

# Tyrosine Augments Acute Clozapine- but not Haloperidol-Induced Dopamine Release in the Medial Prefrontal Cortex of the Rat: An *in vivo* Microdialysis Study

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*Tyrosine availability can influence dopamine (DA) synthesis in highly electrophysiologically active DAergic neurons, such as those innervating the medial prefrontal cortex (MPFC). Whether tyrosine concentrations can also affect MPFC extracellular DA concentrations, measured in vivo, is not known. Since clozapine preferentially activates mesocortical DA neurons, we posited that tyrosine administration to a clozapine-pretreated rat would enhance the clozapine-induced augmentation of MPFC extracellular DA concentrations. Tyrosine alone (25–50mg/kg IP) did not affect mesocortical or striatal extracellular DA concentrations measured by in vivo microdialysis. Given 30 minutes after clozapine (10 mg/kg), tyrosine (50 mg/kg)*

*significantly prolonged the clozapine-induced increase in MPFC extracellular DA concentrations but had no effect in the striatum. In contrast, tyrosine (50 mg/kg) significantly prolonged the haloperidol (1 mg/kg) induced increase in striatal extracellular DA concentrations but had no effect in the MPFC. These data constitute the first in vivo evidence that administration of tyrosine can selectively potentiate the clozapine-evoked increase in mesocortical extracellular DA concentrations.*

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In most brain dopamine (DA) systems, levels of the DA precursor tyrosine do not significantly affect dopaminergic transmission. The availability of tyrosine in the brain normally exceeds the capacity of the enzyme tyrosine hydroxylase (TH) to convert it to DOPA (Carlsson and Lindqvist 1978; Morgenroth et al. 1976; Joh et al.

1978). Since the conversion of DOPA to DA is rapid and efficient, DA synthesis usually depends on TH activity and not on tyrosine levels (Wurtman et al. 1974; Carlsson and Lindqvist 1978). However, precursor dependence of DA synthesis has been demonstrated in the light-activated retina (Fernstrom et al. 1984, 1986) as well as in striatal DA neurons after administration of haloperidol, spiperone, reserpine or amfonelic acid (Scally et al. 1977; Sved et al. 1979; Fuller and Snoddy 1982) or after marked DA depletion (Melamed et al. 1980). The common feature of these paradigms is a marked increase in the electrophysiological activity of the relevant DA system. Such data suggest that precursor dependence of DA synthesis may be a latent property of all DA neurons, but one which emerges only under conditions of increased dopaminergic activity.

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Since mesocortical DA neurons have the highest basal electrophysiological activity of all central DA systems (Chiodo et al. 1984; White and Wang 1984), precursor dependence of medial prefrontal cortical (MPFC) DA synthesis might be expected even under basal conditions. Even within the MPFC, however, tight feedback systems limit the ability of exogenous tyrosine administration to augment DA synthesis (Tam et al. 1990). Intriguingly, in rats pretreated with FG-7142, a beta-carboline known to preferentially increase MPFC synthesis, utilization and release (Tam and Roth 1985, 1990; Bradberry et al. 1991), administration of tyrosine robustly enhances MPFC DA synthesis (Tam et al. 1990). We postulated that such precursor dependence would also be established by other drugs which activate mesocortical dopaminergic activity.

The atypical and clinically superior antipsychotic drug, clozapine, has already been demonstrated to preferentially release DA in the prefrontal cortex of the rat (Moghaddam and Bunney 1990; Pehek and Yamamoto 1994; Yamamoto and Cooperman 1995) as well as of the non-human primate (Youngren et al. 1999) and to preferentially activate DA neurons projecting to cortical regions (White and Wang 1983; Goldstein et al. 1993). Accordingly, we postulated that the co-administration of tyrosine and clozapine would potentiate MPFC DA synthesis. We further postulated that if the increased DA synthesis were reflected in increased DA release, then administration of tyrosine to clozapine-pretreated rats would augment MPFC DA levels as measured by *in vivo* microdialysis. Finally, since haloperidol, but not clozapine, preferentially activates nigrostriatal DA synthesis and release, we anticipated that tyrosine would enhance dialysate DA concentrations in the striatum but not the MPFC of haloperidol-pretreated animals.

