Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 472 (2003) 89–97
www.elsevier.com/locate/ejphar

# Diminished catalepsy and dopamine metabolism distinguish aripiprazole from haloperidol or risperidone

Satoru Nakai[a,*], Tsuyoshi Hirose[a,1], Yasufumi Uwahodo[a,1], Takeshi Imaoka[a,2], Hiroshi Okazaki[a,3], Takashi Miwa[a,1], Masami Nakai[a,4], Sakiko Yamada[a,1], Bob Dunn[b], Kevin D. Burris[c,5], Perry B. Molinoff[c,5], Katsura Tottori[a,6], C. Anthony Altar[b,7], Tetsuro Kikuchi[a,8]

[a] *Second Institute of New Drug Research, Otsuka Pharmaceutical Co. Ltd., 463-10 Kagasuno, Kawauchi, Tokushima 771-0192, Japan*
[b] *Neuroscience Research, Otsuka Maryland Research Institute, 9900 Medical Center Drive, Rockville, MD 20850, USA*
[c] *Neuroscience and Genitourinary Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT 06492, USA*

Received 6 February 2003; received in revised form 9 May 2003; accepted 15 May 2003

**Abstract**

Catalepsy and changes in striatal and limbic dopamine metabolism were investigated in mice after oral administration of aripiprazole, haloperidol, and risperidone. Catalepsy duration decreased with chronic (21 day) aripiprazole compared with acute (single dose) treatment across a wide dose range, whereas catalepsy duration persisted with chronic haloperidol treatment. At the time of maximal catalepsy, acute aripiprazole did not alter neostriatal dopamine metabolite/dopamine ratios or homovanillic acid (HVA) levels, and produced small increases in dihydroxyphenylacetic acid (DOPAC). Effects were similar in the olfactory tubercle. Dopamine metabolism was essentially unchanged in both regions after chronic aripiprazole. Acute treatments with haloperidol or risperidone elevated DOPAC, HVA, and metabolite/dopamine ratios in both brain areas and these remained elevated with chronic treatment. The subtle effects of aripiprazole on striatal and limbic dopamine metabolism, and the decrease in catalepsy with chronic administration, illustrate fundamental differences in dopamine neurochemical actions and behavioral sequelae of aripiprazole compared to haloperidol or risperidone.


*Keywords:* Aripiprazole; Haloperidol; Risperidone; Catalepsy; Dopamine; Partial agonist; Atypical antipsychotic

## 1. Introduction

Aripiprazole is a novel antipsychotic with a unique mech anism of action that differs from currently available antipsychotics (Petrie et al., 1998; Kane et al., 2002). Preclinical studies have provided evidence that aripiprazole acts as a dopamine–serotonin system stabilizer, with potent partial agonist activity at dopamine $D_2$ receptors (Burris et al., 2002) and serotonin 5-$HT_{1A}$ receptors (Jordan et al., 2002), and antagonist activity at 5-$HT_{2A}$ receptors (unpublished data). Aripiprazole exhibits functional antagonist properties in animal models of dopaminergic hyperactivity (e.g. inhibition of apomorphine-induced stereotypy) and functional agonist activities in an animal model of dopaminergic hypoactivity (blockade of increased dopamine synthesis in reserpine-treated mice and rats) (Kikuchi et al., 1995). Aripiprazole induces catalepsy in mice and rats at doses higher than those at which it blocks apomorphine-induced stereotypy (Kikuchi et al., 1995). Clinical studies

* Corresponding author. Present address: Research Institute of Pharmacological and Therapeutical Development, Otsuka Pharmaceutical Co. Ltd., 463-10 Kagasuno, Kawauchi, Tokushima 771-0192, Japan. Tel.: +81-88-665-2126; fax: +81-88-665-6974.
*E-mail address:* s_nakai@research.otsuka.co.jp (S. Nakai).
[1] Present address: Research Institute of Pharmacological and Therapeutical Development.
[2] Present address: Tokushima Research Institute.
[3] Present address: Otsuka Maryland Research Institute.
[4] Present address: Second Institute of New Drug Discovery.
[5] Present address: Palatin Technologies, 4-C Cedar Brook Drive, Cedar Brook Corporate Center, Cranbury, NJ 08512, USA.
[6] Present address: Human Resources Department, Otsuka Pharmaceutical Co. Ltd.
[7] Present address: Gene Discovery, Psychiatric Genomics, Inc., 19 Firstfield Road, Gaithersburg, MD 20878, USA.
[8] Present address: Therapeutic Application Development Group, Otsuka Pharmaceutical Co. Ltd.

0014-2999/03/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0014-2999(03)01857-0

have shown that aripiprazole-treated subjects exhibit extrapyramidal symptoms comparable to subjects receiving placebo, while it possesses antipsychotic efficacy superior to placebo and equivalent to haloperidol (Kane et al., 2002). Based on these data, it is postulated that the decreased catalepsy and extrapyramidal symptoms observed with aripiprazole are due to its partial agonist activity at dopamine $D_2$ receptors.

Several well-characterized systems for evaluating the dopamine $D_2$ receptor agonist or antagonist properties of a drug are based on the degree to which the drug induces catalepsy or alters dopamine metabolism in mesotelencephalic dopamine neurons. The induction of catalepsy in rodents is a well-established animal model for the prediction of extrapyramidal symptoms in humans and is mediated via the nigrostriatal dopamine system (Arnt et al., 1997). Increased dopamine metabolism in the striatum is associated with increased liability for extrapyramidal symptoms whereas in the limbic region it is associated with antipsychotic activity. Dopamine $D_2$ receptor antagonists induce catalepsy (Andersen and Kilpatrick, 1996; Barnes et al., 1990), and increase dopamine metabolism in striatal and limbic brain areas (Boyar and Altar, 1987; Wood and Altar, 1988; Arnt and Skarsfeldt, 1998; Essig and Kilpatrick, 1991). Conversely, potent and full dopamine $D_2$ receptor agonists do not induce catalepsy and suppress brain dopamine metabolism (Altar et al., 1987; Robertson et al., 1993).

Induction of catalepsy and changes in dopamine metabolism in striatal and limbic neurons have been used to evaluate the long-term effects of antipsychotic agents. For example, acute administration of typical antipsychotics such as haloperidol induces catalepsy through a blockade of postsynaptic striatal dopamine $D_2$ receptors, and continued treatment with haloperidol attenuates the cataleptic response (Asper et al., 1973; Campbell and Baldessarini, 1981; Ezrin-Waters and Seeman, 1977). Furthermore, the increase (Karolewicz et al., 1996) and decrease (Altar et al., 1988) in dopamine metabolism produced by acute administration of dopamine $D_2$ receptor antagonists and agonists, respectively, is attenuated with chronic treatment.

The present study investigated whether repeated administration of aripiprazole at doses which acutely induce catalepsy in mice produces a change in cataleptic response over time, as compared with responses elicited by haloperidol or risperidone. In addition, the effects of repeated administration of aripiprazole, haloperidol, and risperidone over time on dopamine metabolism in the striatum and olfactory tubercle were evaluated.

## 2. Materials and methods

### 2.1. Animals

Study animals were male ICR-strain mice (Japan CLEA) aged 4–5 weeks and weighing 25.7–34.6 g. The mice were housed at a temperature of 23 ± 2 °C, a relative humidity of 60% ± 10%, and 12 h light/dark cycle per day (7:00–19:00). Food and water were available ad libitum. The care and handling of the animals were in accordance with "The Guidelines for Animal Experimentation in Otsuka Pharmaceutical; October 1, 1994".

