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Short communication

The effects of nitric oxide on striatal serotoninergic transmission involve multiple targets: an in vivo microdialysis study in the awake rat

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Abstract

The role of endogenous nitric oxide (NO) in *N*-methyl-D-aspartate (NMDA)-induced modulation of serotonin (5-HT) release in the striatum of freely moving rats has been studied using microdialysis technique. NMDA-induced increase in 5-HT release was significantly inhibited by selective nitric oxide synthase (nNOS) inhibitor *S*-methylthiocitrulline (S-Me-TC), $ONOO^-$ scavenger L-cysteine (L-cys), and guanylate cyclase (GC) inhibitor 1*H*[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ). These data suggest that modulation of 5-HT levels is linked to the formation of NO produced by NMDA receptor activation and that endogenously produced NO increases 5-HT concentrations both by stimulating formation of 3′–5′-cyclic monophosphate (cGMP) and conversion of $ONOO^-$.

Theme: Neurotransmitters, modulators, transporters, and receptors
Topic: Serotonin

Keywords: Nitric oxide; Serotonin; Striatum

L-glutamate (Glu) receptors have been shown to be widely distributed throughout the brain and are found in particularly high densities in structures such as the hippocampus, substantia nigra, and striatum. The striatum receives major glutamatergic input from the cerebral cortex and thalamus, and Glu exerts an excitatory influence on striatal neurons mediated via at least two main receptor subtypes, namely, ionotropic receptors, coupled to ligand-gated ion channels, and metabotropic receptors, coupled to G-proteins. Ionotropic receptors are further divided into at least three subtypes, defined by their preferential activation by the agonist *N*-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), or kainate [24]. Although all subtypes are represented in the striatum, there is a particularly high density of NMDA receptors compared with other basal ganglia nuclei [1,9,37].

Activation of NMDA receptors has been shown to induce Ca^{2+} influx into neurons to stimulate Ca^{2+}-dependent nitric oxide synthase (nNOS) with subsequent elevation of nitric oxide (NO) formation [3,6,28].

NO has been suggested to have multiple targets. It has been demonstrated that NO is a powerful stimulator of soluble guanylate cyclase (sGC), leading to an increase in levels of 3′–5′-cyclic monophosphate (cGMP) by coupling with NMDA receptors [26]. The resulting increase in cGMP levels can then modulate the activities of cGMP-dependent protein kinases, phosphodiesterases, and ion channels [15]. However, several effects of NO are independent of the activation of sGC. Indeed, NO is known to target SH groups in proteins, and an increasing number of proteins have been shown to be modified by NO. It has been also demonstrated that NO reacts with metal-containing proteins in biological

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systems [29]. It has been shown that NO mediates NMDA receptor-induced activation of p21 ras [38]. On the other hand, NO can rapidly combine with superoxide anions to form peroxynitrite anion ($ONOO^-$) [10].

In the striatum, NO has potent neuromodulatory actions. Indeed, several studies have shown that NO modulates extracellular concentrations of various neurotransmitters in the central nervous system (CNS) [11,34]. In this regard, our previous studies have demonstrated that exogenous NO can modulate extracellular concentrations of striatal neurotransmitters both by stimulating formation of cGMP and conversion to $ONOO^-$ via superoxide [31,32].

Furthermore, a number of observations have demonstrated that NMDA receptors can regulate the release of various neurotransmitters via the endogenous formation of NO within the brain [19–21,35].

In this regard, current evidence suggests that 5-HT release in several brain areas is partly regulated by glutamatergic receptors, especially the NMDA receptor [30], and it has been shown that serotonergic and NOS-containing neurons are colocalised within the CNS [23]. However, information concerning the modulation of 5-HT release by endogenous NO is scarce. Indeed, it has not been clarified whether the effects of endogenously produced NO on striatal serotonergic system are mediated through changes in sGC activity, or by means of different targets of NO.

In the present study, we have, firstly, attempted to clarify whether NO plays a role in the NMDA-induced modulation of 5-HT release in the striatum of freely moving rats. Therefore, we have investigated whether the in vivo effects of endogenous NO on the serotonergic system are mediated by its action on the sGC–cGMP signalling pathway, or through NO interacting with superoxide anions to form $ONOO^-$.