## MATERIALS AND METHODS

### Animals and surgery

Experimentally naive, male, Sprague-Dawley rats (210–340g) were used (Zivic-Miller). Rats were anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (Rompun, 6 mg/kg). Small holes were drilled into the skull, dura was removed and 21-gauge, stainless steel guide cannulae were implanted on the brain surface above either the MPFC (AP + 3.2, ML  $\pm$  0.8) or the anterior caudate-putamen (AP + 1.2, ML  $\pm$  3.4) (Paxinos and Watson 1986). This procedure was accomplished by the placement of the guide cannula on the surface of the brain, the fabrication of the guide cannula to the precise length of 11 mm, and the use of a 26-ga needle with an attached "stop" at a pre-measured distance on the shaft of the needle such that the point of the needle could not be lowered further than 0.5 mm beyond the end of the guide cannula. The guide cannula was low-

ered under stereotaxic control through a 1.5 mm diameter hole drilled through the skull. The surface of the brain can be seen clearly through this hole while slowly lowering the guide cannula onto the cortical surface. Two to four days after surgery, awake animals were placed in cylindrical buckets. Microdialysis probes were lowered through the guide cannulae, terminating in the structures of interest. Rats were used only once. After each experiment, probe placements were verified histologically. Data from rats with improper probe placement were excluded from analysis. All procedures were in strict accordance with the *NIH Guide for the Care and Use of Laboratory Animals* and were approved by the local animal care committee.

### Microdialysis

Microdialysis probes were of concentric flow design as described previously (Yamamoto and Pehek 1990). Membrane lengths were 5.0 and 4.5 mm for the MPFC and striatum, respectively. Animals were tethered to liquid swivels that permitted free movement. The perfusion medium consisted of Dulbecco's phosphate-buffered saline (138 mM NaCl, 32.7 mM KCl, 0.5 mM MgCl<sub>2</sub>, 1.5 mM KH<sub>2</sub>PO<sub>4</sub>, 8.1 mM Na<sub>2</sub>HPO<sub>4</sub>, 1.2 mM CaCl<sub>2</sub>, and 5.0 mM glucose, pH = 7.4) and was pumped through the probes at a rate of 1.5  $\mu$ l/min. Beginning three hours after probe insertion, baseline samples were collected every 30 minutes for 1.5 hours. Vehicle, clozapine or haloperidol was administered immediately after the last baseline sample. Vehicle or tyrosine was administered 30 minutes after initial drug administration, immediately after the first post-drug sample collection. Post-drug samples were collected every 30 minutes for five hours.

### Drugs

All drugs were delivered intraperitoneally. Clozapine (10 mg/kg, Sandoz Research Institute) was dissolved initially in 1.0 M tartaric acid and then brought to pH ~ 5.1–5.4 with 1.0 M NaOH. The clozapine dose was the lowest previously found to increase MPFC DA release (Pehek and Yamamoto 1994). Haloperidol (Sigma Chemical Company) was dissolved in 1% acetic acid and then diluted dH<sub>2</sub>O for final delivery of 1 mg/kg (pH ~ 5.1–5.4). L-Tyrosine-methyl-ester was dissolved in saline. Both tyrosine doses (25 mg/kg or 50 mg/kg) refer to the free base. Vehicle for each drug was prepared in tandem. Vehicles were prepared and pH matched as for each drug.

### Chromatography

Twenty microliter (20  $\mu$ l) dialysate samples were assayed for dopamine content by HPLC coupled with

electrochemical detection. Dopamine metabolites were not quantitated. Samples were injected immediately after collection onto a C18 reversed phase column (Phenomenex, Ultracarb, ODS, 2.0 × 100 mm, 3 μm particle size) maintained at 33°C. The mobile phase was pumped at a rate of 0.25 ml/min and consisted of 32 mM citric acid, 54 mM sodium acetate, 0.1 mM EDTA, 0.2 mM octylsulfonic acid (OSA), and 3% methanol (vol/vol), pH = 4.2. A BAS LC-4C electrochemical detector was used with BAS glassy carbon electrode and maintained at a potential of +0.6 V, relative to a Ag/AgCl reference electrode. The detection limit for the assay of DA was 60 femtograms/20 μl at a 3 to 1 signal to noise ratio.

