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Involvement of Adenosine A_{2A} Receptors in the Induction of C-Fos Expression by Clozapine and Haloperidol

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Acute administration of the atypical antipsychotic clozapine induced a regional pattern of c-fos expression characterized by an increase in Fos–like-immunoreactivity (FLI) in the prefrontal and prelimbic/infralimbic cortices, nucleus accumbens, and lateral septum and a weak activation of FLI in the striatum. Haloperidol, similarly to clozapine, increased FLI in the nucleus accumbens and lateral septum, but it did not induce FLI in prefrontal and prelimbic/infralimbic cortices. Moreover, haloperidol increased FLI in the striatum. To gain insight into the mechanism by which clozapine and haloperidol induced FLI in these brain structures, we evaluated whether blockade of adenosine A_{2A} receptors could influence these effects. The selective and high-affinity A_{2A} receptor antagonist SCH 58261 (5 mg/kg) completely abolished FLI induced by clozapine (20 mg/kg) in all subdivisions of the nucleus accumbens (rostral pole, shell and core) and striatum, but did not affect the number of Fos-like positive neurons in the prefrontal, prelimbic/infralimbic cortices, and lateral septum. SCH 58261 (5 mg/kg) reduced FLI induced by haloperidol (0.1 mg/kg) in the striatum, lateral septum, and all nucleus accumbens subdivisions. In contrast, FLI induced by 0.5 mg/kg of haloperidol in the shell and core of the nucleus accumbens was not affected by SCH 58261. The results show that adenosine A_{2A} receptors participate in the induction of FLI by clozapine and haloperidol and support the concept that A_{2A} receptors are involved in the mediation of antipsychotic effects.
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KEY WORDS: *Clozapine; Haloperidol; Adenosine A_{2A} receptor; Early-genes; Fos–like-immunoreactivity; Antipsychotic*

The mechanism and the site of drug action have been widely studied through examination of the induction of early-genes in the CNS. The immunohistochemical mapping of the c-fos encoded protein Fos has been used to detect activation of specific brain areas by drugs as antipsychotics, antidepressants, and drugs of abuse. This experimental approach has shown that classic and atypical antipsychotics can be differentiated on the basis of their pattern of Fos–like-immunoreactivity (FLI) distribution (Deutch et al. 1992; Fibiger 1994; MacGibbon et al. 1994; Robertson et al. 1994).

Clozapine, the most used atypical antipsychotic, increased FLI in several mesolimbic areas (prefrontal, prelimbic/infralimbic cortices, nucleus accumbens and lateral septum); whereas, contrary to such typical antipsychotics as haloperidol, clozapine had minimal effect in the striatum (Deutch et al. 1992; Deutch and Duman 1996; MacGibbon et al. 1994; Merchant et al. 1996; Nguyen et al. 1992; Robertson and Fibiger 1992; Robertson et al. 1994).

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The receptor types contributing to the increase in FLI by clozapine are still debated, and contrasting data emerged on the role played by dopamine (DA) D_3-D_4 receptors in this effect; whereas, blockade of D_2 receptors seems to play the major role in FLI induced by haloperidol (Carta and Gerfen 1997; Deutch and Duman 1996; Guo et al. 1995; Merchant et al. 1996; Vahid-Ansari and Robertson 1996).

A_{2A} adenosine receptors are concentrated in richly DA innervated areas (Jarvis and Williams 1989) and negatively influence DA-mediated responses (Ferré et al. 1997; Kafka and Corbett 1996; Morelli et al. 1994; Popoli et al. 1994; Sebastiao and Ribeiro 1996; Vellucci et al. 1993). On the basis of these studies and in consideration of the most recent findings showing a specific involvement of A_{2A} receptors in the modulation of DA-mediated mesolimbic functions, it has been postulated that A_{2A} receptors might play an important role in antipsychotic effects (Barraco et al. 1993; Ferré et al. 1994; Hauber and Koch 1997; Heffner et al. 1989; Kafka and Corbett 1996; Martin et al. 1993; Rimondini et al. 1997). Moreover, stimulation of A_{2A} receptors induced c-fos expression in mesolimbic areas (Pinna et al. 1997); whereas, blockade of A_{2A} receptors counteracted FLI induced by haloperidol in the striatum (Boegman and Vincent 1996).

