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The Atypical Neuroleptics Clozapine and Olanzapine Differ Regarding Their Antinociceptive Mechanisms and Potency

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SCHREIBER, S., V. GETSLEV, M. M. BACKER, R. WEIZMAN AND C. G. PICK. *The atypical neuroleptics clozapine and olanzapine differ regarding their antinociceptive mechanisms and potency.* PHARMACOL BIOCHEM BEHAV **64**(1) 75–80, 1999.—Using the mouse tail-flick assay, we evaluated the antinociceptive effect and the interaction with the opioid, adrenergic, and serotonergic systems of the two "atypical" neuroleptic agents clozapine and olanzapine. Clozapine induced a potent antinociceptive effect in a dose-dependent manner with ED_{50} of 8.7 mg/kg. This effect was antagonized by the nonselective opioid antagonist naloxone ($p < 0.05$), implying an opioid mechanism of action involved in clozapine-induced antinociception. Further evaluation demonstrated the involvement of μ_1-, μ_2-, κ_1- opioid receptor subtypes and of α_2-adrenoreceptors in clozapine antinociception but not the serotonin receptors. Olanzapine induced a weak antinociceptive effect. The highest effect found was a 50% antinociception following an injection of 10 mg/kg. As the olanzapine dose increased beyond 10 mg/kg, latencies declined almost back to baseline. Yohimbine (an α_2-adrenoreceptor antagonist) significantly reduced olanzapine's antinociceptive effect almost completely (to 10%; $p < 0.05$), while both naloxone and metergoline (a nonselective 5-HT receptor antagonist) reduced it only partially. These results indicate the possible involvement of the α_2-adrenoreceptors in olanzapine antinociception and to a less extent the involvement of opioid and serotonergic receptors. Although both clozapine and olanzapine are dibenzodiazepines with similar "atypical" antipsychotic properties, it seems that they differ notably not only regarding their hematological side effects, but regarding their interaction with the opioid system as well. © 1999 Elsevier Science Inc.

Antinociceptive effect Atypical neuroleptic Clozapine Olanzapine Mouse tail-flick assay Pain

TRADITIONAL neuroleptics do not have a well-established place in the management of pain. The clinical evidence for the analgesic efficacy of this class of drugs is controversial at best (6). The most extensive study of neuroleptic-induced analgesia examined patients with perioperative pain, and five out of nine phenothiazines studied were found consistently beneficial (5). However, because of prominent side effects (i.e., extrapyramidal side effects, tardive dyskinesia, and elevation of serum prolactine levels), the use of phenothiazines and other traditional neuroleptics for the treatment of pain remains controversial (12).

Research in molecular pharmacology has brought the field of neuroleptics a very long way in recent years. The so-called "atypical" neuroleptics are characterized by a combination of high antipsychotic efficacy, minimal extrapyramidal side effects, and low risk for the development of tardive dyskinesia. The characteristic mechanism of action of the new "atypical" neuroleptics involve their lower affinity for dopamine D_2 receptors compared with that for serotonin 5-HT_{2A} receptors (13,23). The interactions of this group of drugs with muscarinic receptors (1,2,26), histamine H_1 receptors (22), and the α-adrenoreceptors (2) have been extensively investigated. However, the issue of the antinociceptive effects and the possible interaction of the "atypical" neuroleptics with the opioid system have not been addressed yet.

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In a previous study we reported that the "novel" benzisoxazole neuroleptic risperidone has a potent antinociceptive effect in the tail-flick assay. This effect was found to be antagonized by naloxone, indicating that it is at least partially mediated by an opioid mechanism of action. Further evaluation of risperidone with selective opioid antagonists revealed the involvement of μ_1-, μ_2- and κ_1-opioids, and to a lesser extent,δ-opioid mechanisms (20).

In the present study, we evaluated the antinociceptive effects, using the tail-flick analgesic assay and the interaction with specific opioid receptors of the two structurally similar dibenzodiazepine ("atypical" neuroleptics) clozapine and olanzapine.

METHOD

Animals and Surgery:

Male ICR mice from Tel-Aviv University colony (Tel-Aviv, Israel), weight 25–35 g, were used. The mice were maintained on a 12 L:12 D cycle, with Purina rodent chow and water available ad lib. Animals were housed in groups of 20 under standard conditions, and were divided into groups of five 1 day before testing. Mice were used only once. Intrathecal (IT) injections were made under light ethrane anesthesia, using a Hamilton 10-ml syringe fitted to a 30-G needle with V_1 tubing. The IT injections were introduced by lumbar puncture (8). The volume for IT injections was 1 ml/mouse.