### Statistics

Absolute concentrations were expressed as pg/20 μl and were analyzed by 2-factor (time X drug) ANOVA with repeated measures, followed by Newman-Keuls *post hoc* comparisons. Significance level was set at  $p < .05$ . Data were expressed as percentages of the average of three pre-drug baseline levels. Since the basal concentrations of dopamine differed for the cortex and striatum, the graphical depiction of percent baseline data permits more accurate comparisons of the relative magnitude of effects between brain areas.

## RESULTS

Basal dialysate concentrations of DA in the MPFC prefrontal cortex were  $0.51 \pm 0.04$  pg/20 μl, equivalent to  $0.11$  fmol/μl ( $n = 76$ ). Basal concentrations in the caudate-putamen were  $2.88 \pm 0.08$  pg/20 μl, equivalent to  $0.627$  fmol/μl ( $n = 65$ ). Clozapine (10 mg/kg) produced a transient increase (225%) in MPFC dialysate DA concentrations (Figure 1, Panel A) but no significant change in striatal dialysate DA concentrations (Figure 1, Panel B). Tyrosine alone (50 mg/kg) did not significantly affect dialysate DA concentrations either in the MPFC or striatum. Although the increase in extracellular DA concentration in the MPFC after co-administration of clozapine (10 mg/kg) and tyrosine (50 mg/kg) was comparable in magnitude (200–250%), the duration of increase was much longer than that produced by clozapine alone (Figure 1, Panel A). Mesocortical dialysate DA levels were still significantly elevated by 200% at the termination of the experiment (5 hours after injection of tyrosine). In contrast, the co-administration of tyrosine and clozapine did not affect striatal dialysate DA levels.

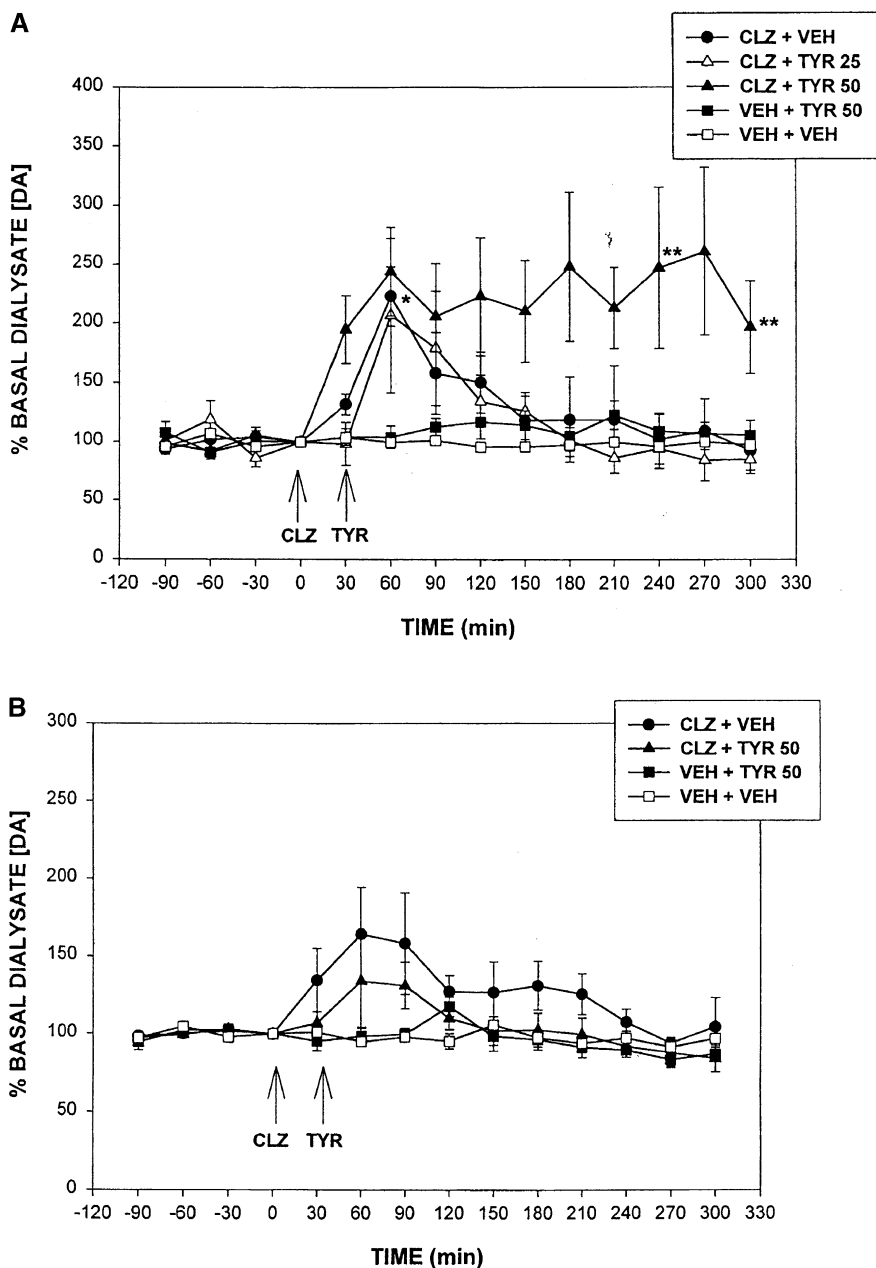
Haloperidol (1 mg/kg) alone significantly increased (150%) striatal dialysate DA by 60 minutes, but had no significant effect on DA in the MPFC (Figure 2, Panels A and B). Co-administration of tyrosine and haloperi-

