blake *et al.* reported that a mixture of ordinary doses of the iron chelators desferrioxamine (hydrophilic) and prochlorperazine (lipophilic) produces a profound and long-lasting coma in humans (2–3 days) and rats (1 day) as well as raised levels of iron in the blood and slow waves in the electroencephalogram (EEG). Neither compound by itself produced any such effect. The coma is exacerbated in iron-deficient rats. This suggests that the coma may be due to depletion of intraneuronal iron.

Any connection between intraneuronal iron levels and the maintenance of consciousness is quite unexpected. The following mechanism to explain this is suggested. Depletion of intraneuronal iron would lead to collapse of the postulated iron–catecholamine dismuting complex and so to a rise of intraneuronal superoxide levels. The NMDA receptor possesses a redox-sensitive switch that responds to raised levels of oxidants by down-regulating the receptor (Aizenman *et al.*, 1989). The excess superoxide could therefore switch off the NMDA receptor. The coma induced by ketamine is also due to switching off the NMDA receptor by a different mechanism (channel blockade). Alternatively (or in addition), depletion of iron inside the catecholaminergic synaptic vesicle could lead to disruption of catecholaminergic synaptic transmission.

Thus, catecholamines can have antioxidant functions relevant to their signaling role by a number of different mechanisms. But, under other circumstances, they can also lead to the production of neurotoxic metabolites. It is now certain that DA and norepinephrine are metabolized in the body to produce *o*-quinones, some of which are highly neurotoxic, as part of the neuromelanin synthetic pathway (Smythies and Galzigna, 1998). Neuromelanin is not present in the brain at birth but first appears at around 6 months of age. Then it steadily increases in the substantia nigra (from DA) and locus coeruleus (from norepinephrine) throughout life. There is also some present in a proportion of the adrenergic C2 neurons in the medulla. The physiological function of this metabolic pathway, and any signaling function it may subserve, is obscure (Smythies, 1996). Neuromelanin has been regarded as a mere waste product of catecholamine metabolism dictated by the inescapable chemistry of catecholamines. It has also been regarded as neuroprotective, owing to its ability to chelate large quantities of heavy metal ions. The substantia nigra is poorly equipped with antioxidant defenses and is yet under heavy oxidative stress. Possibly neuromelanin is synthesized to fill this gap. But this protection, if it exists, comes at a price. The well-known neurotoxic effects of DA are mediated mainly by the action of its quinone metabolites acting not on DA receptors but on NMDA receptors (Michel and Hefti, 1990; Cadet and Kahler, 1994; Ben-Sacher *et al.*, 1995; Ohmori *et al.*, 1996). Furthermore, this pathway very probably plays a role in the pathophysiology of Parkinson's disease (see below).

The metabolic sequence that leads from DA to neuromelanin is the formation of dopamine quinone, its cyclization to form dopaminochrome, which is in equilibrium with two further products—the *o*-hydroquinone and the highly neurotoxic free radical *o*-semiquinone (Fig. 2). These are further metabolized to 5,6-dihydroxyindole which polymerizes to form the main constituent of neuromelanin. Dopamine quinone itself can be metabolized by two further routes, 5-cysteinylization and 5-glutathionylization. Cheng *et al.* (1996) have suggested that the two latter pathways are the normal ones and that neuromelanin is only formed during periods of severe oxidative stress when intracellular levels of the antioxidants cysteine and glutathione are low. Furthermore, the intermediates in neuromelanin synthesis, such as 5,6-dihydroxyindole, could have some as yet still unknown physiological function. The other two brain catecholamines follow similar metabolic pathways.