Agent

Several agents were generously donated as follows: clozapine by Sandoz Pharma AG (Basel, Schweiz), olanzapine by Eli Lilly and Co. (Indianapolis, IN), morphine by TEVA (Jerusalem, Israel), naloxonazine by Dr. G. W. Pasternak from Memorial Sloan-Kettering Cancer Center, New York, NY, U50,488-H {trans-3,4-dchloro-*N*-methyl-N-[2- (1-pyrrolindinyl)-cyclohexyl]-benzeneacetamide} by Upjohn Pharmaceutics (West Sussex, UK), (D-Pen2,D-Pen5)enkephalin (DPDPE), β-funaltrexamine (β-FNA), Naltrindole HCl, nalorphine HCl, naloxone HCl, and nor-binaltorphamine (Nor-BNI) were obtained from the Research Technology Branch of NIDA. Ethrane (Enflurane) was purchased from Abbott (Campoverde, Italy). Yohimbine HCl, Metergoline (N-CBZ-[8b)-1,6dimethylergolin-8 yl] methylamine), serotonin [5-hydrotryptamine creatinine sulphate (5-HT)], and clonidine HCl were purchased from Sigma (Israel). All other compounds were purchased from commercial sources. Clozapine was dispensed into saline, and a small amount of Tween 80 was added. Yohimbine HCl was dissolved in distilled water. All other drugs were dissolved in saline.

Antinociception Assessment

Antinociception was determined by utilizing the radiant heat tail-flick technique (4), using the tail-flick apparatus (Ugo, Basile). The latency to withdraw the tail from a focused light stimulus was measured electronically, using a photocell. Baseline latencies (2.0–3.0 s) were determined before experimental treatments for all animals as the means of two trials. Posttreatment latencies were determined as indicated for each experiment, and a maximal latency of 7 s was used to minimize tissue damage. Antinociceptive effect was defined quantally as a doubling or more of baseline values for each mouse. For each point (dose), at least 10 different mice were tested, and their scores were summarized, showing the percentage of animals that became analgesic. Each mouse had been tested once. Posttreatment latencies were determined after 30 min for opioids, which were subcutaneously (SC) administrated, and after 60 min for clozapine and olanzapine, which were intraperitoneally administrated (IP). Posttreatment latencies for intrathecal administration (IT) were determined 15 min postinjections. The indicated doses were chosen according to the literature and our previous experimental experience.

Procedure

The study was conducted in three experiments.

Experiment 1. In the first stage of the study, groups of mice (n = 10) were injected intraperitonealy with different doses of clozapine (from 1 to 30 mg/kg) or olanzapine (from 2.5 to 50 mg/kg) to determine the effect of the drug in eliciting analgesia.

Experiment 2. The sensitivity of clozapine or of olanzapine to specific opioid, adrenoreceptor, and serotonin receptor antagonists was examined. First, we determined the effect of the nonselective opioid antagonist naloxone (10 mg /kg SC) on both drugs. Naloxone inhibited only the clozapine antinociceptive effect, and did not affect olanzapine analgesia. Due to these results, we continued examining the effect of the specific opioid antagonists only with clozapine. Mice (10 each group) administrated with clozapine were treated with one of the following drugs: β-FNA (μ_1 and μ_2 antagonist; 40 mg/kg SC) or naloxonazine (μ_1 antagonist; 35 mg/kg SC), 24 h before clozapine challenge. Naltrindole (δ antagonist) 20 mg/kg SC, nor-BNI (κ antagonist) 10 mg/kg SC, or saline were injected at the same time with clozapine. For comparison, β-FNA and naloxonazine were tested against morphine, nor-BNI against U50,488H, and naltrindole against DPDPE, in separate groups of mice.

Subsequently, we examined the effects of metergoline (a serotonergic antagonist; 2 mg/kg IP) and yohimbine (an adrenergic antagonist; 4 mg/kg IP). The drugs were injected 30 min after clozapine or olanzapine administration.

Experiment 3. The sensitivity of clozapine or olanzapine to specific opioids, adrenergic and serotonin receptor agonists was examined.