### 2.2. Drugs

Aripiprazole (Otsuka Pharmaceutical), haloperidol, and risperidone (Research Biochemicals) were used. All drugs were suspended in 5% gum arabic-saline and were prepared

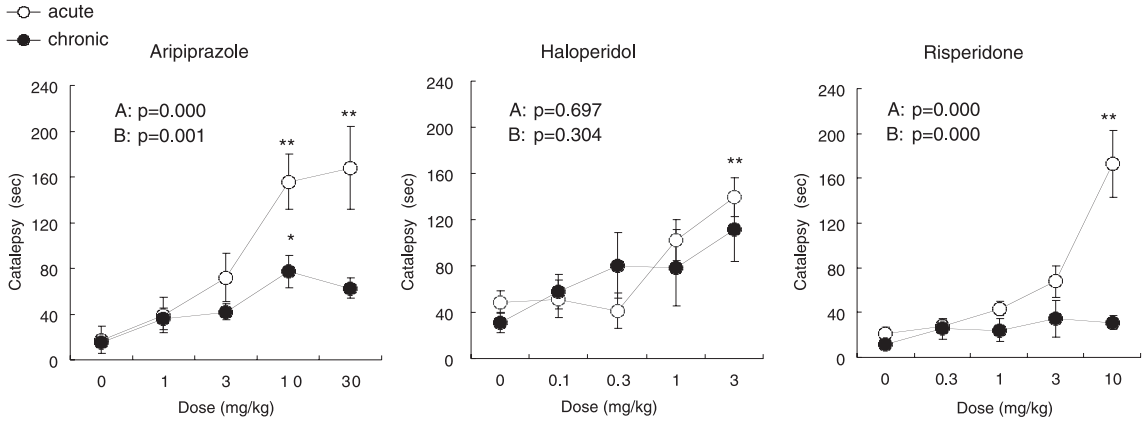


Fig. 1. The effect of acute or chronic administration of aripiprazole, haloperidol, and risperidone on the induction of catalepsy in mice. Data are expressed as means ± S.E.M. [$n=8$ except for aripiprazole 0 group in chronic treatment ($n=7$)]. The duration of catalepsy represents the maximum response in all observation times from 2 to 10 h after final drug administration (aripiprazole: 6 and 10 h after the acute and chronic dose, haloperidol: 10 h after either acute or chronic dose, risperidone: 6 h after either acute or chronic dose). Statistical differences between acute and chronic treatment groups were evaluated by ANOVA on split-plot design and are shown as $P$ values (A: main effect, B: interaction). *$P<0.05$, **$P<0.01$: significant difference versus corresponding vehicle group by two-tailed Dunnett's test.

to a volume of 10 ml/kg. Aripiprazole (1, 3, 10, 30 mg/kg), haloperidol (0.1, 0.3, 1, 3 mg/kg), and risperidone (0.3, 1, 3, 10 mg/kg) or vehicle were administered orally to mice in a single dose (acute treatment) or once daily for 21 successive days (chronic treatment).

### 2.3. Experimental schedule

Mice (eight per treatment group) were tested for catalepsy on the first and 21st day of chronic drug administration. For the biochemical assays, the animals were sacrificed after a single dose, or on the 22nd day of chronic drug administration at the same post-dose interval when the peak catalepsy response occurred on the prior day.

### 2.4. Catalepsy

Duration of catalepsy (Kikuchi et al., 1995) was measured as the time required for each mouse to remove both forepaws from their placement on a 7 cm high platform (cut off time: 300 s). Measurement points were 2, 4, 6, 8, and 10 h after the administration of each drug. Data evaluations were performed for each drug dose at those times which produced the maximum duration of catalepsy. All assessments and drug administrations were performed by a blind investigator.

### 2.5. Monoamine measurements

Monoamine contents in the brain were measured as previously reported (Kikuchi et al., 1995) with minor

Table 1
Effects of acute or chronic administration of aripiprazole, haloperidol, and risperidone on dopamine and its metabolites in the striatum

| | Dopamine | | Dihydroxyphenylacetic acid | | Homovanillic acid | |
|---|---|---|---|---|---|---|
| | nmol/g tissue (*n*) | % | nmol/g tissue (*n*) | % | nmol/g tissue (*n*) | % |
| *Acute* | | | | | | |
| Aripiprazole (mg/kg p.o.) | | | | | | |
| 0 | 42.7 ± 5.9 (8) | 100 | 2.1 ± 0.19 (8) | 100 | 3.4 ± 0.31 (8) | 100 |
| 1 | 49.5 ± 3.8 (8) | 116 | 3.0 ± 0.24 (8)[a] | 148 | 4.3 ± 0.33 (8) | 127 |
| 3 | 44.1 ± 3.2 (8) | 103 | 3.2 ± 0.19 (8)[b] | 156 | 4.3 ± 0.25 (7) | 127 |
| 10 | 38.6 ± 3.4 (8) | 91 | 2.4 ± 0.19 (8) | 115 | 3.3 ± 0.26 (8) | 96 |
| 30 | 41.9 ± 6.7 (7) | 98 | 2.9 ± 0.38 (8) | 142 | 4.0 ± 0.44 (8) | 117 |
| Haloperidol (mg/kg p.o.) | | | | | | |
| 0 | 41.1 ± 4.7 (8) | 100 | 2.2 ± 0.20 (8) | 100 | 3.0 ± 0.29 (8) | 100 |
| 0.1 | 40.8 ± 6.0 (8) | 99 | 2.7 ± 0.32 (8) | 125 | 4.1 ± 0.51 (7) | 136 |
| 0.3 | 38.2 ± 3.7 (8) | 93 | 3.2 ± 0.36 (8) | 149 | 4.5 ± 0.54 (8) | 148 |
| 1 | 26.2 ± 1.8 (7) | 64 | 6.6 ± 0.27 (8)[b] | 306 | 7.4 ± 0.47 (6)[b] | 242 |
| 3 | 23.4 ± 2.4 (8)[a] | 57 | 4.0 ± 0.40 (8)[b] | 185 | 4.4 ± 0.32 (6) | 143 |
| Risperidone (mg/kg p.o.) | | | | | | |
| 0 | 28.6 ± 2.7 (8) | 100 | 1.7 ± 0.14 (8) | 100 | 2.5 ± 0.22 (8) | 100 |
| 0.3 | 25.0 ± 4.1 (8) | 87 | 6.2 ± 0.94 (8)[b] | 371 | 7.4 ± 1.64 (5)[b] | 294 |
| 1 | 23.4 ± 4.0 (8) | 82 | 5.5 ± 0.98 (8)[b] | 331 | 7.3 ± 1.30 (7)[b] | 290 |
| 3 | 20.5 ± 1.1 (8) | 72 | 4.7 ± 0.22 (8)[a] | 279 | 6.5 ± 0.31 (8)[b] | 255 |
| 10 | 17.6 ± 2.2 (8)[a] | 61 | 4.2 ± 0.57 (8)[a] | 250 | 5.5 ± 0.62 (8)[a] | 216 |
| *Chronic* | | | | | | |
| Aripiprazole (mg/kg p.o.) | | | | | | |
| 0 | 33.0 ± 3.2 (7) | 100 | 2.1 ± 0.21 (7) | 100 | 3.2 ± 0.33 (7) | 100 |
| 1 | 29.2 ± 3.1 (8) | 89 | 1.7 ± 0.20 (8) | 83 | 3.1 ± 0.28 (8) | 97 |
| 3 | 27.2 ± 2.9 (8) | 82 | 1.8 ± 0.16 (8) | 85 | 3.2 ± 0.24 (8) | 100 |
| 10 | 24.6 ± 1.9 (8) | 75 | 1.9 ± 0.23 (8) | 94 | 3.5 ± 0.29 (8) | 109 |
| 30 | 24.5 ± 1.9 (8) | 74 | 1.7 ± 0.11 (8) | 82 | 2.8 ± 0.19 (8) | 88 |
| Haloperidol (mg/kg p.o.) | | | | | | |
| 0 | 45.3 ± 5.0 (8) | 100 | 1.9 ± 0.21 (8) | 100 | 3.0 ± 0.30 (8) | 100 |
| 0.1 | 39.5 ± 6.0 (8) | 87 | 2.0 ± 0.27 (8) | 108 | 3.4 ± 0.46 (8) | 112 |
| 0.3 | 33.3 ± 4.0 (8) | 74 | 2.1 ± 0.32 (8) | 113 | 3.5 ± 0.49 (8) | 115 |
| 1 | 35.2 ± 4.6 (8) | 78 | 2.5 ± 0.30 (8) | 136 | 4.2 ± 0.49 (8) | 137 |
| 3 | 33.2 ± 4.2 (8) | 73 | 3.1 ± 0.39 (8)[a] | 168 | 4.7 ± 0.51 (8)[a] | 155 |
| Risperidone (mg/kg p.o.) | | | | | | |
| 0 | 42.3 ± 4.2 (8) | 100 | 1.8 ± 0.15 (8) | 100 | 3.1 ± 0.24 (8) | 100 |
| 0.3 | 30.0 ± 5.1 (8) | 71 | 1.8 ± 0.28 (8) | 101 | 3.1 ± 0.44 (8) | 100 |
| 1 | 31.7 ± 4.9 (8) | 75 | 2.6 ± 0.41 (8) | 148 | 4.0 ± 0.81 (8) | 129 |
| 3 | 31.2 ± 3.7 (8) | 74 | 2.8 ± 0.34 (8) | 159 | 4.7 ± 0.46 (8) | 151 |
| 10 | 30.5 ± 4.3 (8) | 72 | 4.2 ± 0.66 (8)[b] | 235 | 6.2 ± 0.84 (8)[b] | 200 |

