Antisense Inhibition of 5-Hydroxytryptamine$_{2A}$ Receptor Induces an Antidepressant-Like Effect in Mice

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SUMMARY

Treatment with different antidepressants is invariably accompanied by the down-regulation of the 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptor. To determine whether receptor down-regulation is an essential part of antidepressant action, we manipulated levels of the 5-HT$_{2A}$ receptor by using a nonpharmacological approach. Here, we report that down-regulation of the 5-HT$_{2A}$ receptor by intracerebroventricular injection of antisense oligonucleotides resulted in an antidepressant-like effect in mice. Animals with 5-HT$_{2A}$ receptor deficiency showed less immobility in the Porsolt’s forced swim test, a well established animal model that is used to identify drugs with an antidepressant effect. The overall locomotor activity of the receptor-deficient animals was not altered, demonstrating the specificity of the behavioral change in the Porsolt’s forced swim test. Reduced immobility in this test was accompanied by a greater c-Fos response in piriform cortex. Because 5-HT$_{2A}$ receptors have been localized on γ-aminobutyric acid interneurons, the inhibitory activity of these neurons may be impaired at low receptor levels, leading to a greater c-Fos response in the piriform cortex and increased mobility in the Porsolt’s forced swim test. These experiments demonstrate that down-regulation of the 5-HT$_{2A}$ receptor alone is sufficient to achieve an antidepressant-like effect in mice and suggest that receptor down-regulation may be an essential part of the antidepressant drug action.

A variety of different compounds have been found to have antidepressant activity. Although the pharmacological actions of these antidepressants are prompt, the clinical effects require weeks or even months to become manifest (see review in Ref. 1). This delayed response suggests that the development of antidepressant effect requires a plastic change in brain initiated by the drug treatment. A representative change, induced by long term antidepressant treatment, is the modulation of the 5-HT$_{2A}$ receptor. Virtually all antidepressants down-regulate the level of 5-HT$_{2A}$ receptor, and this down-regulation is temporally correlated with the onset of clinical efficacy (2–5). Antidepressants that down-regulate the 5-HT$_{2A}$ receptor include tricyclics, SSRIs, monoamine oxidase inhibitors, and atypical antidepressants such as mianserin (3). Tricyclic antidepressants block both norepinephrine and 5-HT uptake; SSRIs inhibit 5-HT transport; and monoamine oxidase inhibitors prevent the inactivation of monoamines. These drugs can be considered indirect agonists because they increase the availability of monoamines, especially 5-HT, in synaptic cleft. Increased levels of 5-HT in turn may initiate receptor down-regulation (6, 7). It is paradoxical that mianserin, a 5-HT$_{2A/C}$ receptor antagonist with an antidepressant effect also elicits receptor down-regulation (2) because chronic treatment with antagonists generally induces disuse supersensitivity, a state characterized by an increase in receptor density (8). Nevertheless, the extent of down-regulation with mianserin is comparable to that achieved by tricyclics and SSRIs (2, 9).

Because treatment with different antidepressants modulates the level of 5-HT$_{2A}$ receptor, it is intriguing to hypothesize that receptor down-regulation is involved in or even required for the development of antidepressant effect. If receptor down-regulation is indeed an essential part of the antidepressant drug action, drugs with selectivity to the 5-HT$_{2A}$ receptor could be used to relieve certain symptoms of depression. On the other hand, if receptor down-regulation is not directly linked to the therapeutic effect, drugs that avoid receptor effect may be more selective in the treatment of depression. To determine whether receptor down-regulation is an essential part of antidepressant drug action, the 5-HT$_{2A}$