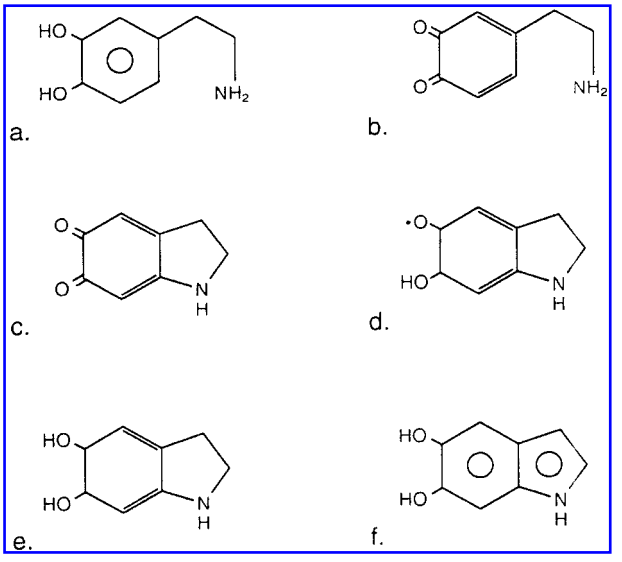

FIG. 2. The metabolic route to neuromelanin. (a) Dopamine; **(b)** dopamine quinone; **(c)** dopaminochrome; **(d)** dopamine *o*-semiquinone; **(e)** dopamine *o*-hydroquinone; **(f)** 5,6-dihydroxyindole.

CLINICAL ASPECTS

However obscure may be the normal physiological role for the autooxidative pathway via quinones for catecholamine metabolism, there is considerable evidence that it is closely related to the genesis of Parkinson's disease (PD) and there is some evidence that it may be related to schizophrenia.

Parkinson's disease

This disease is accompanied by the loss of the pigmented dopaminergic neurons in the substantia nigra and locus coeruleus. The most significant finding in the substantia nigra in PD is low levels of GSH together with normal levels of its oxidized metabolite GSSG (Jenner and Olanow, 1998). This suggests that the GSH is not

being used up by its usual antioxidant function but in other ways, such as combating excessive formation of dopamine quinone by 5-cysteinylization (Jenner and Olanow, 1998). This prevents formation of the toxic *o*-semiquinone.

A key role for DA *o*-semiquinone in at least some cases of PD is supported by the report by Rowe *et al.* (1998) that albumin with covalently attached dopamine quinones is specifically recognized by immunoglobulin G (IgG) from a subgroup (7/21) of PD cases. This indicates that in these cases the brain contains a quinoprotein in which the lysine residues have been attacked by dopamine *o*-semiquinone. In the severely degenerated substantia nigra in cases of PD, raised levels of 5-cysteinyl dopamine have been reported (Fornstedt *et al.,* 1989). This also indicates increased activity along the DA quinone metabolic pathway. It is possible that this pathway may play a normal physiological role in spine deletion via attack on synaptic proteins by DA *o*-semiquinone, in which case the observation of this mode of attack in PD brains by Rowe *et al.* (1998) might represent an exaggeration of a normal process. There is as yet, however, no direct evidence for the hypothesis that catecholamine *o*-quinones have any normal physiological function including this one. This needs to be tested by further research.

Low GSH levels also impair synaptic vesicular storage of dopamine resulting in higher levels of DA in the pro-oxidant environment of the cytoplasm and thus increased levels of dopamine quinone formation. In the synaptic vesicle, DA is protected by high levels of antioxidants (Drukarch *et al.,* 1999).

Schizophrenia

Two theories of the pathogenesis of schizophrenia involve catecholamines. The first is the DA hypothesis, which was based on the observation that drugs such as phenothiazines used in treatment are DA receptor antagonists. So it was suggested that overactivity of some part of the DA system is involved. Attention in this theory has been paid until now mainly to DA receptors, and little attention has been paid to DA post-synaptic cascades or to the antioxidant effects of DA detailed above.

The second theory was put forward by Hoffer *et al.* in 1954, who reported that adrenochrome, the oxidative product of adrenaline, is a psychotomimetic substance. This was confirmed by three other groups (Schwartz *et al.,* 1956; Taubman and Jantz, 1957; Grof, 1963). However, it could not be demonstrated at that time that adrenochrome was ever an *in vivo* metabolite of adrenaline, and so interest in this hypothesis lapsed. We now know that its close relatives dopaminochrome and noradrenochrome certainly occur in the brain, but it is not known if these share the psychotomimetic properties of adrenochrome. Gai *et al.* (1993) reported that some 20% of phenethanolamine-*N*-methyl-transferase (PNMT)-positive adrenergic neurons in the C2 group in the medulla are pigmented. This suggests that these neurons may contain adrenochrome, which could be a necessary precursor of neuromelanin formation in adrenergic neurons. However, this pigment has never formally been identified as neuromelanin. Furthermore, any neuromelanin in adrenergic neurons could actually be derived from dopamine and/or norepinephrine, which are necessary metabolic precursors in these cells of adrenaline. However, kinetic considerations make this unlikely (Gai, personal communication).