Data represent mean ± S.E.M. ($n = 5–8$).

[a] $P < 0.05$: significant difference versus corresponding vehicle group evaluated by two-tailed Dunnett's test.

[b] $P < 0.01$: significant difference versus corresponding vehicle group evaluated by two-tailed Dunnett's test.

modification. Mice were sacrificed by exposure to microwaves for 8 s in a microwave oven (MR-P2000, Hitachi). After cooling the head in crushed ice, the whole brain was removed, and the olfactory tubercle and striatum were dissected. Tissues from both hemispheres were pooled, immediately weighed, and homogenized in 0.5 ml of 0.1 N perchloric acid solution with an ultrasonic disrupter (Model UR-200P, Tomy Seiko) while cooled in ice. The homogenates were centrifuged at 4 °C at 20,000 *g* for 15 min (Himac CR20B3, Hitachi) and the supernatants were harvested and stored frozen at −80 °C.

The amounts of dopamine and its metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were assayed by a high-performance liquid chromatography (HPLC) system equipped with an electrochemical detector (Eicom) using a separation column (Eicompak MAS-ODS, 25 cm × 4.6 mm). The mobile phase was 0.1 M citric acid/0.1 M sodium acetate buffer (pH 2.70–2.85) containing 0.275 or 0.55 mM sodium-l-octane-sulfonate, 0.01 mM 2Na EDTA and 10–14% v/v methanol, and the flow rate was set at 1 ml/min. To detect dopamine and its metabolites, the electrode potential was set at +0.75 V against an Ag/AgCl reference electrode potential. The HPLC peaks corresponding to dopamine, DOPAC, and HVA were measured and quantified automatically using UniPoint system software (Gilson).

The contents of dopamine, HVA acid, and DOPAC per wet weight of tissue were calculated (nmol/g tissue). The dopamine metabolite to dopamine ratio was calculated to evaluate HVA and DOPAC turnover relative to dopamine, using the

Table 2
Effects of acute or chronic administration of aripiprazole, haloperidol, and risperidone on dopamine and its metabolites in the olfactory tubercle