The action of clozapine and olanzapine on selective opioid receptor subtype agonists was tested as follows: (a) groups of mice (n = 10) were given increasing doses of morphine, a μ-receptor agonist with an inactive dose of clozapine or olanzapine (0.5 or 0.05 mg/kg IP, respectively); (b) DPDPE, a selective δ-receptor agonist was injected intrathecally (IT), alone or with an inactive dose of clozapine or olanzapine; (c) U50,488H, a selective κ_1-receptor agonist, was injected SC alone or with an inactive dose of clozapine or olanzapine; (d) nalorphine a κ_3-receptor agonist, was injected SC alone or with an inactive dose of clozapine or olanzapine; (e) clonidine, an adrenoreceptor agonist, was injected SC alone or with an inactive dose of clozapine or olanzapine; (f) serotonin, a serotonergic receptor agonist, was injected SC alone or with an inactive dose of clozapine or olanzapine. The inactive dose of each drug was determined empirically.

Statistics

Dose–response curves were analyzed with the SPSS computer program. This program maximizes the log-likelihood function to fit a parallel set of Gaussian normal sigmoid curves to the dose–response data. Single-dose antagonist studies were analyzed with Fisher's exact test.

RESULTS

Clozapine and Olanzapine Analgesia

The evaluation of the clozapine or olanzapine in the tail-flick analgesic assay in mice was performed. Groups of mice ($n = 10$) were injected with various doses of clozapine or olanzapine. Clozapine induced a potent analgesic effect following an IP injection in a dose-dependent manner with ED_{50} 8.7 mg/kg (5.6; 13.4; 95% CL; Fig. 1). Olanzapine induced only a weak antinociceptive effect, the highest effect found was a 50% antinociception following an injection of 10 mg/kg. As the olanzapine dose increased beyond 10 mg/kg, latencies declined almost back to baseline (Fig. 1).

Sensitivity of Clozapine and Olanzapine Antinociceptive Effect to Selective Antagonists

Clozapine. High doses of clozapine (20 mg/kg), which produced 80% antinociception following IP, were injected with the nonspecific opioid antagonist naloxone (10 mg/kg). This analgesic effect was antagonized almost completely to 10% ($p < 0.05$; Fig. 2). The fact that the clozapine's analgesic effect was easily blocked by naloxone implies that there is an opioid mechanism of action involved in clozapine-induced antinociception.

Potential involvement of μ-, δ-, and κ_1-opioid receptor subtypes in clozapine antinociceptive effect was studied, using selective opioid antagonists (Fig. 2). We found that β-FNA (40 mg/kg; selective μ_1 and μ_2-opioid receptor antagonist) and naloxonazine (35 mg/kg; selective μ_1-antagonist), reversed clozapine antinociception at the same dose that they antagonized morphine's antinociceptive effect ($p < 0.005$), suggesting a role for μ_1- and μ_2-receptors in clozapine analgesia. Nor-BNI (10 mg/kg; SC selective κ_1-opioid receptor antagonist) reversed the clozapine-induced antinociceptive effect at the same dose that it antagonized the κ_1-antinociception, mediated by U50,488H ($p < 0.005$). The dose of naltrindole that reversed the DPDPE antinociceptive effect did not effect the clozapine-induced antinociceptive effect. The activity of each of the antagonists was confirmed with its prototypic agonists (data not shown). None of the antagonists mediated antinociception by themselves, nor did they change the baseline latencies of the pretreated animals.