To study the possible role of A_{2A} receptors in the induction of c-fos expression by antipsychotics in different brain areas, we examined whether A_{2A} receptor blockade by the selective and high-affinity receptor antagonist SCH 58261 (Monopoli et al. 1994; Zocchi et al. 1996) influenced the induction of FLI by clozapine and haloperidol, two reference antipsychotics having atypical and typical profiles, respectively.

METHODS

Experimental Protocol

Male Sprague–Dawley rats (200 to 250 g) were used in all the experiments. Different groups of rats received one of the following treatments: vehicle (saline SC, saline pH 6.0 IP) or 0.5% suspension of methylcellulose IP), clozapine (20 mg/kg IP) dissolved in slightly acidified (pH 6.0) saline, haloperidol HCl (0.1 or 0.5 mg/kg SC) diluted with saline from serenase (Lusofarmaco,

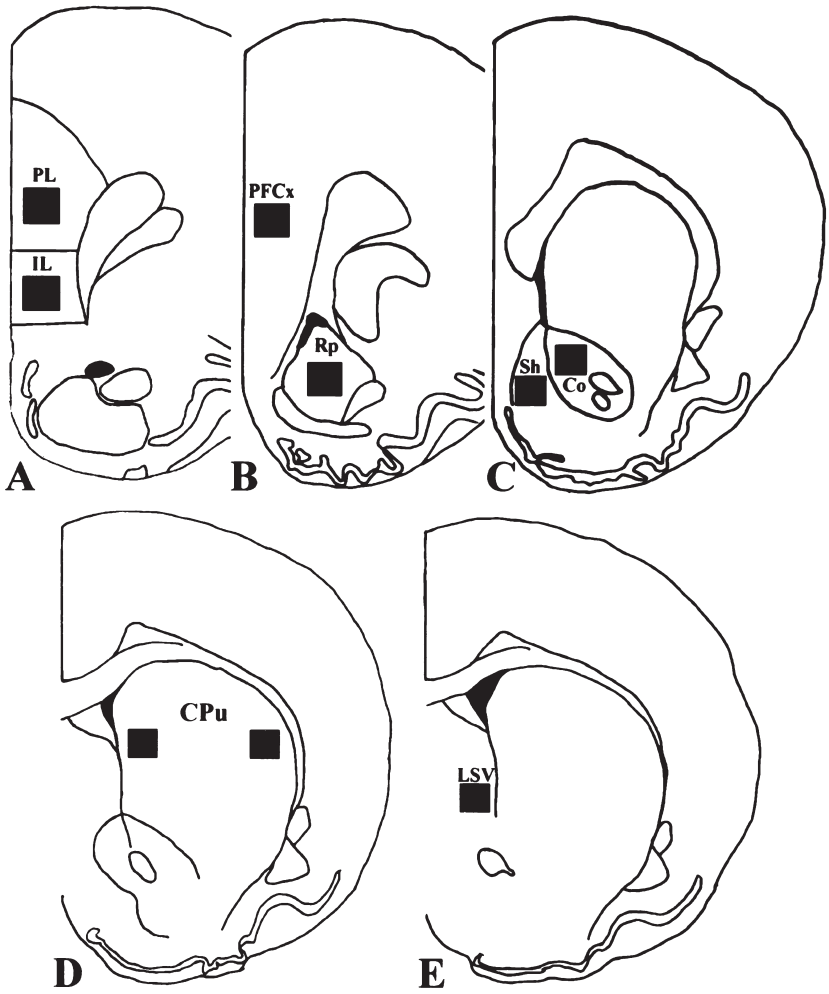

Figure 1. Drawing of representative sections used for Fos-like positive neurons counting. A: prelimbic and infralimbic cortex (PL and IL). B: nucleus accumbens rostral pole (Rp) and prefrontal cortex (PFCx). C: nucleus accumbens shell (Sh) and core (Co). D: dorsomedial and dorsolateral striatum (CPu). E: lateral septum (LSV). Sections were taken from the atlas of Paxinos and Watson (1986).