| | Dopamine | | Dihydroxyphenylacetic acid | | Homovanillic acid | |
|---|---|---|---|---|---|---|
| | nmol/g tissue (*n*) | % | nmol/g tissue (*n*) | % | nmol/g tissue (*n*) | % |
| *Acute* | | | | | | |
| Aripiprazole (mg/kg p.o.) | | | | | | |
| 0 | 17.1 ± 2.7 (7) | 100 | 1.6 ± 0.18 (7) | 100 | 2.5 ± 0.32 (8) | 100 |
| 1 | 16.7 ± 1.4 (8) | 97 | 2.4 ± 0.15 (8)[a] | 153 | 3.4 ± 0.27 (7) | 135 |
| 3 | 12.5 ± 0.77 (8) | 73 | 2.4 ± 0.19 (8)[a] | 151 | 3.3 ± 0.22 (8) | 131 |
| 10 | 15.4 ± 1.5 (8) | 90 | 2.6 ± 0.23 (8)[b] | 164 | 3.6 ± 0.35 (6)[a] | 143 |
| 30 | 13.9 ± 1.3 (8) | 81 | 2.5 ± 0.16 (8)[b] | 158 | 3.4 ± 0.18 (8) | 135 |
| Haloperidol (mg/kg p.o.) | | | | | | |
| 0 | 18.4 ± 1.3 (8) | 100 | 1.5 ± 0.09 (8) | 100 | 1.9 ± 0.15 (8) | 100 |
| 0.1 | 17.7 ± 1.1 (8) | 96 | 1.7 ± 0.13 (8) | 118 | 2.4 ± 0.10 (8) | 126 |
| 0.3 | 17.0 ± 1.7 (8) | 92 | 2.1 ± 0.24 (8) | 143 | 2.7 ± 0.26 (8) | 140 |
| 1 | 14.5 ± 1.0 (8) | 79 | 4.5 ± 0.25 (8)[b] | 302 | 5.0 ± 0.31 (8)[b] | 257 |
| 3 | 17.0 ± 1.1 (8) | 92 | 3.5 ± 0.27 (8)[b] | 239 | 4.2 ± 0.41 (8)[b] | 219 |
| Risperidone (mg/kg p.o.) | | | | | | |
| 0 | 16.1 ± 0.75 (7) | 100 | 1.6 ± 0.22 (8) | 100 | 2.2 ± 0.37 (8) | 100 |
| 0.3 | 14.7 ± 0.80 (8) | 92 | 3.9 ± 0.21 (8)[b] | 247 | 5.1 ± 0.41 (8)[b] | 232 |
| 1 | 15.7 ± 0.70 (8) | 98 | 3.7 ± 0.27 (8)[b] | 233 | 4.6 ± 0.48 (8)[b] | 209 |
| 3 | 14.2 ± 1.0 (8) | 88 | 3.4 ± 0.12 (8)[b] | 218 | 4.6 ± 0.28 (8)[b] | 207 |
| 10 | 12.4 ± 0.66 (8)[a] | 77 | 3.6 ± 0.23 (8)[b] | 226 | 4.5 ± 0.31 (8)[b] | 204 |
| *Chronic* | | | | | | |
| Aripiprazole (mg/kg p.o.) | | | | | | |
| 0 | 21.6 ± 2.3 (7) | 100 | 1.4 ± 0.24 (7) | 100 | 2.2 ± 0.36 (7) | 100 |
| 1 | 21.9 ± 1.5 (8) | 101 | 1.6 ± 0.09 (8) | 112 | 2.1 ± 0.31 (8) | 94 |
| 3 | 23.1 ± 1.1 (8) | 107 | 1.7 ± 0.10 (8) | 123 | 3.0 ± 0.10 (8) | 136 |
| 10 | 22.1 ± 1.6 (8) | 102 | 1.7 ± 0.09 (8) | 123 | 2.9 ± 0.17 (8) | 130 |
| 30 | 20.3 ± 0.74 (8) | 94 | 1.4 ± 0.07 (8) | 101 | 2.2 ± 0.08 (8) | 100 |
| Haloperidol (mg/kg p.o.) | | | | | | |
| 0 | 23.9 ± 4.5 (8) | 100 | 1.6 ± 0.11 (8) | 100 | 2.3 ± 0.11 (8) | 100 |
| 0.1 | 21.9 ± 1.6 (8) | 91 | 2.1 ± 0.18 (8) | 135 | 3.0 ± 0.26 (8) | 128 |
| 0.3 | 16.9 ± 0.80 (8) | 71 | 1.8 ± 0.15 (8) | 117 | 2.6 ± 0.18 (8) | 112 |
| 1 | 18.6 ± 1.5 (8) | 78 | 2.2 ± 0.19 (8)[a] | 142 | 3.4 ± 0.28 (8)[b] | 143 |
| 3 | 17.7 ± 1.4 (8) | 74 | 2.6 ± 0.21 (8)[b] | 167 | 3.8 ± 0.21 (8)[b] | 161 |
| Risperidone (mg/kg p.o.) | | | | | | |
| 0 | 20.5 ± 1.4 (7) | 100 | 1.7 ± 0.13 (7) | 100 | 2.3 ± 0.24 (7) | 100 |
| 0.3 | 20.0 ± 1.5 (8) | 98 | 2.1 ± 0.15 (8) | 126 | 2.9 ± 0.19 (8) | 126 |
| 1 | 20.4 ± 1.0 (8) | 99 | 2.7 ± 0.13 (8)[b] | 158 | 3.9 ± 0.21 (8)[b] | 166 |
| 3 | 21.0 ± 0.88 (8) | 102 | 2.9 ± 0.18 (8)[b] | 170 | 4.2 ± 0.27 (8)[b] | 179 |
| 10 | 19.1 ± 0.74 (8) | 93 | 3.8 ± 0.25 (8)[b] | 224 | 4.9 ± 0.26 (8)[b] | 212 |

Data represent mean ± S.E.M. ($n = 6–8$).

[a] $P < 0.05$: significant difference versus corresponding vehicle group evaluated by two-tailed Dunnett's test.

[b] $P < 0.01$: significant difference versus corresponding vehicle group evaluated by two-tailed Dunnett's test.

following formula: dopamine metabolite ratio (%)=(DOPAC or HVA nmol/g tissue)/(dopamine nmol/g tissue) × 100.

### 2.6. Statistics

The significance of differences between acute and chronic treatment for each drug in terms of cataleptic response was evaluated by analysis of variance (ANOVA) on a split plot design. Differences between acute and chronic treatment in terms of dopamine, DOPAC, and HVA levels, and dopamine metabolite/dopamine ratios were evaluated by two-way ANOVA. The significance of differences between vehicle and each dose of test drug was evaluated by a two-tailed Dunnett's test. A $P$ value of less than 5% was adopted as statistically significant. All statistical analyses were carried out using the SAS system for Windows, version 6.12.

## 3. Results

### 3.1. Catalepsy

A maximal duration of catalepsy was observed at 6 h after acute treatment with aripiprazole (day 1) and 10 h after the last chronic dose of aripiprazole (day 21; data not shown). A maximal duration of catalepsy was found 10 h after acute or chronic treatment with haloperidol, and at 6 h after acute or chronic treatment with risperidone (data not shown). The dose–response relationship for the duration of catalepsy at the peak time for each acutely or chronically administered drug is shown in Fig. 1. Acute treatment with aripiprazole and risperidone increased the duration of catalepsy at the higher doses (aripiprazole: 10 and 30 mg/kg, p.o., risperidone: 10 mg/kg, p.o.). These increases were attenuated by chronic treatment with each drug (aripiprazole, main effect: $P=0.0001$, interaction: $P=0.0014$; risperidone, main effect: $P=0.0001$, interaction: $P=0.0001$, ANOVA on a split-plot design). In contrast, acute haloperidol increased the duration of catalepsy at a dose of 3 mg/kg, p.o., but this increase was not attenuated by chronic administration (main effect: $P=0.6976$, interaction: $P=0.3043$, ANOVA on a split-plot design).

### 3.2. Dopamine metabolism

#### 3.2.1. Dopamine and metabolite contents

The effect of acute and chronic drug treatments on dopamine, DOPAC, and HVA in the striatum and olfactory tubercle is shown in Tables 1 and 2.

*3.2.1.1. Acute treatment.* In the striatum (Table 1, upper half), aripiprazole did not alter concentrations of dopamine or either metabolite, except at doses of 1 and 3 mg/kg which produced small increases in DOPAC. The highest doses of haloperidol (3 mg/kg) and risperidone (10 mg/kg) significantly decreased dopamine content. Substantial increases in DOPAC occurred with 1 and 3 mg/kg doses of haloperidol, and 0.3–10 mg/kg doses of risperidone. Increases in HVA occurred with a 1 mg/kg dose of haloperidol and 0.3–10 mg/kg doses of risperidone. In the olfactory tubercle (Table 2, upper half), only the highest dose of risperidone decreased dopamine content. Aripiprazole produced modest increases in DOPAC at all doses and did not change HVA except at 10 mg/kg. In contrast, DOPAC and HVA were elevated by greater degrees following haloperidol (1 and 3