Male Wistar rats (Harlan, S. Pietro al Natisone, UD, Italy) weighing 200–250 g were used. Animals were provided with food and water ad libitum, and maintained in a temperature-controlled room (22 ± 1 °C) and at constant relative humidity (55 ± 5%) under a light/dark cycle (lights on/off at 0700/1900 h).

The study was performed in accordance with guidelines released by the Italian Ministry of Health (DL 116/92), the Declaration of Helsinki, and the *Guide for the Care and Use of Laboratory Animals*, as adopted and promulgated by the National Institutes of Health.

NMDA and L-cysteine (L-cys) were purchased from Sigma (St. Louis, MO, USA). 1*H*[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ), *S*-methylthiocitrulline (S-Me-TC), and $ONOO^-$ were purchased from Alexis Biochemicals (Nottingham, UK). All drugs were freshly prepared immediately before each experiment and diluted in the perfusion solution to the appropriate concentration. Rats were anaesthesised with Equithesin (3 ml/kg, i.p.) and placed on a stereotaxic frame (David Kopf Instruments, Tujinga, CA, USA). A transversal microdialysis probe (AN69 Hospal; 20,000 Da cutoff; 4 + 4 mm membrane length) was implanted in the striatum. Stereotaxic coordinates were as follows: AP = 8.8, H = 5.6 from the interaural line with the incisor bar set at −2.4 mm, according to the atlas of Paxinos and Watson [25]. Rats were allowed to recover from anaesthesia for at least 15 h before starting the neurotransmitter release study. On the day of the experiment, the fibers were perfused using a perfusion solution containing 138 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$, 11 mM $NaHCO_3$, and 1 mM NaH_2PO_4 in distilled water (pH 7.4) at a constant flow rate of 2.0 μl/min and samples were collected every 20 min [33]. A liquid switch (CMA/110; CMA Microdialysis) was placed between the syringe pump and the microdialysis probe to enable different drugs to be administered locally without introducing air bubbles into the probe. The dead space between the liquid switch and the end of the outlet tubing was calculated to be 10.5 μl, and this was taken into account when switching between solutions. 5-HT levels were determined by high-performance liquid chromatography (HPLC) as previously described [20]. The position of the microdialysis probe was verified by histological procedures at the end of each experiment.

Neurochemical data were expressed as percentage of baseline, which was defined as the average of at least two consecutive samples with stable neurotransmitter concentrations. For statistical analysis, the mean substance concentrations in the two samples prior to a challenge with NMDA alone, or in the presence of S-Me-TC, ODQ, or L-cys, were calculated and compared with that during the challenge. Statistical analysis between basal concentrations and NMDA- or $ONOO^-$-evoked effects was then carried out using the Wilcoxon test. The relative magnitude of evoked effects following different treatments was calculated and a Kruskal–Wallis ANOVA was carried out. Where this was significant, a Dunn's multiple comparison test was performed to assess the significance of specific treatments.

Basal release of 5-HT was 0.51 ± 0.15 nM (mean ± S.E.M. value not corrected for in vitro probe recovery). Retrodialysis applications of 100 μM NMDA for 20 min evoked a significant short-lasting increase in extracellular concentrations of 5-HT. These levels peaked concurrently with the NMDA administrations and returned to baseline levels immediately after NMDA was withdrawn from the perfusion medium. Repeated challenge with 100 μM NMDA (3 h apart) led to a similar pattern of 5-HT release (Fig. 1).

S-Me-TC (100 and 500 μM), a compound that selectively blocks nNOS [14], was retrodialysed into the striatum for 2 h and then NMDA (100 μM) was added to the perfusion buffer for 20 min in the presence of S-Me-TC. Coperfusion of NMDA (100 μM) and S-Me-TC (100 μM) did not affect NMDA-induced increase in extracellular 5-HT levels, whereas a trend towards a decrease in extracellular 5-HT concentrations was observed during S-Me-TC (100 μM) perfusion. However, although retrodialysis application of S-Me-TC (500 μM) did not modify basal transmitter release, it significantly decreased NMDA-induced release of 5-HT (Fig. 2A).