Italy), SCH 58261 IP suspended in 0.5% methylcellulose. SCH 58261 was injected 40 min before clozapine or haloperidol.

Fos Immunohistochemistry

The different groups of rats were anesthetized with chloral hydrate 120 min after clozapine or haloperidol administration. Rats were then perfused transcardially with saline, followed by 4% paraformaldehyde dissolved in 0.1 m sodium phosphate buffer, pH 7.4, and their brains, postfixed in the same solution, were cut coronally on a vibratome (40 μm) 2 days later. Sections were incubated for 48 h with a Fos primary antibody selected from a conserved region of mouse and human c-fos (OA-11-824, Cambridge Research Biochemical) at a dilution of 1:1400. The reaction was visualized using biotinylated secondary antisera and by standard avidin-biotin horseradish peroxidase technique. Control sections were incubated in the presence of the Fos peptide.

Fos-immunoreactivity was quantified with an image analyzer (IBAS, Zeiss) by counting the number of Fos-like positive nuclei. We considered as Fos-like positive only those neurons showing gray levels ranging between 0 and 110/120 (total range was from 0 to 255). The number of stained cells in each structure was counted in the two brain sides and the values were averaged.

Drugs

Clozapine was kindly donated by Polfa (Starogard, Poland), SCH 58261 by Schering Plough (Milano, Italy), haloperidol (serenase, Lusofarmaco, Italy) was purchased from commercial sources. Drugs were injected in a volume of 0.3 ml IP or 0.1 ml SC/100 g body weight, drugs suspended in methylcellulose were injected in 1 ml/100 g IP.

Statistics

Mean and SEM were calculated. Significance between groups was evaluated by analysis of variance followed by Student–Newman–Keuls test.

RESULTS

Figure 1 shows the levels at which FLI determinations were done. In agreement with previous studies (Merchant et al. 1996; Robertson et al. 1994) clozapine 20 mg/kg IP increased FLI in the prefrontal and prelimbic/infralimbic cortices, nucleus accumbens, and lateral septum (Table 1). A small increase in FLI was observed in the striatum both in the dorsomedial and dorsolateral part (Table 1). Examination of FLI in the different accumbal subdivision showed intense FLI in the rostral pole and shell (Figures 2 and 3), in the core, the absolute number of Fos-like positive neurons was less than that observed in the shell and rostral pole (Table 1).

Table 1. Effect of the A_{2A} Receptor Antagonist SCH 58261 on Clozapine-Induced Fos-Like Immunoreactivity.

	Fos-Like Positive Nuclei (0.5 mm² grid)			
	Vehicle	SCH 58261 (5 mg/kg)	Clozapine (20 mg/kg)	SCH 58261 + Clozapine
PL/IL	12 ± 2	12 ± 2	19 ± 2*	19 ± 2
PFCx	30 ± 11	28 ± 4	56 ± 5*	50 ± 4
l. septum	11 ± 1	18 ± 5	104 ± 10**	94 ± 10
Acb Rp	14 ± 3	10 ± 2	56 ± 6**	16 ± 2##
Acb shell	23 ± 3	16 ± 3	55 ± 5**	27 ± 3##
Acb core	2 ± 1	1 ± 0.4	9 ± 1**	3 ± 1##
mCPu	2 ± 0.5	1 ± 0.1	11 ± 2*	4 ± 1##
lCPu	0.2 ± 0	0 ± 0	8 ± 1**	4 ± 1#

Number ± SEM of Fos-like positive neurons in the prelimbic (PL)/infralimbic (IL) cortex, prefrontal cortex (PFCx), lateral septum (l.septum), nucleus accumbens rostral pole (Acb Rp), shell (Acb shell), core (Acb core), dorsomedial striatum (mCPu) and dorsolateral striatum (lCPu).