dol did not modify haloperidol-induced effects in the MPFC but significantly enhanced both the magnitude and duration of the haloperidol-induced increase in striatal dialysate DA concentrations (225% at 90 minutes after tyrosine). By 150 minutes after haloperidol injection, striatal dialysate DA in rats treated with haloperidol alone was comparable to that in controls. In contrast, in rats co-treated with haloperidol and tyrosine, striatal dialysate DA concentrations remained elevated 270 minutes after the haloperidol injection.

## DISCUSSION

The present study examined the hypothesis that co-administration of tyrosine and clozapine would potentiate the increase in mesocortical dialysate DA produced by clozapine alone. Tyrosine administered after clozapine treatment augmented dialysate DA concentrations in the MPFC but not in the striatum. Tyrosine administered after haloperidol treatment augmented striatal but not mesocortical dialysate DA concentrations.

DA synthesis and release are modulated by presynaptic and dendritic autoreceptors (Nowycky and Roth 1978), by changes in the firing rate of DA neurons (Farnebo and Hamberger 1971) and by end product inhibition of TH (Nagatsu et al. 1964; Lovenberg and Victor 1974). These systems effectively maintain brain DA concentrations within a narrow range. DA synthesis and or release under basal conditions is generally not precursor dependent. Indeed, brain tyrosine concentrations can be increased by up to 700% with little if any effect on whole brain DA or its metabolites (Badawy and Williams 1982). Scally et al. (1977) were the first to demonstrate that exogenous tyrosine could potentiate haloperidol-induced increases in striatal DA metabolites, suggesting an increase in DA utilization (Scally et al. 1977). These results were confirmed by others who found that exogenous tyrosine augmented the haloperidol-induced increase in striatal DOPA accumulation (Carlsson and Lindqvist 1978; Westerink and Wirix 1983). Tyrosine-induced potentiation of DA synthesis, as suggested by changes in either DA metabolites or DOPA accumulation, was also reported after pretreatment with amfonelic acid, spiperone (Fuller and Snoddy 1982), reserpine (Sved et al. 1979) or in animals with near total striatal DA depletion (Melamed et al. 1980). Furthermore, tyrosine administration augmented, and tyrosine depletion reduced, DA synthesis in the light-activated retina (Fernstrom et al. 1984, 1986). The common feature of all these experimental paradigms was an electrophysiological activation of the relevant DA system. However, tyrosine effects on striatal DOPA accumulation have also been noted in rats treated with gamma-butyrolactone (Sved and Fernstrom 1981), a drug which reduces nigrostriatal impulse