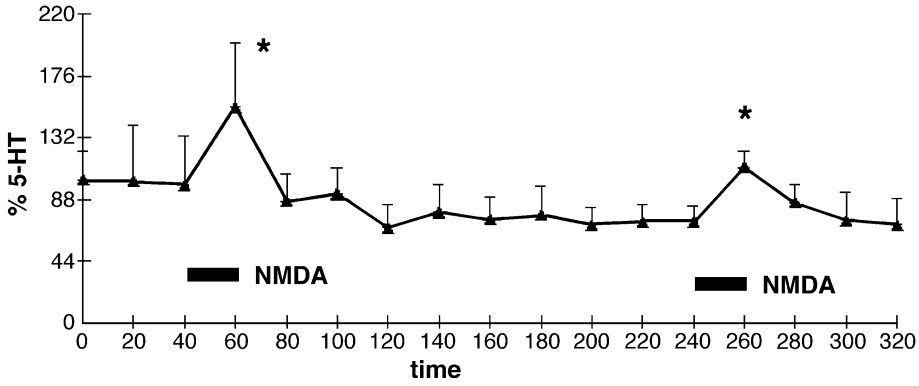

Fig. 1. Mean ± S.E.M. ($n = 8$ rats) percentage changes in striatal 5-HT concentrations following 20-min retrodialysis challenges with 100 μM NMDA (horizontal bar). *$P < 0.05$ vs. basal levels.

To assess whether $ONOO^-$ formation could play a role in the modulation of basal and NMDA-induced release of 5-HT, we first investigated the effects of the coadministration of NMDA with the $ONOO^-$ scavenger, L-cys [31]. Results showed that L-cys (10 mM) did not modify basal 5-HT extracellular concentrations. However, coperfusion of 10 mM L-cys with 100 μM NMDA partly reduced NMDA-evoked increased 5-HT levels (Fig. 2B).

In order to investigate whether sGC activation was involved in NMDA-evoked release of 5-HT, the striatum was retrodialysed with ODQ. This compound has been defined as a potent and selective GC inhibitor [16], although it has been shown that it is also able to inhibit NOS, but only at relatively high concentrations [12]. ODQ (100 μM) was perfused for 1 h prior to, during, and 1 h after NMDA challenge (100 μM). ODQ retrodialysis administration did not significantly influence the basal release of 5-HT. However, NMDA-induced increase of 5-HT extracellular concentrations was significantly reduced in the presence of ODQ (Fig. 2C).

The results of the present study confirm the potent ability of NO to modulate neurotransmitter release in the striatum of freely moving rats. In particular, we show that NO is able to increase serotoninergic activity. Moreover, we have demonstrated that endogenously produced NO can increase 5-HT concentrations both by stimulating formation of cyclic GMP and conversion of $ONOO^-$ via superoxide.

Our findings showing a modulatory effect of NMDA administration on 5-HT levels are in agreement with previous in vitro and in vivo studies [20,27,36]. Indeed, the striatal neurons have the capacity to release 5-HT in response to the stimulation of NMDA receptors. This NMDA-induced increase in 5-HT release was significantly inhibited by the selective nNOS inhibitor, S-Me-TC. Then, our data, with those reported above, suggest that the modulation of 5-HT levels analyzed in the present study is linked to the formation of NO produced by the activation of NMDA receptors.

It is well known that overproduction of NO by NMDA receptor activation produces neuronal cell damage [5,7]. Furthermore, it has been demonstrated that the doses of the significant NMDA-induced neurotoxicity are more than 300 or 500 μM in primary brain cell culture [5,7], and it has been shown, in vivo, that NMDA produces neuronal damage in the striatum at 30–300 mM [2,4]. However, in the present experiments, 100 μM NMDA was perfused through a dialysis membrane. Since the relative recovery rate of the microdialysis probe membrane was approximately 10–12%, the effective extracellular NMDA concentration in the striatum was about 10–12% of the perfusing dose. Moreover, repeated challenges with NMDA (3 h apart) led to a similar pattern of neurotransmitter release, indicating that the levels of NO produced did not lead to permanent perturbation of the responsivity of the striatum, which might have indicated that the dose of NMDA used was neurotoxic. In fact, baseline levels after the first NMDA challenge were not actually significantly different from those before it, even though there was a slight trend downwards. This could be due to storage depletion rather than toxic damage, and the fact that the dynamics and magnitude of the response to a second NMDA challenge were similar to the first one suggests that there was no significant toxic damage since the whole system continued to respond normally.