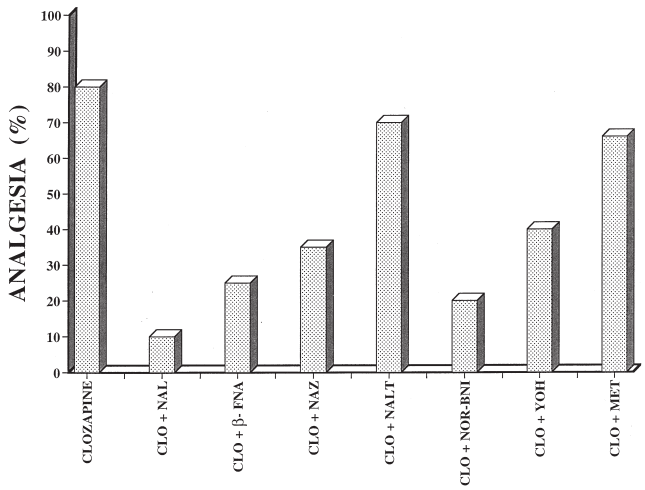

FIG. 2. Effects of naloxone (Nax; 10 mg/kg), β-FNA (40 mg/kg), nalaxonazine (NAZ; 35 mg/kg), naltrindole (NALT; 10 mg/kg), NOR- BNI (10 mg/kg), yohimbine (YOH; 4 mg/kg), and metergoline (MET; 2 mg/kg) on the antinociceptive activity of clozapine (CLO). Groups of mice ($n \geq 10$) were treated with clozapine alone (20 mg/kg) or were challenged in addition with one of the additional drugs. naloxone, β-FNA, naloxonazine, and Nor-BNI, and yohimbine significantly antagonized clozapine analgesia ($p < 0.05$). naltrindole (ICV). Neither naltrindole nor metergoline significantly antagonized clozapine analgesia.

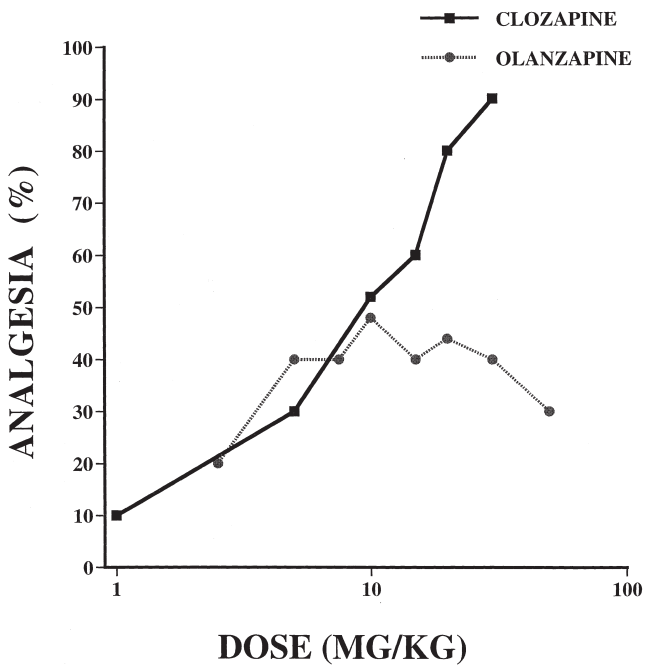

FIG. 1. The analgesic effect of clozapine and olanzapine in the tail-flick analgesic assay. Groups of mice ($n = 10$) were injected with various doses of clozapine or olanzapine. Posttreatment latencies were determined after 60 min. Clozapine induced a potent analgesic following an IP injection in a dose-dependent manner with ED_{50} 8.7 mg/kg. Olanzapine's highest effect found was a 50% antinociception following an injection of 10 mg/kg.

The clozapine-induced antinociceptive effect was significantly reduced by yohimbine (4 mg/kg IP; $p < 0.005$), an α_2-adrenergic antagonist. Only after injection of metergoline—a nonselective 5-HT receptor antagonist—was no significant reduction found (2 mg/kg IP). These experiments demonstrated the involvement of μ_1-, μ_2-, κ_1-opioid receptor, and of α_2-adrenoreceptor in clozapine antinociception.

Olanzapine. The antinociceptive effect of olanzapine (10 mg/kg), which produced a 50% antinociception following IP injection, was only slightly (and nonsignificantly) antagonized by the nonspecific opioid antagonist naloxone (10 mg/ kg). These results provide no evidence of opioid mechanism of the olanzapine-inducing antinociceptive effect. Yohimbine, an α_2-adrenergic antagonist, significantly reduced the antinociceptive effect induced by olanzapine almost completely to 10% ($p < 0.05$; Fig. 3). Metergoline, a nonselective 5-HT receptor antagonist, did not significantly reduce the olanzapine antinociceptive effect. These results indicated the involvement of the α_2-adrenoreceptor in clozapine antinociception and, a lesser extent, the involvement of the opioid and serotonergic systems.