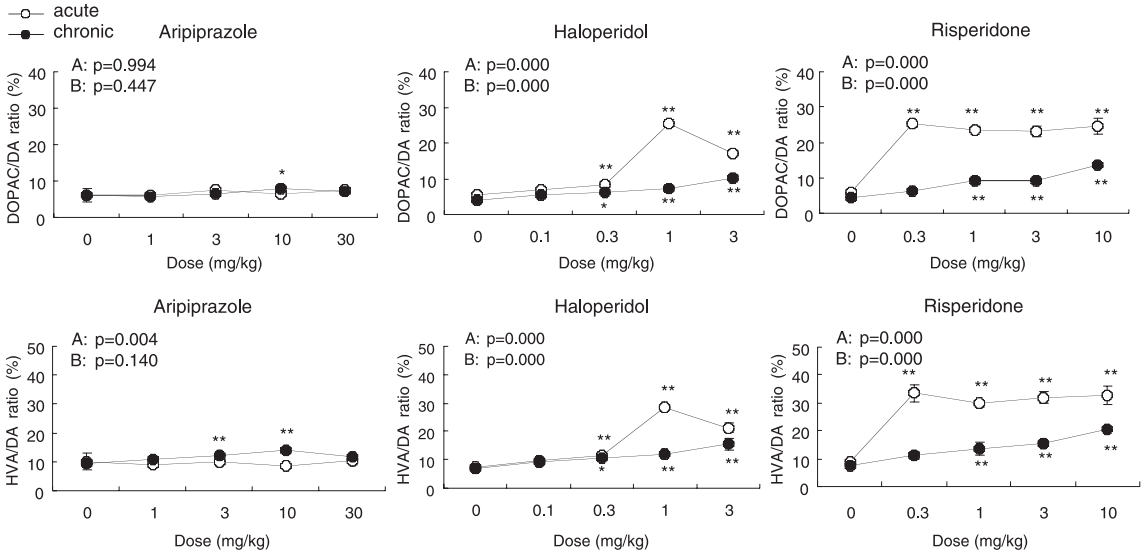


Fig. 2. Effects of acute or chronic administration of aripiprazole, haloperidol, and risperidone on dopamine metabolite ratios in the striatum. Data represent mean ± S.E.M. ($n=5–8$). Statistical differences between acute and chronic treatment groups by two-way ANOVA are shown as $P$ values (A: main effect, B: interaction). *$P<0.05$, **$P<0.01$: significant difference between vehicle and each drug treatment groups by two-tailed Dunnett's test.

mg/kg) and by all doses of risperidone which produced consistently significant increases in both metabolites.

*3.2.1.2. Chronic treatment.* Chronic aripiprazole did not increase striatal or olfactory tubercle dopamine, DOPAC, or HVA as compared with the vehicle group (Tables 1 and 2, bottom half). Chronic haloperidol and risperidone treatments produced non-significant and smaller decreases in dopamine than obtained with acute treatment. Similarly, the increases in DOPAC or HVA contents were smaller than with acute treatment, and were observed at higher doses of haloperidol or risperidone.

*3.2.2. Comparison between acute and chronic treatment in metabolite to dopamine ratios*

In the striatum (Fig. 2), neither acute nor chronic aripiprazole increased either metabolite/dopamine ratio, except for small increases in the DOPAC/dopamine (10 mg/kg) and HVA/dopamine (3 and 10 mg/kg) ratios following chronic treatment. In contrast, the HVA/dopamine or DOPAC/dopamine metabolite ratios following acute haloperidol and risperidone treatment increased at several doses (haloperidol: 0.3, 1, and 3 mg/kg, p.o.; risperidone: 0.3–10 mg/kg) compared to the corresponding vehicle treated group. These increases were attenuated by the chronic administration of either drug (both haloperidol and risperidone, main effect: $P=0.0001$, interaction: $P=0.0001$, two-way ANOVA).

In the olfactory tubercle (Fig. 3), acute treatment with aripiprazole elevated both dopamine metabolite/dopamine ratios more than in the striatum. Both ratios following haloperidol and risperidone exhibited a very similar pattern to the results obtained in the striatum. Highly significant interactions and main effects were obtained by two-way ANOVA for DOPAC/dopamine (main effect: $P=0.0001$, interaction: $P=0.0001$ for haloperidol and risperidone) and HVA/dopamine (main effect: $P=0.0001$, $P=0.0001$, interaction: $P=0.0001$, $P=0.0011$ for haloperidol and risperidone respectively). Especially significant were the increases in the DOPAC/dopamine ratio following acute aripiprazole treatment (3, 10, and 30 mg/kg), yet DOPAC/dopamine was not elevated following chronic aripiprazole treatment (main effect: $P=0.0001$, interaction: $P=0.0007$, two-way ANOVA). The HVA/dopamine ratio tended to be reduced overall by chronic treatment (main effect: $P=0.0001$, interaction: $P=0.5289$, two-way ANOVA), but neither acute nor chronic aripiprazole altered individual HVA/dopamine ratios as compared with the vehicle group.

## 4. Discussion

The results of the present studies reveal that, in contrast to the typical antipsychotic haloperidol or the atypical antipsychotic risperidone, the antipsychotic aripiprazole produces relatively modest effects on striatal or limbic dopamine metabolism, even at the high doses required to elicit catalepsy. Whereas the increase in dopamine metabolism following acute haloperidol or risperidone was lessened with chronic administration, chronic administration of aripiprazole continued to produce little perturbation of the dopamine pathway. Chronic administration of aripiprazole or risperidone attenuated the cataleptic response compared with acute treatment, whereas the duration of catalepsy following haloperidol was not reduced with chronic treatment. Thus, aripiprazole can be distinguished from risperidone and haloperidol by its modest alteration of striatal and limbic dopamine metabolism, and by its lack of catalepsy with chronic administration.

A different action of aripiprazole at dopamine $D_2$ receptors is a likely mechanism to explain how it differs from

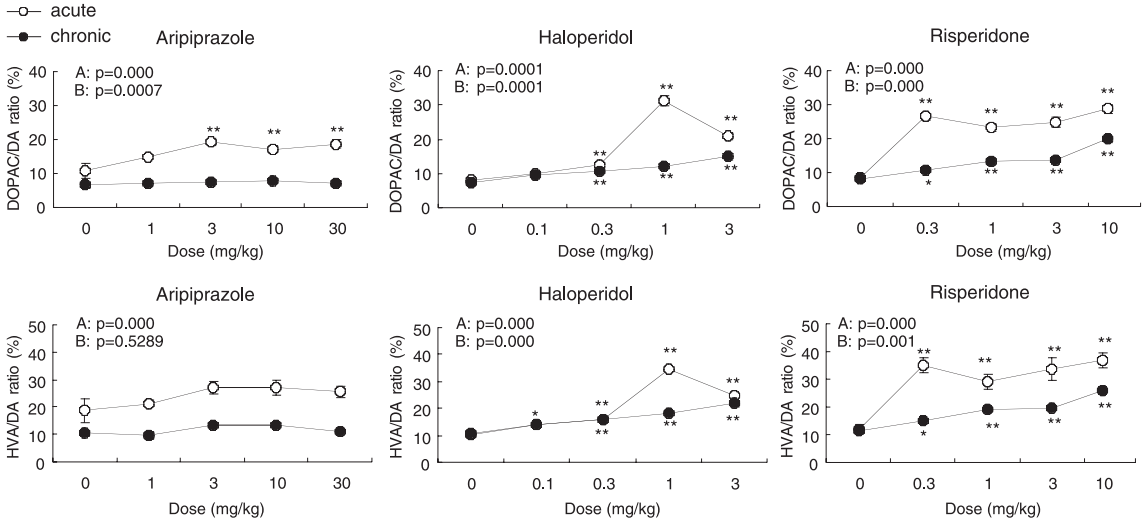


Fig. 3. Effects of aripiprazole, haloperidol, and risperidone on dopamine metabolite ratios in the olfactory tubercle. Data represent mean ± S.E.M. ($n=6–8$). Statistical difference between acute and chronic treatment groups by two-way ANOVA are shown as $P$ values (A: main effect, B: interaction). *$P<0.05$, **$P<0.01$: significant difference between vehicle and each drug treatment groups by two-tailed Dunnett's test.