Thus, it is unlikely that 100 μM NMDA used in the present microdialysis study is a toxic concentration to striatal neurons, and it is possible to argue a physiological role of NMDA at this concentration.

It has been shown that NO binds and activates sGC [22], thereby producing an increase in cGMP in target cells. Our results show that the inhibitor of guanylyl cyclase ODQ did not influence the basal release of 5-HT. However, in the presence of ODQ, NMDA failed to increase the release of 5-HT. These results suggest that sGC activation may be essential for the stimulatory action of NMDA receptor on the release of 5-HT from striatal neurons, and show that cGMP is implicated in the modulation of 5-HT release by endogenous NO. Interestingly, our data also indicate that endogenous NO in the striatum would appear to be able, at least in part, to modulate extracellular 5-HT concentrations through its conversion to $ONOO^-$ via superoxide.

In our recent studies, we have demonstrated that striatal 5-HT levels were increased by two NO donors' administra-

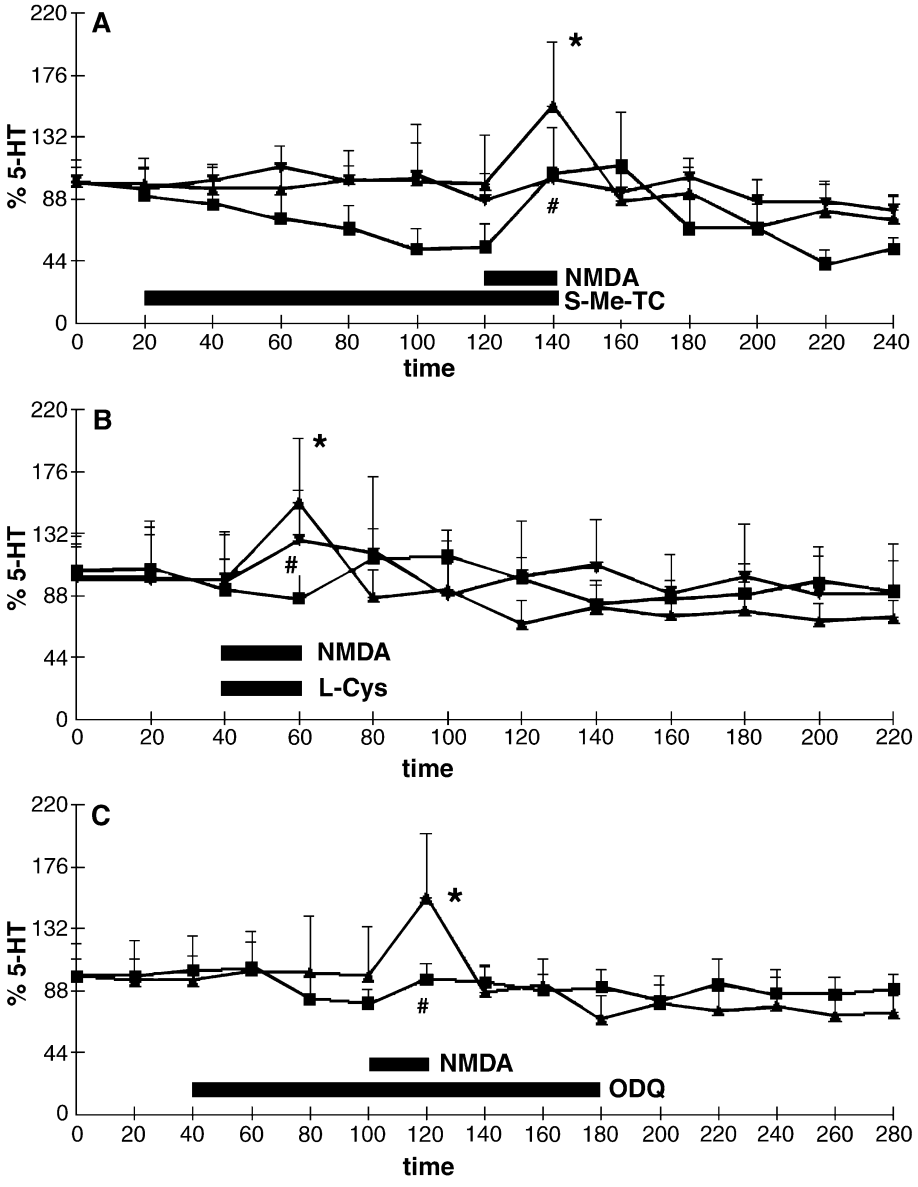

Fig. 2. Mean ± S.E.M. ($n = 8-10$ rats) percentage changes in striatal 5-HT concentrations following: (A) retrodialysis challenges with 100 μM NMDA (▲) alone or in the presence of 100 μM (■) or 500 μM (▼) S-Me-TC; (B) retrodialysis challenges with 10 mM L-cys (■) alone, 100 μM NMDA (▲) alone, or in the presence of 10 mM L-cys (▼); (C) retrodialysis challenges with 100 μM NMDA (▲) alone or in the presence of 100 μM ODQ (■). Duration of treatments is indicated by horizontal bars. $^{*}P < 0.05$ vs. basal levels; $^{\#}P < 0.05$ vs. NMDA group.

tion, SNAP and Deta NONOate. It is interesting to note that the presence of an $ONOO^-$ scavenger, like L-cys, had no effects on NO donor-evoked release of striatal 5-HT, while the activation of NO–sGC signalling pathway was involved in the modulation of 5-HT release [31]. Therefore, it seems that the exogenous administration of NO increases 5-HT levels via sGC-dependent route, whereas endogenously produced NO modulates 5-HT levels both through $ONOO^-$ and cGMP formation.