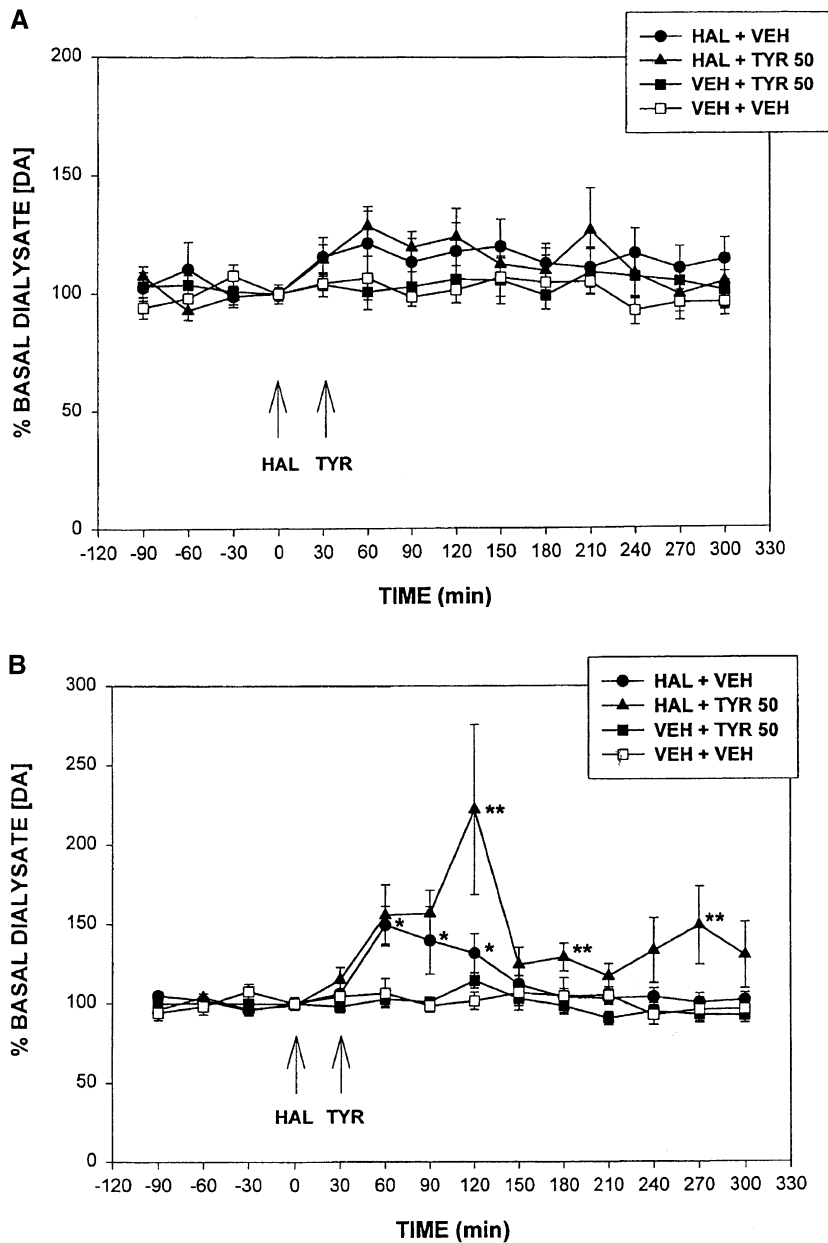
**Figure 1.** Effects of intraperitoneal injection of tyrosine (TYR) or vehicle (VEH) on percent basal extracellular dopamine release from the medial prefrontal cortex (Panel A) or caudate-putamen (Panel B) induced by clozapine (CLZ). CLZ (10 mg/kg) or VEH was administered at time 0. TYR (25 or 50 mg/kg) was injected at time 30. Values are expressed as mean  $\pm$  SEM percent predrug (baseline) levels. Data were analyzed by 2-way ANOVA (treatment  $\times$  time), followed by Student Newman-Keul's *post hoc* comparison.  $p < .05$ . \*Significantly different from VEH + VEH group. \*\*Significantly different from CLZ + VEH group.  $n = 8-11$  per group, except Panel A: CLZ + TYR 25 group ( $n = 6$ ).

flow (Walters and Roth 1976) but activates striatal TH (Walters and Roth 1974; Morgenroth et al. 1976). Thus it is probably not increased DA neuronal activity *per se* but the resultant activation of TH that is critical to the induction of precursor dependence (Sved and Fernstrom 1981).