risperidone and haloperidol in elevating dopamine metabolism and inducing catalepsy. It is generally accepted that catalepsy reflects the decrease in dopamine signaling at postsynaptic striatal dopamine $D_2$ receptors (Stanberg, 1980), while dopamine metabolite levels reflect activity at dopamine $D_2$ autoreceptors (Chesselet, 1984; Nowak et al., 1990). Presynaptic dopamine $D_2$ autoreceptor blockade elevates dopamine metabolism and release (Van Rossum, 1967; Boyar and Altar, 1987; Wood and Altar, 1988), whereas dopamine $D_2$ agonists suppress dopamine metabolism and release (Altar et al., 1987). In addition, acute treatment with haloperidol and risperidone markedly elevated DOPAC/dopamine and HVA/dopamine ratios in the striatum and olfactory tubercle. These elevations were reduced after 22 days of repeated treatment with either drug, particularly in the striatum for DOPAC and HVA. These findings are consistent with prior evidence that acute treatment with dopamine $D_2$ antagonists elevates dopamine metabolism, and that this elevation is reduced following chronic administration (Boyar and Altar, 1987; Patterson and Schenk, 1991; Essig and Kilpatrick, 1991; Karolewicz et al., 1996; Stathis et al., 1996). Aripiprazole, however, produced few changes in HVA, DOPAC, or either metabolite/dopamine ratio in the striatum after acute or chronic treatment, even at doses which induced prominent catalepsy. The diminished effects on catalepsy or dopamine metabolism following chronic treatment with aripiprazole are not due to lack of in vivo efficacy, however. The potent inhibitory effect of aripiprazole on reserpine-induced increases in tyrosine hydroxylase activity in the mouse forebrain is largely preserved with daily oral administration for 3 weeks (unpublished observations). In addition, Inoue et al. (1998) revealed that [$^3$H]spiperone binding and $D_{2L}$ and $D_{2S}$ mRNA in rat pituitary were decreased after repeated aripiprazole treatment for 21 days, which suggested that the partial agonist activity of this drug might be sustained after chronic treatment. Therefore, our results reveal a different mode of action of aripiprazole on dopamine $D_2$-like receptors in the striatum from that of dopamine $D_2$ antagonists such as haloperidol or risperidone, which increase dopamine metabolites, and unlike dopamine $D_2$ agonists such as apomorphine, which lower these metabolites.

The present findings are also consistent with the results from in vivo microdialysis studies conducted by Semba et al. (1995), in which the effects of single doses of aripiprazole on extracellular dopamine and its metabolites resembled the effects seen here. Extracellular dopamine in the striatum was decreased, but only slightly, after aripiprazole administration at the higher doses of 10 and 40 mg/kg. DOPAC and HVA were increased at low doses of 2.5 and 10 mg/kg but returned to control levels at the 40 mg/kg dose. The use of in vivo microdialysis has repeatedly shown that typical antipsychotics such as haloperidol increase extracellular dopamine and its metabolites in the rat striatum (Imperato and Di Chiara, 1985; Moghaddam and Bunney, 1990; Timmerman et al., 1990; Zetterström et al., 1984, 1986). Conversely, dopamine receptor agonists such as apomorphine, quinpirole, (+)3-PPP, and B-HT 920 decrease both extracellular dopamine and its metabolites in the rat striatum (Zetterström et al., 1984; Imperato et al., 1988; Timmerman et al., 1990; Robertson et al., 1993). The few differences observed with aripiprazole between the present findings and those of Semba et al. (1995) could be due to the different time intervals used between administration and measurement or differences between extracellular and whole tissue measures.

The present findings are also consistent with the few and relatively small effects on dopamine release evoked by aripiprazole from rat striatal slices. Unlike aripiprazole, the dopamine $D_2$ antagonist (−)-sulpiride increases, and the dopamine $D_2$ agonist quinpirole decreases dopamine release (Yamada et al., 1997). The ability of aripiprazole to antagonize both dopamine agonist- and antagonist-induced changes in evoked dopamine release (Yamada et al., 1997), and its actions in the present study, are consistent with the potent binding of aripiprazole to the dopamine $D_2$ receptor, and its relatively low agonist activity at this site (Kikuchi et al., 1995; Burris et al., 2002). In vivo, this action at presynaptic dopamine $D_2$ autoreceptors suppresses dopamine biosynthesis when synthesis has been elevated by dopamine depletion, whereas an antagonist action predominates at postsynaptic dopamine $D_2$ receptors when dopaminergic tone is high and few spare receptors are thought to exist (Kikuchi et al., 1995). These findings are consistent with a dopamine $D_2$ partial agonist and a dopamine system stabilizing effect of aripiprazole. In contrast, conventional antipsychotic drugs like haloperidol and atypical antipsychotics like risperidone are antagonists at both pre- and postsynaptic receptor sites.

Interestingly, acute aripiprazole treatment elevated the DOPAC/dopamine ratio in the olfactory tubercle, as did haloperidol and risperidone, but to a lesser degree. These data suggest that a more subtle, antagonistic effect of aripiprazole on postsynaptic dopamine $D_2$ receptors emerges in a limbic area, the olfactory tubercle, compared with the neostriatum. This observation is consistent with the postulated limbic site of antipsychotic action and striatal site for the induction of catalepsy (Borison and Diamond, 1983) and with the higher turnover of dopamine in limbic versus striatal areas (Wood and Altar, 1988), where the antagonist property of aripiprazole may predominate because of higher dopamine tone. Alternatively, the potent but partial agonist action of aripiprazole at 5-$HT_{1A}$ receptors (Jordan et al., 2002), such as those on serotonergic neurons or their targets (Andersen and Kilpatrick, 1996), or its antagonist action at 5-$HT_{2A}$ receptors (unpublished observations) may produce this phenomenon (Altar et al., 1986; Meltzer, 1999). Aripiprazole has moderate affinities at rat 5-$HT_{1A}$ and 5-$HT_{2A}$ receptors, with $K_i$ values of 17.3 and 18.6 nM, respectively. However, these affinities are more than 10 times lower than for the rat dopamine $D_2$ receptor. The relative contribution

of 5-$HT_{1A}$, 5-$HT_{2A}$, and dopamine $D_2$ receptors to the in vivo effects on dopamine metabolism and catalepsy remains to be evaluated.

The low catalepsy liability of aripiprazole may be explained by its property as a partial dopamine $D_2$ receptor agonist. By definition, partial dopamine $D_2$ receptor agonists transmit relatively small postsynaptic signals. Higher doses of aripiprazole may induce catalepsy because the occupancy of more striatal dopamine $D_2$ receptors decreases overall $D_2$ signaling, and diminishes transmission sufficiently to induce a cataleptic response (Svensson et al., 1993). Such effects would occur independently of dopamine release from presynaptic terminals, which is essentially unchanged by aripiprazole (Semba et al., 1995; Yamada et al., 1997). Relatively normal dopamine release would also be expected to maintain normal signaling at dopamine $D_1$, $D_4$, and $D_5$ receptors, sites at which aripiprazole has low affinity (Lawler et al., 1999) but where the affinity for dopamine itself is high. This selective action at dopamine $D_2$ receptors may lessen the propensity for catalepsy, as cooperative interactions between dopamine $D_1$- and $D_2$-like receptors would tend to preserve overall dopamine tone (Parashos et al., 1989).