The detailed mechanism of action underlying this remains to be determined and the characterization of these systems is presently under investigations. However, as a consequence, combining the above evidences, it could be hypothesized that the mechanisms underlying the effects of NO on 5-HT release in the striatum critically depend on the ways by which NO is generated. Indeed, NO donors produce NO in the extracellular space, while NMDA is thought to yield NO in the cells through NMDA receptor-mediated mechanism. During the NO donor treatment, the extracellular NO concentration could be higher than the intracellular one, while the retrodialysis application of NMDA might increase the intracellular concentration of NO more than that in the extracellular space. Furthermore, NO produced by NMDA receptor activation may diffuse out through the neuronal membrane to induce the increase of 5-HT release extracellularly. However, the exact site of action of NO to evoke the release of 5-HT from the neurons is unclear at present and further studies are clearly warranted.

Other possible mechanisms cannot be excluded. Indeed, it has been shown that, under biologically relevant conditions, NO reacts with catecholamine neurotransmitters to give the corresponding nitro-derivatives by a mechanism probably involving the generation of semiquinone intermediates as the crucial step [8]. It has been also demonstrated that NO transforms 5-HT into 4-nitroso-5-HT and this affects neuromodulation by changing its regulatory action on synaptic transmission [13]. Furthermore, NO has been shown to promote regulation through nitrosylation [18]. Nevertheless, the existence of a possible storage mechanism of NO should be taken into account [17].

In conclusion, the present microdialysis study on 5-HT release in awake rats demonstrated that endogenous NO could modulate serotoninergic activity in the striatum both by sGC-dependent pathway and $ONOO^-$ formation.

References

[1] R.L. Albin, R.L. Makowiec, Z.R. Hollingsworth, L.S. Dure, J.B. Penney, A.B. Young, Excitatory amino acid binding sites in the basal ganglia of the rat: a quantitative autoradiographic study, Neuroscience 46 (1) (1992) 35–48.

[2] M. Buisson, I. Margaill, J. Callebert, M. Plotkine, R.G. Boulu, Mechanisms involved in the neuroprotective activity of a nitric oxide synthase inhibitor during focal cerebral ischemia, J. Neurochem. 61 (1993) 690–696.

[3] J. Collier, P. Vallance, Second messenger role for NO widens to nervous and immune system, Trends Pharmacol. Sci. 10 (1989) 427–431.

[4] B.P. Connop, R.J. Boegman, K. Jhamandas, R.J. Beninger, Excitotoxic action of NMDA agonists on nigrostriatal dopaminergic neurons: modulation by inhibition of nitric oxide synthesis, Brain Res. 676 (1995) 124–132.