The functional implications of these early data are limited by several factors. Most DOPA accumulation studies involve administration of the DOPA decarboxylase inhibitor NSD-1015; the latter can alter brain concentrations of tyrosine (Westerink and Wirix 1983) as well as concentrations and intracellular distribution of DA (Wurtman et al. 1981; Milner and Wurtman 1986). Inferring changes in DA utilization from changes in DA

metabolites is similarly problematic. Finally, changes in DA synthesis do not necessarily result in changes in DA release (Westerink et al. 1982; Westerink and Wirix 1983). Accordingly, the later report by During et al. (1989) that tyrosine administration augmented the haloperidol-induced increase in striatal dialysate DA concentrations as measured by *in vivo* microdialysis (albeit in anesthetized animals) provided critical support for the possible functional importance of precursor dependence in DA systems.

The high basal firing rate (Chiodo et al. 1984; White and Wang 1984) and the large fraction of activated TH (Iuvone and Dunn 1986) of mesocortical DA neurons suggested that precursor dependence might be a nor-



**Figure 2.** Effects of intraperitoneal injection of tyrosine (TYR) or vehicle (VEH) on percent basal extracellular dopamine release from the medial prefrontal cortex (Panel A) or caudate-putamen (Panel B) induced by haloperidol (HAL). HAL (1 mg/kg) or VEH was administered at time 0. TYR (50 mg/kg) was injected at time 30. Values are expressed as mean  $\pm$  SEM percent predrug (baseline) levels. Data were analyzed by 2-way ANOVA (treatment  $\times$  time), followed by Student Newman-Keul's *post hoc* comparison.  $p < .05$ . \*Significantly different from VEH + VEH group. \*\*Significantly different from HAL + VEH group.  $n = 8-11$  per group.

mal feature of DA synthesis and release in the MPFC. While several groups demonstrated that experimental reductions in brain tyrosine concentrations reduced MPFC DA synthesis as measured *in vivo* (Bradberry et al. 1989; Tam et al. 1990), increases in MPFC DA synthesis after administration of exogenous tyrosine appeared to be modest and highly transient (Tam et al. 1990). However, exogenous tyrosine administration robustly increased MPFC DA synthesis after pretreatment with FG-7142, an inverse benzodiazepine agonist which preferentially increases MPFC DA synthesis and release (Tam et al. 1990; Bradberry et al. 1991). Such data suggested that whereas precursor dependence was not a constant feature of mesocortical DA neurons, their high basal electrophysiological activity notwithstanding,

precursor dependence did become evident when these DA neurons were activated above baseline levels.

The typical antipsychotic drug, haloperidol, increases the firing rate of DA neurons originating in regions A9 and A10 (Bunney and Grace 1978; White and Wang 1983) whereas clozapine may preferentially activate DA neurons originating in A10 (White and Wang 1983; Goldstein et al. 1993, but see also Chiodo and Bunney 1983). Terminal DA release within the striatum at least, is impulse dependent (Gonon and Buda 1985). Acute haloperidol administration increases dialysate DA concentrations in most DA terminal fields (Moghaddam and Bunney 1990) but the relative magnitude of the haloperidol-induced DA increase appears to be greater in the striatum than in the MPFC (Moghad-

dam and Bunney 1990; Pehek and Yamamoto 1994). In contrast, acutely administered clozapine induces a greater relative increase in mesocortical than striatal dialysate DA concentrations (Moghaddam and Bunney 1990; Pehek and Yamamoto 1994; Yamamoto and Cooperman 1995). Since clozapine preferentially increases the firing rate of mesocortical DA neurons (Melis et al. 1999) and given the usual relationship between impulse flow and TH activation (Murrin et al. 1976; Haycock 1987), it is likely that clozapine preferentially activates TH in MPFC DA terminals. The latter could provide a mechanism by which exogenous tyrosine administration increases clozapine-induced MPFC DA synthesis. On the other hand, the link between clozapine's electrophysiological effects and clozapine-induced MPFC DA release are not well defined.