The values are the means of 6 to 12 rats. When not receiving the drugs, rats were treated with the vehicle. SCH 58261 and clozapine were injected IP.

Statistically different from saline treated rats, $^{*}p < .05$, $^{**}p < .005$; statistically different from clozapine treated rats, $^{\#}p < .05$, $^{\#\#}p < .005$.

Blockade of adenosine A_{2A} receptors by SCH 58261 (5 mg/kg IP) tended to decrease the basal levels of FLI (Table 1): however, this decrease was never statistically significant. As shown previously (Pinna et al. 1996) higher doses of SCH 58261 (10 mg/kg IP) significantly decreased by themselves the number of Fos-like positive neurons.

SCH 58261 (5 mg/kg IP) completely prevented the increase of FLI by clozapine in the nucleus accumbens rostral pole (Figure 2), shell (Figure 3) and core (Table 1 and Figure 3). A significant decrease in the number of clozapine-induced Fos-like positive neurons by SCH 58261 was also observed in the dorsomedial and dorsolateral striatum (Table 1). In contrast, in the prefrontal, prelimbic/infralimbic cortices, and the lateral septum, SCH 58261 did not modify the induction of FLI by clozapine (Table 1).

Administration of haloperidol (0.1 and 0.5 mg/kg SC) induced FLI in rostral pole (Figure 2), shell, and core of the nucleus accumbens (Table 2), in the lateral septum (Figure 4) and in the dorsomedial and dorsolateral striatum (Table 2). The increase in FLI was dose-dependent only in the lateral septum, whereas in the other brain areas, FLI resulted already maximal after 0.1 mg/kg of haloperidol (Table 2). Blockade of A_{2A} adenosine receptors by 5 mg/kg IP of SCH 58261 counteracted the increase in FLI induced by 0.5 mg/kg of haloperidol in the dorsomedial and dorsolateral striatum, in the rostral pole of the nucleus accumbens (Figure 2) and in the lateral septum (Figure 4), whereas the number of Fos-like