ABBREVIATIONS: 5-HT, 5-hydroxytryptamine; GABA, γ-aminobutyric acid; SSRI, selective serotonin reuptake inhibitor; AS, antisense; MS, mismatched; aCSF, artificial cerebrospinal fluid; LSD, lysergic acid diethylamide; FST, Porsolt’s forced swim test; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-amino propane; PTZ, pentylentetrazol; PCR, polymerase chain reaction.
receptor was down-regulated directly and specifically by intracerebroventricular injection of a receptor-specific AS oligonucleotide. In contrast to the pharmacological approach, which blocks receptor function by antagonists, the AS approach provides down-regulation of the 5-HT₂A receptor number that is more analogous to the effect of chronic antidepressant treatment. Moreover, selectivity of AS oligonucleotides is greater than that of most receptor antagonists. AS oligonucleotides can specifically recognize receptor mRNA, facilitate its degradation, or interfere with its translation, resulting in a reduced receptor level (10). Here, we report that AS-induced down-regulation of the 5-HT₂A receptor results in an antidepressant-like effect in mice. This result suggests that down-regulation of 5-HT₂A receptor alone may have some therapeutic benefit in the treatment of mood disorders.

**Materials and Methods**

**Oligonucleotide treatment.** Balb/C mice (6–8 weeks old) were injected alternatively into the left and right lateral ventricles every 2.5 mg/kg; Abbot Laboratories, King-of-Prussia, PA) and perfused cardiially with 4% paraformaldehyde. Free floating sections (40 μm) were incubated in 5 μM mianserin. The assay was performed as described previously (13). Briefly, total RNA was prepared from frontal cortex by using TRIZOL Reagent (GIBCO BRL, Gaithersburg, MD). Then, 9 μg of total RNA was incubated with 1 unit of RNase-free DNase I (GIBCO BRL) in the presence of 20 units of RNasin. The total RNA, for primer corresponding to bases 381 to 399 in the 5′-untranslated region of the 5-HT₂A receptor (5′-AAACAGCATGAGATCCAA-3′) reverse-transcribed cDNA, corresponding to 62, 31, and 15.5 ng of total RNA, was used for PCR amplification. Primers complementary to bases 381 to 399 (see sequence above) and 781 to 765 (5′-CTCAAGAGGGAGGTCCACA-3′) yielded a 400-bp product. During PCR, [32P]dATP was incorporated into the product to allow for quantification in a PhosphorImager (Molecular Dynamics, Sunnyvale, CA).

**Behavioral studies.** Headshakes were registered during a 10-min period at 30 min after a 2.5 mg/kg intraperitoneal dose of DOI. In FST, mice were forced to swim in a 8-in wide water-filled cylinder, essentially as described by Forsolt et al. (14). In this test, immobility of the mice is measured in blocks of 2 min for a total of 6 min. All animals were tested naive and submitted only once to each test. The open field apparatus consisted of a 15 × 21-inch black box divided into six (2 × 3-inch) even-sized rectangles. The number of crosses in open field was recorded for 10 min. The elevated plus maze was performed according to standard procedures (15) using a cross-maze with 12 × 2-inch arms. The number of entries into and time spent in the open arms as well as the total number of entries were recorded in a 10-min test. Care of all mice in this work was in accordance with institutional guidelines.

**Seizure susceptibility measured by PTZ test.** Mice were injected with 85 mg/kg PTZ intraperitoneally, and seizure events were videotaped during an observation period of 20 min. Mice were scored for the sequence of four seizure behaviors produced by the drug (i.e., myoclonic jerks, clonic convulsions, tonic phase, and death). A human-guided computer-assisted scoring system was used to evaluate seizures (16). The timing of the seizure behaviors, as well as their duration after the PTZ injection, was recorded. Myoclonus was defined as a single movement of the mouse that involved a downward motion of the head, combined with a single jerk of the body, and a brief upward extension of the tail. Clonus usually was the second seizure behavior to occur chronologically after PTZ injection; it was defined as rapidly repetitive jerks of the mouse that involved the entire body such that the mouse would fall to the side. The tonic stage of the seizure, when reached, was defined as a slow hindlimb extension. In these mice, the tonic stage was invariably followed by death.

**Statistical analysis.** Performance in behavioral studies, absorbance of autoradiographs, and c-Fos positive nuclei were compared between groups using a one-way analysis of variance followed by Scheffé's post hoc test. Statistical difference was determined at a level of p < 0.05. For autoradiography and c-Fos quantification, multiple successive sections were quantified in each sample sector, and the average for this sector was calculated in each mouse. The results of the PTZ test were calculated by nonparametric analysis of variance followed by the χ² test.