Clozapine increases burst firing of mesocortical DA neurons (Melis et al. 1999) and by classical impulse-dependent mechanisms would be expected to increase MPFC DA release. However, some of us (Pehek and Yamamoto 1994) as well as others (Gessa et al. 2000) have demonstrated that MPFC DA release is also potently stimulated when clozapine is administered *locally* into the MPFC. The recent report that changes in mesocortical DA firing do not correlate with MPFC DA release following the administration of clozapine and other antipsychotic drugs (at least in anesthetized animals), led the authors to postulate that antipsychotic-drug induced MPFC DA release results from direct actions on the MPFC (Gessa et al. 2000). Thus, at the present time it is not known what fraction of the MPFC DA release evident after systemic administration of clozapine is mediated by a direct MPFC as opposed to an impulse-dependent effect. It is conceivable that whereas local effects of clozapine within the MPFC affect DA release, impulse-dependent activation of TH controls terminal DA synthesis. In that case, the duration of clozapine-induced MPFC DA release could be limited by the pool of releasable DA. Tyrosine could prolong clozapine-induced MPFC DA release by preventing depletion of that DA pool.

Indeed both we and During et al. (1989) found a time lag of 75–120 minutes between the administration of tyrosine and its maximal potentiation of the haloperidol-induced increase in dialysate DA concentrations. The tyrosine potentiation then persisted for several hours. During this time dialysate DA concentrations in animals treated only with haloperidol, returned to control levels (During et al. 1989). We postulate, as others have (During et al. 1989), that the delay between the administration of tyrosine and its maximal effect on haloperidol-induced striatal DA release is due to both pharmacokinetic and pharmacodynamic factors. Tyrosine injected intraperitoneally rapidly enters plasma and crosses the blood brain barrier. Maximal brain concentrations occur within 10 minutes of an intraperitoneal injection (Ng and Ander-

son 1992). How soon the newly available tyrosine becomes intraneuronally available and needed for DA synthesis is not known. Data from *in vitro* studies suggest that there is an intraneuronal reserve of tyrosine which is preferentially used during periods of increased DA synthesis and that extraneuronal sources are mobilized only after repeated or prolonged neuronal stimulation (Milner and Wurtman 1984, 1985; Milner et al. 1987). The latter may contribute to the delay of 120 minutes between the administration of tyrosine and the detection of tyrosine potentiation of haloperidol-induced increase in dialysate DA concentrations in our study. However, it does not explain why at 120 minutes after haloperidol administration tyrosine potentiates peak release, not just duration (Figure 2, Panel B).

Our data extend earlier work in two important respects. First, we provide the first *in vivo* data that tyrosine administration can increase MPFC dialysate DA concentrations. Second, we find that tyrosine administration increases haloperidol-induced striatal dialysate DA concentrations in unanesthetized animals. The latter differs from the report of one other group who conducted trans-striatal microdialysis and used different drug doses as well as a shorter evaluation time than we did (Westerink and de Vries 1991).

Precursor influences, particularly on mesocortical DA transmission, merit further investigation for several reasons. Cortical DA systems have been implicated in normal cognition and emotionality as well as in the pathophysiology of several neuropsychiatric disorders. Pharmacologic manipulation of brain tyrosine levels could provide a safe, selective and heuristically useful probe for studying experimental increases or decreases in brain DA transmission. For instance, experimental reduction (McTavish et al. 1999) in cortical or striatal DA in schizophrenia and Parkinson's Disease respectively would be expected to potentiate symptoms and cognitive impairments. Alternatively, potentiation of cortical and striatal DA release through co-administration of tyrosine and appropriate agents could prove therapeutic in these conditions.

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