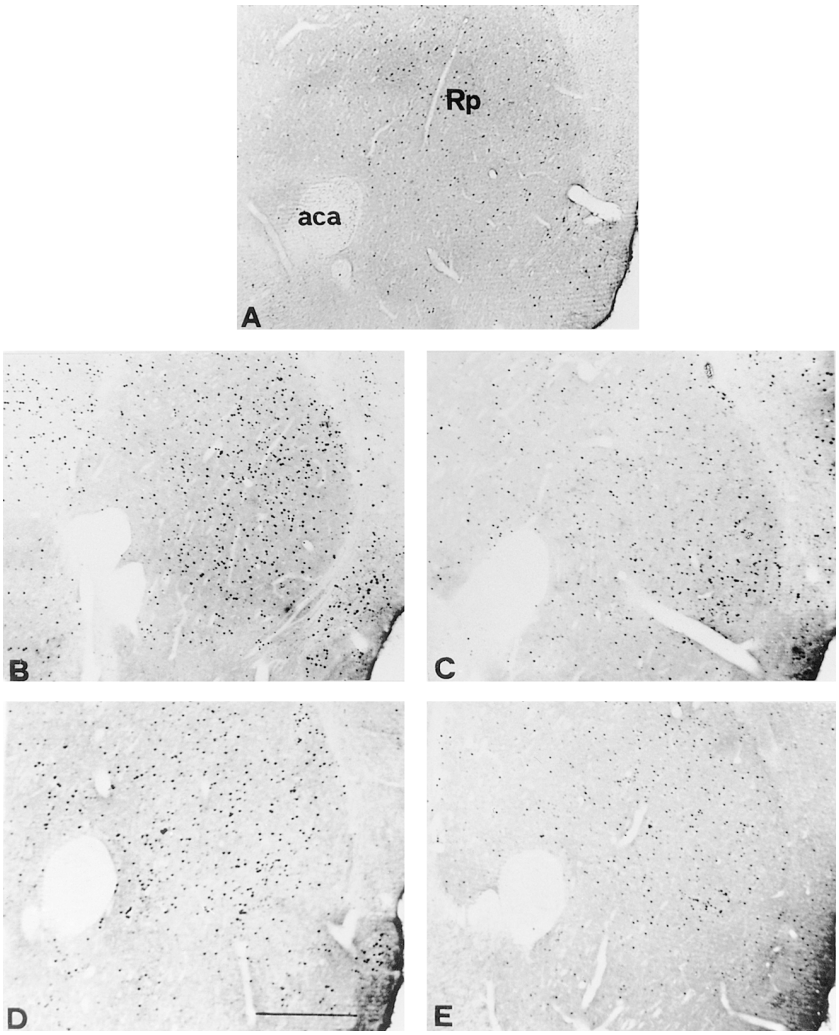

Figure 2. Photomicrographs showing Fos-like positive neurons in the nucleus accumbens rostral pole (Rp) after clozapine and haloperidol. A: saline, B: clozapine (20 mg/kg IP), C: SCH 58261 (5 mg/kg IP) + clozapine (20 mg/kg IP), D: haloperidol (0.5 mg/kg SC), E: SCH 58261 (5 mg/kg IP) + haloperidol (0.5 mg/kg SC). Anterior commissure (aca), Bar = 0.5 mm.

positive nuclei was not affected in the shell and core of the nucleus accumbens (Table 2). At variance, SCH 58261 (5 mg/kg IP) counteracted FLI induced by 0.1 mg/kg of haloperidol also in the shell and core of the nucleus accumbens (Table 2).

As shown by previous studies, the dose of SCH 58261 used in these experiments seems to be fully selective in antagonizing A_{2A} receptors (Monopoli et al. 1994).

DISCUSSION

As previously reported, acute administration of haloperidol and clozapine induced a different pattern of c-fos expression in the rat brain, which is predictive of their ability to induce extrapyramidal side-effects and to be effective on the negative symptoms of schizophrenia (Deutch et al. 1992; Fibiger 1994; MacGibbon et al. 1994; Robertson et al. 1994).

To explain the unique therapeutic profile of clozapine, many hypotheses have been proposed by taking into account the different affinity of clozapine for 5-HT_2, α_1, M_1, and D_4 receptors (Brunello et al. 1995). However, it cannot be excluded that other receptors interacting with those to which clozapine binds may contribute to the therapeutic profile of clozapine.

To evaluate the possibility that adenosine A_{2A} receptors participate to the induction of FLI by clozapine and to explore whether blockade of A_{2A} receptors differentially interacts with c-fos expression induced by typical and atypical neuroleptics, we have studied the ability of SCH 58261, a selective and high affinity antagonist of adenosine A_{2A} receptors (Zocchi et al. 1996), to counteract FLI induced by clozapine and haloperidol.

Equivalent doses of clozapine and haloperidol were selected on the basis of previous dose-response studies (Robertson et al. 1994) and also on the basis of their ability to induce a similar increase of FLI in the nucleus accumbens. In this brain area, in fact, FLI has been shown to be activated by all antipsychotics (Robertson et al. 1994).

SCH 58261 completely antagonized FLI induced by clozapine in the nucleus accumbens rostral pole, shell,