[5] C.J. Davenport, H. Monyer, D.W. Choi, Tetrahydroaminoacridine selectively attenuates NMDA receptor-mediated neurotoxicity, Eur. J. Pharmacol. 154 (1988) 73–78.

[6] T.M. Dawson, V.L. Dawson, S.H. Snyder, A novel neuronal messenger molecule in brain: the free radical, nitric oxide, Ann. Neurol. 32 (1992) 297–311.

[7] V.L. Dawson, T.M. Dawson, D.A. Bartley, G.R. Uhl, S.H. Snyder, Mechanism of nitric oxide-mediated neurotoxicity in primary brain cultures, J. Neurosci. 13 (1993) 2651–2661.

[8] M. d'Ischia, C. Costantini, Nitric oxide-induced nitration of catecholamine neurotransmitters: a key to neuronal degeneration? Biol. Med. Chem. 3 (1995) 923–927.

[9] R. Dohovics, R. Janaky, V. Varga, A. Hermann, P. Saransaari, S.S. Oja, Regulation of glutamatergic neurotransmission in the striatum by presynaptic adenylyl cyclase-dependent processes, Neurochem. Int. 42 (1) (2003) 1–7.

[10] M.J. Eliasson, Z. Huang, R.J. Ferrante, M. Sasamata, M.E. Molliver, S.H. Snyder, M.A. Moskowitz, Neuronal nitric oxide synthase activation and peroxynitrite formation in ischemic stroke linked to neural damage, J. Neurosci. 19 (14) (1999) 5910–5918.

[11] J.V. Esplugues, NO as a signal molecule in the nervous system, Br. J. Pharmacol. 135 (2002) 1079–1095.

[12] M. Feelisch, P. Kotsonis, J. Siebe, B. Clement, H.H.H.W. Schmidt, The soluble Guanylyl Cyclase Inhibitor 1*H*-[1,2,4]Oxadiazolo-[4,3,-*a*]quinoxalin-1-one is a nonselective heme protein inhibitor of nitric oxide synthase and other cytochrome *p*-450 enzymes involved in nitric oxide donor bioactivation, Mol. Pharmacol. 56 (1999) 243–253.

[13] P. Fossier, B. Blanchard, C. Ducrocq, C. Leprince, L. Tauc, G. Baux, Nitric oxide transforms serotonin into an inactive form and this affects neuromodulation, Neuroscience 93 (2) (1999) 597–603.

[14] E.S. Furfine, M.F. Harmon, J.E. Paith, R.G. Knowles, M. Salter, R.J. Kiff, C. Duffy, R. Hazelwood, J.A. Oplinger, E.P. Garvey, Potent and selective inhibition of human nitric oxide synthases. Selective inhibition of neuronal nitric oxide synthase by *S*-methyl-L-thiocitrulline and *S*-ethyl-L-thiocitrulline, J. Biol. Chem. 269 (43) (1994) 26677–26683.

[15] J. Garthwaite, C.L. Boulton, Nitric oxide signaling in the central nervous system, Annu. Rev. Physiol. 57 (1995) 683–706.

[16] J. Garthwaite, E. Southam, C.L. Boulton, E.B. Nielsen, K. Schmidt, B. Mayer, Potent and selective inhibition of nitric oxide-sensitive guanylyl cyclase by 1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one, Mol. Pharmacol. 48 (1995) 184–188.

[17] C., Griffiths, J. Garthwaite, The shaping of nitric oxide signals by a cellular sink, J. Physiol. 536.3 (2001) 855–862, 855.

[18] S.R. Jaffrey, H. Erdjument-Bromage, C.D. Ferris, P. Tempst, S.H. Snyder, Protein *S*-nitrosylation: a physiological signal for neuronal nitric oxide, Nat. Cell Biol. 3 (2001) 193–197.

[19] S.T. Kaehler, N. Singewald, C. Sinner, A. Philippu, Nitric oxide modulates the release of serotonin in the rat hypothalamus, Brain Res. 835 (2) (1999) 346–349.

[20] K.M. Kendrick, R. Guevara-Guzman, C. De la Riva, J. Christensen, K. Ostergaard, P.C. Emson, NMDA and kainate-evoked release of nitric oxide and classical transmitter in the rat striatum: in vivo evidence that nitric oxide may play a neuroprotective role, Eur. J. Neurosci. 8 (1996) 2619–2634.

