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Research Report

Chronic treatment with fluoxetine decreases cerebral metabolic responses to the 5-HT_{1A} agonist 8-hydroxy-2(di-*N*-propylamino)tetralin and increases those to the 5-$HT_{2A/2C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane and to the dopaminergic agonist apomorphine

Ulderico Freo[a,*], *Antonio Merico*[b], *Mario Ermani*[c], *Carlo Ori*[a]

[a]*Dipartimento di Farmacologia e Anestesiologia, Università di Padova, I-35121 Padova, Italy*
[b]*Istituto di Cura San Camillo, Ospedale/IRCCS, I-30126 Venezia-Lido, Italy*
[c]*Dipartimento di Neuroscienze, Università di Padova, I-35121 Padova, Italy*

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ABSTRACT

Fluoxetine is a selective serotonin (5-HT) reuptake inhibitor that, when given chronically, alters different neurotransmitter systems. To assess functional changes occurring in the 5-HT and dopaminergic systems, we investigated the effects of 5-HT_{1A} agonist 8-hydroxy-2(di-*N*-propylamino)tetralin (8-OH-DPAT), of the 5-$HT_{2A/2C}$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and of the dopamine $D_{1/2}$ agonist apomorphine (APO) on behavior and on regional cerebral metabolic rates for glucose (rCMRglc) in rats pretreated for 3 weeks with saline or fluoxetine (8 mg/kg/day). Behavioral effects were assessed for 8-OH-DPAT by scoring the 5-HT syndrome, for DOI by counting head shakes and for APO with an activity monitor. rCMRglc were measured with quantitative autoradiographic [^{14}C]2-deoxyglucose technique in 60 brain regions at 10 min after acute administration of 8-OH-DPAT 1 mg/kg, at 30 min after DOI 5 mg/kg or at 10 min after APO 1 mg/kg. Chronic fluoxetine did not alter the 5-HT syndrome by 8-OH-DPAT, decreased head shakes by DOI and enhanced hyperlocomotion by APO. 8-OH-DPAT produced rCMRglc increases in sensorimotor regions that were unaffected by fluoxetine pretreatment and diffuse metabolic decrements that were attenuated by fluoxetine in limbic and raphe areas (17% and 4% mean decreases, respectively, in saline control and fluoxetine-pretreated rats). DOI produced widespread rCMRglc declines that were intensified by fluoxetine (14% and 20% decreases, in control and fluoxetine rats). APO caused rCMRglc increases in 22

* *Corresponding author*. Dipartimento di Farmacologia e Anestesiologia, Università di Padova, Via C. Battisti, 267, I-35121 Padova, (PD), Italy. Fax: +39 49 875 5093.
E-mail address: ulderico.freo@unipd.it (U. Freo).

Abbreviations: APO, apomorphine; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; rCMRglc, regional cerebral metabolic rates for glucose; SSRI, selective serotonin reuptake inhibitor; [^{14}C]DG, [^{14}C]-2-deoxy-d-glucose; 5-HT, serotonin; 8-OH-DPAT, 8-hydroxy-2(di-*N*-propylamino)tetralin

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brain regions that were potentiated by fluoxetine in dopaminergic motor areas (10% and 25% increases, in control and fluoxetine rats). In conclusion, fluoxetine enhances 5-HT neurotransmission by blunting responsivity of 5-HT_{1A} autoreceptors and increasing that of 5-$HT_{2A/2C}$ postsynaptic receptors and enhances dopaminergic $D_{1/2}$ receptor neurotransmission.

1. Introduction

Fluoxetine is classified as a serotonin reuptake inhibitor (SSRI) because of its predominant pharmacological action and because it lacks significant affinity for neuroreceptors (Baumann, 1996). A 2- to 3-week delay in the onset of clinical effects is typically seen with all antidepressant drugs and has led several authors to question the hypothesis that therapeutic actions of fluoxetine are due to acute blockade of serotonin (5-HT) reuptake. It is now generally accepted that therapeutic effects of fluoxetine are due to adaptive changes that occur during chronic treatment.