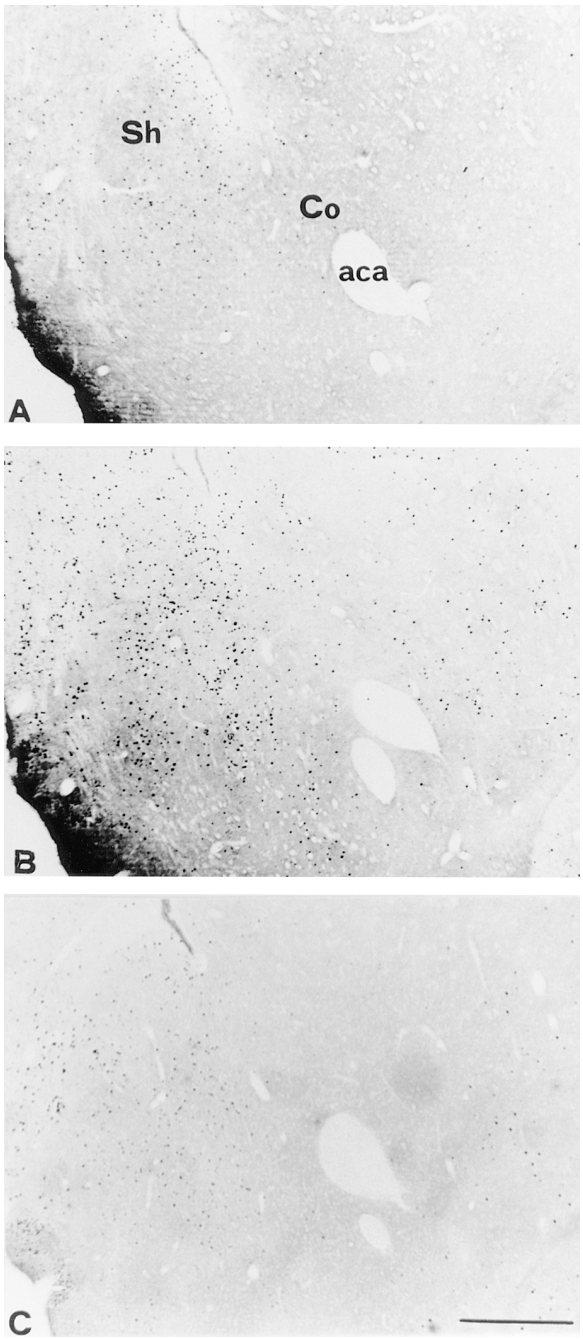

Figure 3. Photomicrographs showing Fos-like positive neurons in the nucleus accumbens shell (Sh) and core (Co) after clozapine. A: saline, B: clozapine (20 mg/kg IP), C: SCH 58261 (5 mg/kg IP) + clozapine (20 mg/kg IP). Anterior commissure (aca). Bar = 0.5 mm.

and core, whereas FLI induced by haloperidol was reduced but not completely antagonized. After 0.5 mg/kg of haloperidol, SCH 58261 affected only the nucleus accumbens rostral pole, whereas after 0.1 mg/kg of haloperidol, SCH 58261 reduced FLI also in the nucleus accumbens shell and core. Therefore, blockade of A_{2A} receptors differently affected FLI induced by clozapine and haloperidol, because the effect on haloperidol was partial and did not bring the levels of FLI to control even when lower doses of the drug were used.

SCH 58261 reduced FLI induced by clozapine and haloperidol also in the striatum, and differently affected FLI in the lateral septum. In this area, only FLI induced by haloperidol was, in fact, counteracted. These results show both qualitative and quantitative differences in the effect of SCH 58261 on clozapine and haloperidol-induced FLI.

As mentioned above, binding studies showed that clozapine is an antagonist at 5-HT_2, α_1, M_1, and D_4 receptors; whereas, haloperidol mainly binds D_2 receptors (Brunello et al. 1995). Therefore, it is unlikely that the mechanism by which SCH 58261 contrasted FLI induced by clozapine and haloperidol is directly related to an antagonism at the A_{2A} receptor level but must involve an indirect interaction.