Chronic treatment with risperidone and aripiprazole reduced the duration of catalepsy seen with acute treatment. In contrast, the catalepsy seen following acute haloperidol treatment was not reduced with chronic treatment. The lack of tolerance to haloperidol-induced catalepsy that we saw here has been reported by some researchers (György et al., 1969; Møller-Nielsen et al., 1974) but not by others (Asper et al., 1973; Campbell and Baldessarini, 1981; Ezrin-Waters and Seeman, 1977). A review by Barnes et al. (1990) concluded that dose, drug administration schedule, and behavioral test conditions all influence the evolution of catalepsy during chronic haloperidol treatment. When the above-mentioned studies are compared to clarify the difference between treatments that did and did not produce tolerance to haloperidol catalepsy, neither the dose of drug, administration schedule, or catalepsy test conditions appear to explain differences in the degree of tolerance. However, while most studies were performed with rats, György et al. (1969) conducted experiments with mice and, as in the present study, did not find a tolerance to haloperidol-induced catalepsy. Thus, the use of mice may explain why the cataleptic response to haloperidol was not reduced after chronic treatment in the present study. These results suggest that aripiprazole and risperidone may be expected to have a diminished liability to induce extrapyramidal symptoms compared with haloperidol in a long-term treatment. These predictions have been borne out in clinical studies (Petrie et al., 1998; Kane et al., 2002; Owens, 1994; Stock et al., 2002).

The potent blockade of serotonin 5-$HT_{2A}$ receptors, as exemplified by risperidone (Leysen et al., 1994), might also contribute to these effects. Lucas et al. (1997) reported that ritanserin, a 5-$HT_{2A/C}$ receptor antagonist, reverses haloperidol-induced catalepsy in rats independently of effects on striatal dopamine release. They also showed that such 5-HT agents appear to act postsynaptically to the dopamine nigrostriatal system. These observations are in agreement with the possibility that 5-$HT_{2A}$ receptor blockade may raise the threshold for extrapyramidal symptoms (Altar et al., 1986), possibly via effects on cholinergic or GABAergic (GABA = γ-aminobutyric acid) systems (Kapur and Remington, 1996). Indeed, 5-$HT_{1A}$ receptor agonism and 5-$HT_{2A}$ receptor antagonism can each diminish catalepsy caused by typical antipsychotics such as haloperidol (Lucas et al., 1997; Prinssen et al., 1999; Andersen and Kilpatrick, 1996; Millan, 2000). Aripiprazole also has antagonist activity at 5-$HT_{2A}$ receptors which may contribute to its low risk for extrapyramidal symptoms observed in acute and long-term clinical studies.

In conclusion, unlike typical antipsychotics such as haloperidol, aripiprazole may have a weaker propensity to induce extrapyramidal symptoms or alterations in striatal and limbic dopamine metabolism, particularly after long-term treatment. These effects may be due to the potent binding but partial agonist activity of aripiprazole at dopamine $D_2$ receptors, which is very different from the dopamine $D_2$ receptor antagonist activity common to haloperidol, risperidone, and all other current antipsychotics. The extent to which activity at other receptors, such as serotonin 5-$HT_{1A}$ or 5-$HT_{2A}$ receptors, is involved in these actions remains to be determined.

## References


Altar, C.A., Wasley, A.M., Neale, R.F., Stone, G.A., 1986. Typical and atypical antipsychotic occupancy of $D_2$ and $S_2$ receptors: an autoradiographic analysis in rat brain. Brain Res. Bull. 16, 517–525.

Altar, C.A., Boyar, W.C., Wood, P.L., 1987. Dopamine autoreceptor agonist including CGS 15855A decreases the in vivo release and metabolism of dopamine in mouse brain. Eur. J. Pharmacol. 134, 303–311.

Altar, C.A., Beall, P., Berner, B., Carlsson, M., Boyar, W.C., 1988. Dopamine release and metabolism after chronic delivery of selective or non-selective dopamine autoreceptor agonists. Mol. Pharmacol. 33, 690–695.

Andersen, H.L., Kilpatrick, I.C., 1996. Prevention by (+/−)-8-hydroxy-2-(di-*n*-propylamino) tertralin of both catalepsy and the rises in rat striatal dopamine metabolism caused by haloperidol. Br. J. Pharmacol. 118, 421–427.

Arnt, J., Skarsfeldt, T., 1998. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. Neuropsychopharmacology 18, 63–101.

Arnt, J., Skarsfeldt, T., Hyttel, J., 1997. Differentiation of classical and novel antipsychotics using animal models. Int. Clin. Psychopharmacol. 12 (Suppl. 1), S9–S17.

Asper, H., Baggiolini, M., Burki, H., Lauener, H., Ruch, W., Stille, G., 1973. Tolerance phenomena with neuroleptics: catalepsy, apomorphine stereotypies and striatal dopamine metabolism in the rat after single and repeated administration of loxapine and haloperidol. Eur. J. Pharmacol. 22, 287–294.

Barnes, D.E., Robinson, B., Csernansky, J.G., Bellows, E.P., 1990. Sensitization versus tolerance to haloperidol-induced catalepsy: multiple determinants. Pharmacol. Biochem. Behav. 36, 883–887.

Borison, R.L., Diamond, B.I., 1983. Regional selectivity of neuroleptic drugs: an argument for site specificity. Brain Res. Bull. 11, 215–218.

Boyar, W.C., Altar, C.A., 1987. Differential modulation of in vivo dopamine release and metabolism by $D_1$ but not $D_2$ receptor agonist and antagonists. J. Neurochem. 48, 824–831.

Burris, K.D., Molski, T.F., Ryan, E., Xu, C., Tottori, K., Kikuchi, T., Yocca, F.D., Molinoff, P.B., 2002. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist of human dopamine $D_2$ receptors. J. Pharmacol. Exp. Ther. 302, 381–389.

Campbell, A., Baldessarini, R.J., 1981. Tolerance to behavioral effects of haloperidol. Life Sci. 29, 1341–1346.

Chesselet, M.F., 1984. Presynaptic regulation of neurotransmitter release in brain: facts and hypothesis. Neuroscience 12, 347–375.

Essig, C.E., Kilpatrick, C.I., 1991. Influence of acute and chronic haloperidol treatment on dopamine metabolism in the rat caudate-putamen, prefrontal cortex and amygdala. Psychopharmacology 104, 194–200.

Ezrin-Waters, C., Seeman, P., 1977. Tolerance to haloperidol catalepsy. Eur. J. Pharmacol. 41, 321–327.

György, L., Pfeifer, K.A., Hajtman, B., 1969. Modification of certain central nervous effects of haloperidol during long-term treatment in mouse and rat. Psychopharmacologia 16, 223–233.

Imperato, A., Di Chiara, G., 1985. Dopamine release and metabolism in awake rats after systemic neuroleptics as studied by trans-striatal dialysis. J. Neurosci. 5, 297–306.

Imperato, A., Tanda, G., Erau, R., Di Chiara, G., 1988. Pharmacological profile of dopamine receptor agonists as studied by brain dialysis rats. J. Pharmacol. Exp. Ther. 245, 257–264.