At one time, it was considered that the adrenergic system in the brain was concerned only with low-level autonomic functions. However, it now appears in primates that these nuclei project massively to the medial thalamus, in particular the paraventricular, parafascicular, and mediodorsal nuclei (Rico and Cavada 1998), as well as to the amygdala, several hypothalamic nuclei, periacqueductal grey, and other limbic areas (Otake *et al.,* 1995; Nagatsu *et al.,* 1998; Herbert and Saper, 1992; Lew *et al.,* 1977). This system may be concerned *inter alia* with psychological stress (Otake *et al.,* 1995). Adrenochrome is a neurotoxic substance (Louis *et al.,* 1992), and, therefore, the possible release of adrenochrome from the adrenergic terminals in key limbic areas such as the medial thalamus may be a factor in schizophrenia. The related aminochromes derived from DA and norepinephrine may also be involved in schizophrenia. Levels of 5-cysteinyldopamine, a metabolite of DA quinone, are raised in the schizophrenic brain (Carlsson *et al.,* 1994).

Stress precipitates schizophrenic breakdowns. Psychological stress elevates dopamine levels in all areas and particularly in the pre-

frontal cortex (Finlay and Zigmund, 1997), the dysfunction of which plays a key role in the disease. There is evidence that schizophrenics are under increased oxidative stress and decreased antioxidant protection (Cadet and Kaher, 1994; Reddy and Yao, 1996; Mahadik and Mukherjee, 1996; Cuénod *et al.*, 1997; Yao *et al.*, 1998). This would tend to make DA oxidation more likely. If the oxidative pathway of catecholamine metabolism is involved in schizophrenia, the most likely culprit would be the highly neurotoxic free radical *o*-semiquinone. Defenses against the production of the *o*-semiquinone include antioxidants (which inhibit the conversion of dopamine to dopamine quinone and also the conversion of the *o*-hydroquinone to the *o*-semiquinone), adequate cysteine uptake for glutathione synthesis, and adequate transmethylation of the *o*-hydroquinone and of 5,6-dihydroxyindole (which diverts metabolites from forming the *o*-semiquinone). Schizophrenics show defects in all these areas (see Smythies, 1999d for details).

After decades of concentration on receptors, the focus of interest in schizophrenia should now switch to include a consideration of the entire synaptic mechanism including post-synaptic cascades and the endocytotic process. This includes post-synaptic redox signaling roles for catecholamines and their oxidative metabolites. For example, the antipsychotic action of chlorpromazine has always been considered in terms of its blockade of dopamine receptors. However, recently chlorpromazine has also been shown powerfully to act on actin polymerization which plays a key role in the formation of dendritic spines (Milzani and Dalledonne, 1999). Schizophrenic neurons show defective dendritic spine formation. Chlorpromazine has also been shown to act on endocytotic mechanisms and to reduce transferrin endocytosis (Subtil *et al.*, 1994). Disturbances in the biochemical mechanisms (that may include catecholamine redox signaling) that mediate synaptic plasticity may well play a key role in schizophrenia (see Smythies, 1999d for details).

ABBREVIATIONS

COMT, Catecholamine-*O*-methyltransferase; DA, dopamine; DAQ, dopamine 0-quinone; GSH, glutathione; GSSG, oxidized form of glutathione; H_2O_2, hydrogen peroxide; MAO, monoamine oxidase; NM, neuromodulator; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; NT, neurotransmitter; PD, Parkinson's disease; PNMT, phenethanolamine-*N*-methyl-transferase; ROS, reactive oxygen species; SN, substantia nigra.

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