A_{2A} receptors are co-localized with D_2 receptors on the same neuronal population in such richly dopaminergic innervated areas as the striatum (Fink et al. 1992; Schiffmann and Vanderhaeghen 1993) and nucleus accumbens (Svenningsson et al. 1997). A_{2A} and D_2 receptors also partially co-localize in the lateral septum (Svenningsson et al. 1997). A_{2A} and D_2 receptors interact and influence cAMP formation in an opposite manner (Ferré and Fuxe 1992; Ferré et al. 1997), and, therefore, through this mechanism, the two receptors might influence in an opposite direction the cAMP response element CRE, which promotes the transcription of several early-genes, including c-fos (Morgan and Curran 1991). This way of interaction might be at the basis of the antagonistic effect played by the A_{2A} antagonist on c-fos expression induced by D_2 receptor blockade. It has been suggested that D_2 receptor blockade would remove an inhibitory tone, allowing c-fos expression mediated by A_{2A} receptors (Boegman and Vincent 1996); therefore, in the presence of an A_{2A} receptor antagonist, drugs blocking D_2 receptors would no longer be able to induce FLI. This mechanism might, therefore, explain how SCH 58261 antagonized c-fos expression induced by D_2 receptor antagonists, such as haloperidol, in areas as the striatum, the nucleus accumbens, and the lateral septum, where the D_2 and A_{2A} receptors are totally or partially co-localized.

Although the mechanism of clozapine-induced c-fos expression is still a matter of debate, dopamine D_2 receptors do not seem to participate in this effect (Guo et al. 1995; Vahid-Ansari and Robertson 1996), and therefore, this mechanism, although it explains the antagonism of SCH 58261 on FLI induced by haloperidol, cannot explain the antagonism of SCH 58261 on clozapine-induced FLI. In addition, the inefficacy of SCH 58261 to antagonize FLI induced by clozapine in the lateral septum and the inability of SCH 58261 to totally antagonize FLI induced by haloperidol in the nucleus accumbens, even when lower

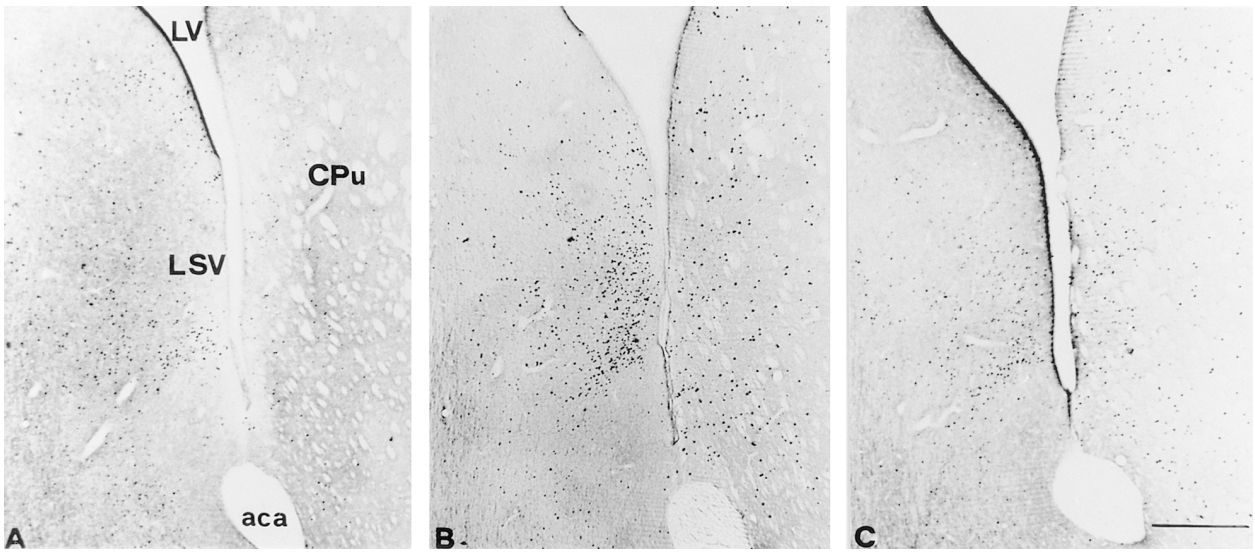

Figure 4. Photomicrographs showing Fos-like positive neurons in the lateral septum (LSV) after haloperidol. A: Saline, B: haloperidol (0.5 mg/kg SC), C: SCH 58261 (5 mg/kg IP) + haloperidol (0.5 mg/kg SC). Lateral ventricle (LV), striatum (CPu) anterior commissure (aca). Bar = 0.5 mm.

doses of the drug are used, support the idea that clozapine and haloperidol induced FLI through a different mechanism. These results, although they do not give direct explanation of the mechanism or the receptor types involved in the interaction between clozapine and SCH 58261, clearly describe differences in the way through which clozapine and haloperidol interact with adenosine A_{2A} receptors.