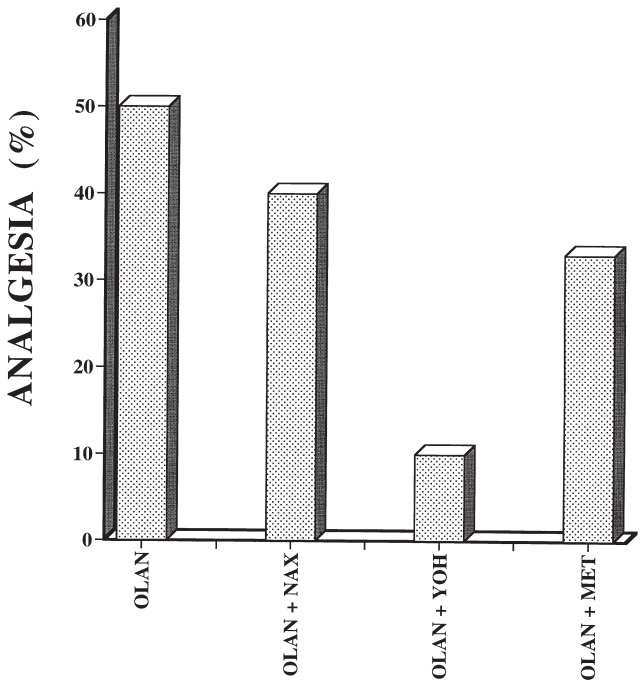

FIG. 3. Effects of naloxone (Nax; 10 mg/kg), yohimbine (YOH; 4 mg/kg), and metergoline (MET; 2 mg/kg) on the antinociceptive activity of olanzapine (OLAN). Groups of mice ($n \geq 10$) were treated with olanzapine alone (10 mg/kg), or were challenged in addition with one of the additional drugs. Only yohimbine, not naloxone or metergoline, significantly antagonized olanzapine analgesia ($p < 0.05$).

Sensitivity of Clozapine and Olanzapine Antinociceptive Effect to Selective Agonists

Clozapine. Groups of mice ($n = 10$) were injected with an inactive dose of clozapine (0.5 mg/kg; IP) in addition to specific opioid, adrenergic, and serotonin receptor agonists. An increasing dose of morphine, U50,488H, or nalorphine was injected 30 min after the clozapine injection. DPDPE was injected 45 min following the clozapine administration. No significant differences were found between the dose-dependent curves with and without clozapine, except for the dose-dependent curve of nalorphine, which was shifted approximately 3.5-fold to the left (Table 1). Although not statistically significant, the addition of morphine to clozapine more than doubled its effect. Administration of an inactive dose of clozapine with an increasing dose of serotonin did not produce a significant difference in the ED_{50} of serotonin (Table 2). When an inactive dose of clozapine (0. 5 mg/kg; IP) was given with an increasing dose of clonidine (a selective α_2 agonist) we found a 15-fold shift to the left of the dose-dependent curve of clonidine. The ED_{50} of clonidine alone was 0.5 mg/kg (0.3; 1.3) and with clozapine 0.04 mg/kg (0.02; 0.08; $p < 0.05$; Table 2).

Olanzapine. Inactive doses (0.05 mg/kg) of olanzapine were given with increasing doses of specific opioid, adrenergic, and serotonin receptor agonists. No significant differences in dose–response curves of morphine (μ-subtype), DPDPE (δ-subtype), and U50,488H (κ_1-subtype) were found when injected with an inactive dose of olanzapine. When administered with an inactive dose with nalorphine (κ_3-subtype), olanzapine shifted fivefold the ED_{50} of nalorphine to the left. The ED_{50} of nalorphine alone was 36.2 mg/kg (16.5; 128.1) and with olanzapine 7.3 mg/kg (4.1; 12.1 ; $p < 0.05$). Given with clonidine (α_2- subtype agonist) olanzapine shifted the curve almost 18-fold to the left the ED_{50} of clonidine. This was in comparison with the ED_{50} of clonidine alone. The ED_{50} of clonidine alone was 0.53 mg/kg (0.31; 1.31) and with olanzapine 0.03 mg/kg (0.01; 0.06; $p < 0.05$). No significant difference in the dose-dependent curve of serotonin was found when it was administrated with an inactive dose of olanzapine.