A large number of studies on antidepressants have focused on the 5-HT systems because SSRI have antidepressant properties and because changes in 5-HT receptors have been linked to psychiatric symptoms and therapeutic responses. Following chronic treatment with fluoxetine, 5-HT_{1A} binding sites were found unchanged (Hensler, 2002; Welner et al., 1989) or decreased (Le Poul et al., 2000) and 5-HT_{2A} sites unchanged or increased (Van Oekelen et al., 2003). After chronic fluoxetine, thermic and hormonal responses to 5-HT_{1A} agonists were decreased (Li et al., 1994), whereas the 5-HT_{1A}-mediated motor syndrome was unaffected (Maj and Moryl, 1993). The hypothermic effect of the 5-$HT_{1B\text{-}2A/2C}$ agonist meta-chlorophenylpiperazine (MCPP) was enhanced and its hypolocomotor effect reduced by fluoxetine (Maj and Moryl, 1993). Finally, chronic fluoxetine potentiated the stimulatory action of 5-HT_{2A} agonists on phospholipase C activity in the cortex but blunted their behavioral and hormonal effects (Damjanoska et al., 2003). Hence, chronic fluoxetine alters 5-HT functions in a heterogeneous fashion.

Fluoxetine and antidepressants affect also non-5-HT neurotransmitter systems. Anhedonia and lack of motivation are among core symptoms of depression and are thought to result from dysfunction of dopaminergic systems (Nutt, 2006). Chronic fluoxetine increases dopamine concentrations in prefrontal cortex (Bymaster et al., 2002), dopaminergic D_2 receptors in striatum (Maj et al., 1996) and firing of dopaminergic neurons in brainstem (Sekine et al., 2007).

The aim of this study was to investigate the effects in the rat of chronic fluoxetine administration on various 5-HT and dopaminergic functions as measured by behavioral and cerebral metabolic responses to three agonists with different receptor specificity: 8-hydroxy-*N*,*N*-dipropyl-2-aminotetralin (8-OH-DPAT), a selective 5-HT_{1A} agonist; 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a 5-$HT_{2A/C}$ agonist; and apomorphine (APO), a dopaminergic $D_{1/2}$ agonist. Doses and times of endpoint measurements were chosen for each drug based upon previous studies in which the time course and relation-to-dose of its effects on behavior (Freo et al., 1991; Freo, 1996; Goodwin and Green, 1985; Swerdlow et al., 1986) and rCMRglc had been characterized (Freo et al., 1991; Freo, 1996; Grasby et al., 1989; Kelly et al., 1988; Orzi et al., 1993). We employed the quantitative [^{14}C]-2-deoxy-D-glucose autoradiographic technique (Sokoloff et al., 1985; Soncrant et al., 1985) to study the regional cerebral metabolic rates for glucose (rCMRglc) in rats.

2. Results

2.1. *Physiological parameters*

Chronic fluoxetine (8 mg/kg/day) reduced the growth rate of rats during the 21-day treatment compared with saline-injected rats (1 ml/kg/day). Mean body weights (±SEM) on the final day of pretreatment were significantly ($P<0.05$) larger in saline- than in fluoxetine-treated rats (297±11 vs 260±9 g).

Arterial blood pressure, heart rate, body temperature and plasma glucose concentrations of control animals were similar to means previously reported (Freo et al., 1991, 2005). 8-OH-DPAT increased ($P<0.05$) plasma glucose concentrations in saline- and fluoxetine-pretreated rats (295±13 and 269±8 mg/dl, 88% and 72%) and decreased heart rate in control rats (319±11 bpm, –31%). In both saline- and fluoxetine-pretreated rats, DOI increased plasma glucose (193±14 and 194±9 mg/dl, 23% and 24%) and arterial mean blood pressure (155±7 and 160±6 mm Hg, 46% and 36%) and decreased heart rate in control rats (350±13 bpm, –24%). APO increased arterial blood pressure in saline- and fluoxetine-pretreated rats (163±5 and 170±9 mm Hg, 48% and 44%).

2.2. *Behavior*

Behavioral measures did not differ after intraperitoneal (ip) injection of saline (1 ml/kg) to rats that had not been pretreated or that had been pretreated with daily ip injection of saline for 21 days (data not shown).

No significant difference ($P<0.05$) was found in the total scores of the 5-HT syndrome in rats given 8-OH-DPAT that had received either chronic saline or chronic fluoxetine (14±2 and 17±3) (Fig. 1).

DOI produced 18±3 head shakes in saline-pretreated, control animals but only 6±2 head shakes ($P<0.05$) in rats pretreated chronically with fluoxetine. The latter frequency is significantly higher than the frequency of saline in rats pretreated with saline or with fluoxetine (2±1 and 2±1) (Fig 1).

Locomotor activity measured in an open field in rats pretreated with saline and acutely injected ip with saline generated 1547±421 counts. Twenty-one-day pretreatment with fluoxetine did not modify ($P<0.05$) locomotor activity (1328±381 counts). Acutely administered APO increased motor activity to a greater degree in animals pretreated chronically with fluoxetine (6591±334 counts) than in animals pretreated with saline (4270±254 counts) (Fig. 1).