[21] K.M. Kendrick, R. Guevara-Guzman, J. Zorrilla, M.R. Hinton, K.D. Broad, M. Mimmack, S. Ohkura, Formation of olfactory memories mediated by nitric oxide, Nature 388 (6643) (1997) 670–674.

[22] R. Knowles, R.M.J. Palmer, S. Moncada, Formation of nitric oxide from L-arginine in the central nervous system: a transduction mechanism for stimulation of the soluble guanylate cyclase, Proc. Natl. Acad. Sci. U. S. A. 86 (1989) 5159–5162.

[23] L. Leger, Y. Charnay, S. Burlet, N. Gay, N. Schaad, C. Buras, R. Cespuglio, Comparative distribution of nitric oxide synthase- and serotonin containing neurons in the raphe nuclei of four mammalian species, Histochem. Cell Biol. 110 (1998) 517–525.

[24] D.T. Monaghan, R.J. Bridges, C.W. Cotman, The excitatory amino acid receptors: their classes, pharmacology, and distinct properties in the function of the central nervous system, Annu. Rev. Pharmacol. Toxicol. 29 (1989) 365–402.

[25] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, Academic Press, Sydney, 1982.

[26] E.M. Schuman, D.V. Madison, Nitric oxide and synaptic function, Annu. Rev. Neurosci. 17 (1994) 153–183.

[27] J.C.E. Smith, P.S. Whitton, Nitric oxide modulates *N*-methyl-D-aspartate-evoked serotonin release in the raphe nuclei and frontal cortex of the freely moving rat, Neurosci. Lett. 291 (2000) 5–8.

[28] S.H. Snyder, Nitric oxide: first in a new class of neurotransmitters? Science 257 (1992) 494–496.

[29] J.S. Stamler, *S*-nitrosothiols and bioregulatory actions of nitrogen oxides through reactions with thiol groups, Curr. Top. Microbiol. Immunol. 196 (1995) 19–36.

[30] R. Tao, S.B. Auerbach, Differential effect of NMDA on extracellular serotonin in rat midbrain raphe and fore brain sites, J. Neurochem. 66 (1996) 1067–1075.

[31] L. Trabace, K.M. Kendrick, Nitric oxide can differentially modulate striatal neurotransmitter concentration via soluble guanylate cyclase and peroxynitrite formation, J. Neurochem. 75 (4) (2000) 1664–1674.

[32] L. Trabace, V. Cuomo, K.M. Kendrick, Involvement of cGMP and $ONOO^-$ formation in the neuromodulatory effects of nitric oxide in the central nervous system, TINS 20 (9) (1997) 17.

[33] L. Trabace, T. Cassano, L. Steardo, C. Pietra, G. Villetti, K.M. Kendrick, V. Cuomo, Biochemical and neurobehavioral profile of CHF2819, a novel, orally active acetylcholinesterase inhibitor for Alzheimer's Disease, Pharmacol. Exp. Ther. 294 (1) (2000) 187–194.

[34] M.J. Wall, Endogenous nitric oxide modulates GABAergic transmission to granule cells in adult rat cerebellum, Eur. J. Neurosci. 18 (2003) 869–878.
[35] G. Wegener, V. Volke, R. Rosenberg, Endogenous nitric oxide decreases hippocampal levels of serotonin and dopamine in vivo, Br. J. Pharmacol. 130 (2000) 575–580.
[36] G. Wegener, V. Volke, B.H. Harvey, R. Rosenberg, Local, but not systemic, administration of serotonergic antidepressants decreases hippocampal nitric oxide synthase activity, Brain Res. 959 (1) (2003) 128–134.
[37] A.R. West, S.B. Floresco, A. Charara, J.A. Rosenkranz, A.A. Grace, Electrophysiological interactions between striatal glutamatergic and dopaminergic systems, Ann. N.Y. Acad. Sci. 1003 (2003) 53–74.
[38] H.Y. Yun, M. Gonzales-Zulueta, V.L. Dawson, T.M. Dawson, Nitric oxide mediates *N*-methyl-D-aspartate receptor-induced activation of p21ras, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 5773–5778.