Inoue, A., Seto, M., Sugita, S., Hide, I., Hirose, T., Koga, N., Kikuchi, T., Nakata, Y., 1998. Differential effect on $D_2$ dopamine receptor and prolactin gene expression by haloperidol and aripiprazole in the rat pituitary. Mol. Brain Res. 55, 285–292.

Jordan, S., Koprivica, V., Chen, R., Tottori, K., Kikuchi, T., Altar, C.A., 2002. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-$HT_{1A}$ receptor. Eur. J. Pharmacol. 441, 137–140.

Kane, J.M., Carson, W.H., Saha, A.R., McQuade, R.D., Ingenito, G.C., Zimbroff, D.L., Ali, M.W., 2002. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J. Clin. Psychiatry 63, 763–771.

Kapur, S., Remington, G., 1996. Serotonin-dopamine interaction and its relevance to schizophrenia. Am. J. Psychiatry 153, 466–476.

Karolewicz, B., Antkiewicz-Michaluk, L., Michaluk, J., Vetulani, J., 1996. Different effects of chronic administration of haloperidol and pimozide on dopamine metabolism in the rat brain. Eur. J. Pharmacol. 313, 181–186.

Kikuchi, T., Tottori, K., Uwahodo, Y., Hirose, T., Miwa, T., Oshiro, Y., Morita, S., 1995. 7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1H)-quinolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic $D_2$ receptor antagonistic activity. J. Pharmacol. Exp. Ther. 274, 329–336.

Lawler, C.P., Prioleau, C., Lewis, M.M., Mak, C., Jiang, D., Schetz, J.A., Gonzalez, A.M., Sibley, D.R., Mailman, R.B., 1999. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. Neuropsychopharmacology 20, 612–627.

Leysen, J.E., Janssen, P.M., Megens, A.A., Schotte, A., 1994. Risperidone: a novel antipsychotic with balanced serotonin–dopamine antagonism, receptor occupancy profile, and pharmacologic activity. J. Clin. Psychiatry 55 (Suppl), 5–12.

Lucas, G., De Deurwaerdére, P., Le Moal, M., Spampinato, U., 1997. 8-OH-DPAT, 5-$HT_{1A}$ agonist and ritanserin, a 5-$HT_{2A/C}$ antagonist, reverses haloperidol-induced catalepsy in rats independently of striatal dopamine release. Psychopharmacology 131, 57–63.

Meltzer, H., 1999. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 21, 106S–115S.

Millan, M.J., 2000. Improving the treatment of schizophrenia: focus on serotonin (5HT)1A receptors. J. Pharmacol. Exp. Ther. 295, 853–861.

Moghaddam, B., Bunney, B.S., 1990. Acute effects of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: an in vivo microdialysis study. J. Neurochem. 54, 1755–1760.

Møller-Nielsen, I., Fjalland, B., Pederson, V., Nymark, M., 1974. Pharmacology of neuroleptics upon repeated administration. Psychopharmacologia 34, 95–104.

Nowak, J.Z., Arbilla, S., Dahl, S.G., Langer, S.Z., 1990. Antagonism of presynaptic dopamine receptors by phenothiazine drug metabolites. Life Sci. 46, 443–451.

Owens, D.G., 1994. Extrapyramidal side effects and tolerability of risperidone: a review. J. Clin. Phychiatry 55 (Suppl), 29–35.

Parashos, S.A., Marin, C., Chase, T.N., 1989. Synergy between a selective $D_1$ antagonist and a selective $D_2$ antagonist in the induction of catalepsy. Neurosci. Lett. 105, 169–173.

Patterson, T.A., Schenk, J.O., 1991. Effects of acute and chronic systemic administration of some typical antipsychotic drugs on turnover of dopamine and potassium ion-induced release of dopamine in the striatum of the rat in vivo. Neuropharmacology 9, 943–952.

Petrie, J.L., Saha, A.R., Ali, M.W., 1998. Safety and efficacy profile of aripiprazole, a novel antipsychotic. Presented at the 37th Annual ACNP Meeting.

Prinssen, E.P.M., Kleven, M.S., Koek, W., 1999. Interactions between neuroleptics and 5-$HT_{1A}$ ligands in preclinical behavioral models for antipsychotic and extrapyramidal effects. Psychopharmacology 144, 20–29.

Robertson, G.S., Tham, C., Wilson, C., Jakubovic, A., Fibiger, H.C., 1993. In vivo comparisons of the effects of quinpirole and the putative presynaptic dopaminergic agonists B-HT 920 and SND 919 on striatal dopamine and acetylcholine release. J. Pharm. Exp. Ther. 264, 1344–1351.

Semba, J., Watanabe, A., Kito, S., Toru, M., 1995. Behavioral and neurochemical effects of OPC-14597, a novel antipsychotic drug, on dopaminergic mechanisms in rat brain. Neuropharmacology 34, 785–791.

Stanberg, P.R., 1980. Haloperidol-induced catalepsy is mediated by postsynaptic dopamine receptors. Nature 284, 472–473.

Stathis, P., Antoniou, K., Papadopoulou-Daifotis, Z., Varonos, D., 1996. Risperidone: a novel antipsychotic with many "atypical" properties. Psychopharmacology 127, 181–186.

Stock, E., Marder, S.R., Saha, A.R., Kaplita, S.B., Archibald, D.G., McQuade, R.D., Iwamoto, T., 2002. Safety and tolerability meta-analysis of aripiprazole in schizophrenia. Int. J. Neuropsychopharmacol. 5 (Suppl. 1), S185.

Svensson, K., Eriksson, E., Carlsson, A., 1993. Partial dopamine receptor agonists reverse behavioral, biochemical and neuroendocrine effects of neuroleptics in the rat: potential treatment of extrapyramidal side effects. Neuropharmacology 32, 1037–1045.

Timmerman, W., De Vries, J.B., Westerink, B.H.C., 1990. Effects of D-2 agonists on the release of dopamine: localization of the mechanism of action. Naunuyn-Schmiedeberg's Archs. Pharmacol. 342, 630–634.

Yamada, S., Harano, M., Yokoo, H., Tanaka, M., 1997. Antagonistic effects of OPC-14597, a novel atipsychotic drug, on quinpirole- and (−)-sulpiride-induced changes in evoked dopamine release in rat striatal slices. J. Pharm. Pharmacol. 49, 206–208.

Van Rossum, J.M., 1967. The significance of dopamine receptor blockade for the action of neuroleptic drugs. In: Brill, H. (Ed.), Neuro-Psycho-Pharmacology. Excerpta Medica, Amsterdam, p. 321.

Wood, P.L., Altar, C.A., 1988. Dopamine release in vivo from nigrostriatal, mesolimbic, and neocortical dopamine neurons: utility of 3-methoxytyramine measurements. Pharmacol. Rev. 40, 163–187.

Zetterström, T., Sharp, T., Ungerstedt, U., 1984. Effect of neuroleptic drugs on striatal dopamine release and metabolism in the awake rat studied by intracerebral dialysis. Eur. J. Pharmacol. 106, 27–37.

Zetterström, T., Sharp, T., Ungerstedt, U., 1986. Effect of dopamine D-1 and D-2 receptor selective drugs on dopamine release and metabolism in rat striatum in vivo. Naunyn-Schmiedeberg's Archs Pharmacol. 334, 117–124.