The results of the present study, in line with previous reports, show that clozapine induces FLI in the prefrontal and prelimbic/infralimbic cortices, whereas haloperidol does not influence FLI in limbic cortex (Deutch and Duman 1996; Merchant et al. 1996). The increase in FLI by clozapine was not counteracted by SCH 58261, indicating that A_{2A} receptors do not play an important role on the effect of clozapine in the limbic cortex, a result probably attributable to the absence of A_{2A} receptors in this area (Svenningsson et al. 1997).

In line with the present results showing an influence of A_{2A} adenosine receptors on the action of antipsychotics, it has been described that chronic haloperidol increased the density of A_{2A} receptors in the striatum (Parson et al. 1995) and that A_{2A} receptor blockade counteracted FLI induced by acute haloperidol in the dorsal striatum (Boegman and Vincent 1996). In addition, we have recently shown that stimulation of A_{2A} receptors induced FLI in

Table 2. Effect of the A_{2A} Receptor Antagonist SCH 58261 on Haloperidol-Induced Fos-Like Immunoreactivity

			Fos-Like Positive Nuclei (0.5 mm² grid)			
		SCH 58261	Haloperidol		SCH 58261 + Haloperidol	
	Vehicle	(5 mg/kg)	(0.1 mg/kg)	(0.5 mg/kg)	(0.1 mg/kg)	(0.5 mg/kg)
PL/IL	6 ± 1	5 ± 1	4 ± 1	5 ± 1	4 ± 1	4 ± 1
PFCx	23 ± 4	18 ± 3	14 ± 2	16 ± 3	14 ± 2	15 ± 2
l.septum	7 ± 2	8 ± 2	13 ± 1*	24 ± 5*	10 ± 0.7$^{\#}$	10 ± 2$^{\#}$
Acb Rp	7 ± 1	5 ± 1	47 ± 4**	49 ± 5**	27 ± 2$^{\#\#}$	36 ± 3$^{\#}$
Acb shell	18 ± 3	12 ± 2	71 ± 3**	64 ± 7**	51 ± 4$^{\#\#}$	53 ± 6
Acb core	1 ± 0.4	1 ± 0.3	17 ± 1**	17 ± 4*	7 ± 1$^{\#\#}$	14 ± 2
mCPu	1 ± 0.1	0 ± 0	22 ± 2**	21 ± 2**	14 ± 1$^{\#\#}$	15 ± 1$^{\#}$
lCPu	0.3 ± 0.1	0 ± 0	30 ± 4**	32 ± 4**	18 ± 2$^{\#}$	18 ± 4$^{\#}$

Number ± SEM of Fos-like positive neurons in the prelimbic (PL)/infralimbic (IL) cortex, prefrontal cortex (PFCx), lateral septum (l.septum), nucleus accumbens rostral pole (Acb Rp), shell (Acb shell), core (Acb core), dorsomedial striatum (mCPu) and dorsolateral striatum (lCPu).

The values are the means of 4 to 12 rats. When not receiving the drugs, rats were treated with the vehicle. SCH 58261 and haloperidol were injected, respectively IP and S.C.

Statistically different from saline treated rats, $^{*}p < .05$, $^{**}p < .005$; statistically different from haloperidol (0.1 or 0.5 mg/kg) treated rats, $^{\#}p < .05$ $^{\#\#}p < .005$.

the same mesolimbic areas where c-fos is induced by administration of antipsychotic drugs (Pinna et al. 1997).

The results of this study, therefore, suggest that antipsychotics besides DA, α_1, and $5HT_2$ receptors might also indirectly affect A_{2A} adenosine receptors, and this mechanism might contribute to their therapeutic effects and their different therapeutic profiles.

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