TABLE 1

OPIOID RECEPTOR SELECTIVE AGONISTS' ED_{50} ALONE OR WITH CLOZAPINE OR WITH OLANZAPINE

Opioid Receptor Subtypes	Alone	With Clozapine	With Olanzapine
Morphine (μ subytpe)	5.9 mg/kg (3.5: 15.1) ($n = 10$)	2.4 mg/kg (1.2; 16.4) ($n = 10$)	6.6 mg/kg (3.9; 20.1) ($n = 10$)
DPDPE (δ subtype)	313 ng (185; 588) ($n = 10$)	482 ng (296; 988) ($n = 10$)	331 ng (180.6; 601.9) ($n = 10$)
U50, 488H (κ1 subtype)	4.4 mg/kg (2.3; 8.4) ($n = 10$)	3.1 mg/kg (1.7; 7.9) ($n = 10$)	5.9 mg/kg (3.7; 11.1) ($n = 10$)
Nalorphine (κ3 subtype)	36.2 mg/kg (16.5; 128.1) ($n = 10$)	10.2 mg/kg* (5.2; 25.3) ($n = 10$)	7.3 mg/kg* (4.1; 12.1) ($n = 10$)

The numbers are the ED_{50} with 95% confidence limits.
*$p < 0.05$ vs. opioid receptor subtypes alone.

DISCUSSION

Using the mouse radiant heat tail-flick assay, we found that clozapine induced a potent antinociceptive effect following an IP injection in a dose-dependent manner. This effect was antagonized by the nonspecific opioid antagonist naloxone, implying a possible opioid mechanism of action involved in clozapine-induced antinociception. Further evaluation demonstrated the involvement of the opioid μ_1-, μ_2-, κ_1- , and

TABLE 2

THE ED_{50} OF CLONIDINE OR SEROTONIN ALONE AND WITH CLOZAPINE OR OLANZAPINE

Receptor Subtypes	Alone	With Clozapine	With Olanzapine
serotonin	0.8 (0.1; 1.0) ($n = 10$)	0.7 (0.2; 1.1) ($n = 10$)	0.5 (0.1; 2.4) ($n = 10$)
clonidine	0.53 (0.31; 1.31) ($n = 10$)	0.04 (0.02; 0.08)* ($n = 10$)	0.03 (0.01; 0.06)* ($n = 10$)

The numbers are the ED_{50} with 95% confidence limits.
* $p < 0.05$ vs. clonidine alone.

κ_3 receptor subtypes and of α_2-adrenoreceptors in clozapine antinociception but not the involvement of the serotonin receptors. Although structurally similar, olanzapine induced, in the same assay, only a weak antinociceptive effect. Moreover, as the olanzapine dose increased beyond 10 mg/kg, latencies declined almost back to baseline, implying a "therapeutic window" pattern for this antinociceptive effect. The α_2-adrenergic antagonist yohimbine significantly reduced the antinociceptive effect induced by olanzapine almost completely, while both naloxone and metergoline (a nonselective 5-HT receptor antagonist) did not significantly reduce olanzapine antinociception. These results indicate the possible involvement of the α_2-adrenoreceptor in olanzapine antinociception, and to a much lesser extent the involvement of opioid and serotonergic receptors.

In a previous study we found risperidone, a benzisoxazole "atypical" neuroleptic to induce potent antinociception through interaction with the opioid system. Because various 5-HT_2 antagonists have already been reported to attenuate naloxone-precipitated withdrawal in both acutely and chronically morphine-treated rats (14,15), we hypothesized that risperidone induced antinociception and the interaction with the opioid system may be due either to risperidone's strong blockade of postsynaptic 5-HT_2 receptors, or to the combined postsynaptic action of risperidone on both dopamine D_2 and 5-HT_2 receptors. However, other properties of risperidone may contribute to its interaction with the opioid receptors. Besides risperidone's strong blockade of the dopamine D_2 and serotonin 5-HT_2 receptors mentioned above, it has also a high affinity for α_1 and α_2-adrenoreceptors and the histamine H_1 receptor. Both noradrenoreceptors (9,16) and serotonin receptors (7,11) have been implicated in complex antinociceptive effects, mediated through opioid receptors.

In the present study we identified and characterized the antinociceptive effects of the two structurally similar dibenzodiazepines, "atypical" neuroleptics clozapine and olanzapine. To date, clozapine, the prototype "atypical" agent, is known to have preferential antagonist activity at the 5-HT_2 receptors followed by antagonist activity at the α-adrenoreceptors, muscarinic receptors, and histamine receptors, and only relatively modest activity at dopamine receptors in the D_1 and D_2 families (2,13). We now add new data regarding a possible interaction of clozapine with the opioid system as well, inducing a potent antinociceptive effect in a dose-dependent manner when injected IP in the mouse tail-flick assay. This is a significant finding, because it may contribute to a better understanding of clozapine's unique therapeutic effect in schizophrenia, where some involvement of the opioid system had been postulated in the past (17,19). However, this new data does not imply a possible use of clozapine in the treatment of pain: albeit clozapine's unique mild adverse effect profile regarding extrapyramidal symptoms and tardive dyskinesia, it may induce troublesome hematologic, hypotensive, sedative, and seizure side effects (10).

Surprisingly, although olanzapine is structurally similar to clozapine, and affects nearly as many different neurotransmitter receptors as clozapine, exerting relatively similar activity at 5-HT_2 receptors, muscarinic receptors, histamine receptors, α-adrenoreceptors and within the D_1 and D_2 receptor families (2,3), it induced only a minimal antinociceptive effect, not mediated through the opioid system. This effect was biphasic, dose-dependent (showing a "therapeutic window" pattern), and was antagonized by the α_2-adrenergic antagonist yohimbine, implying a noradrenergic mechanism of antinociception. Noradrenergic antinociception has been recognized for several years now (18,24), but never before attributed to neuroleptics. This difference between the antinociceptive effects of olanzapine and clozapine suggests a significantly different overall biochemical interactions profile of these two dibenzodiazepine "atypical" neuroleptics, a fact that may contribute to the clinical observation that some schizophrenic patients resistant to clozapine, improve notably when treated with olanzapine. However, regarding its use for the treatment of pain—we believe that olanzapine may be of little clinical use for the treatment of pain because its antinociceptive effect is weak, and its biphasic mode of action necessitates complex dose-adjustment techniques.

The findings of our present study raise three separate questions—one regarding the controversy between our findings and contrasting data about the blocking effect of 5-HT_2 antagonists on morphine analgesia in rodents (25). However, these contrasting findings may be attributed to either different sites of action (i.e., spinal vs. central), or difference between drugs: Different 5-HT_2 antagonists have been reported to act in different manners at the 5-HT_2 receptor (or possibly at different subtypes of receptors) to attenuate the expression of opiate-type withdrawal. Although mianserin was found to be an effective antiwithdrawal agent after acute treatment, ritanserin was found more effective following chronic treatment (15). In all our studies (both performed previously and the present one) we evaluated only the effects of acute drug administrations.

The second question regards the differences between the mechanism of action of the two dibenzodiazepine antipsychotic compounds clozapine and olanzapine and their "individual" interactions. Both clozapine and olanzapine were reported to possess similar profiles of potent interaction at the 5-HT_2 receptors, combined with a weak interaction at the dopamine D_2 receptors. If so, the difference noted regarding the interaction with the opioid system cannot be attributed solely to a combination of these two interactions. Furthermore, these findings impose some readjustment of our previous hypothesis regarding risperidone's mechanism of interaction with the opioid system. Nonetheless, risperidone differs from these two dibenzodiazepines both structurally and by interacting strongly at both serotonin 5-HT_2 receptor and dopamine D_2 receptor sites, it shares a common feature with clozapine—the interaction with the opioid system. Furthermore, these two structurally different "atypical" neuroleptics share a common feature with the tetracyclic antidepressant drug mianserin, found as well to induce a potent, opioid-mediated antinociceptive effect (21). Mianserin is a 5-HT postsynaptic antagonist with a strong potency on the 5-HT_2 receptor, a weak action on 5-HT_1 and 5-HT_3 receptors, and moderate antagonistic effects on both presynaptic α_2-receptors and histamine H_1 receptors. Both risperidone and clozapine interact with serotonin receptors and α-adrenoreceptors as well, and their effect on the opioid receptors may manifest through these interactions.

The third question regards the site and mechanism of interaction of the serotonin and opioid systems to exert the antinociceptive effect. We believe that the major target of antinociceptive action of this interaction is in the central nervous system, through the connections of the dorsal raphe nucleus (DRN) (rich in serotonin) with the periaqueductal gray (PAG) region (which is rich in opioid receptors and endogenous opioids), both located in the midbrain.

To conclude—although both clozapine and olanzapine share a common chemical origin (the dibenzodiazepine structure), a similar "atypical" antipsychotic efficacy, and a rather

similar mild extrapyramidal side effects profile—they differ notably not only regarding their hematological side effects, but regarding their interaction with the opioid system and their antinociceptive potency and mechanism of action as well. Nevertheless, neither of these two "atypical" neuroleptics is suitable for possible clinical use for the management of pain: clozapine because of its problematic hematological side effects, and olanzapine because it lacks significant antinociceptive effects.

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