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AS oligonucleotide treatment selectively down-regulates 5-HT\textsubscript{2A} receptor levels and attenuates receptor function. In the brain, 5-HT\textsubscript{2A} receptors are found mostly in the cortical layers and striatum. Because the most dramatic antidepressant-induced receptor down-regulation occurs in the cortex (3), we tested whether oligonucleotides injected into the lateral ventricles reached the cortical layers. A biotin-labeled oligonucleotide was repeatedly injected (intracerebroventricular injections every 12 hr for 2 days), and its localization was visualized by peroxidase enzymatic staining (Fig. 1A). A predominantly cortical distribution was observed, presumably due to the transport of the oligonucleotide to the subarachnoidal space that overlies the entire cortex and provides a large surface for uptake. Subcortical regions such as striatum or thalamus accumulated fewer oligonucleotides. Intermediate levels were found along the midline, in the septum, and in the hypothalamus. The highest levels of oligonucleotides were found in the choroid plexus, presumably because it was in a direct contact with the oligonucleotides injected into the lateral ventricles. Mice injected with unlabeled oligonucleotide (Fig. 1A), aCSF, or biotin alone (data not shown) did not show any detectable staining.

Repeated intracerebroventricular injection of a 18-mer AS oligodeoxynucleotide, corresponding to the 5\textsuperscript{-}translated region of the 5-HT\textsubscript{2A} receptor (10 \textmu g in 5 \mu l of aCSF every 12 hr for 4 days), resulted in 47%, 46%, and 48% decreases in specific binding in frontal, parietal, and piriform cortices, as measured by autoradiography with \textsuperscript{125}I-labeled LSD (Figs. 1B and 2A). Because the central nervous system has a low nuclease activity, unmodified phosphodiester oligonucleotides were used, avoiding the toxicity inherent to the more stable phosphorothioate oligonucleotides. Injection of neither MS oligonucleotides (three mismatched bases in the AS sequence) nor aCSF altered receptor binding. In the striatum, the down-regulation by the AS oligonucleotide was only 30%, which is in agreement with the lower level of oligonucleotide accumulation in this region (Figs. 1A and 2A). Other regions, such as thalamus, hypothalamus, and hippocampus, showed a low level of specific binding, and the effect of AS oligonucleotide in these regions could not be reproducibly measured.

To evaluate the specificity of the AS oligonucleotide for the 5-HT\textsubscript{2A} receptor, we tested its effect on the 5-HT\textsubscript{2C} receptor. The 5-HT\textsubscript{2A} and 5-HT\textsubscript{2C} receptors are closely related; their ligand binding properties, coupling, and amino acid sequence are similar (17). However, their nucleotide sequences are not entirely identical, and the AS oligonucleotide was selected so it would not interact with the 5-HT\textsubscript{2C} receptor sequence. 5-HT\textsubscript{2C} receptor binding was measured in the choroid plexus, a region abundant in these receptors. Because the choroid plexus contained the highest level of oligonucleotide, it was an ideal brain region in which to assess whether the 5-HT\textsubscript{2A} receptor-specific oligonucleotide can alter 5-HT\textsubscript{2C} receptor binding. As Fig. 2A shows, no attenuation of the 5-HT\textsubscript{2C} receptor was measured after repeated oligonucleotide injection; thus, the effect of AS oligonucleotide was selective for the 5-HT\textsubscript{2A} receptor.
Interestingly, attenuation of receptor binding by AS oligonucleotide injection in the frontal cortex was not accompanied by the down-regulation of 5-HT2A receptor mRNA (Fig. 2B), suggesting a post-transcriptional/translational mechanism for the AS oligonucleotide action. To determine whether the receptor down-regulation was accompanied by a functional attenuation, we measured the number of DOI-induced headshakes (18). Headshakes induced by DOI are thought to originate in the brainstem and be facilitated by diencephalic structures (19), but alterations in 5-HT2A receptor density in frontal cortex can also modify the headshake response (20, 21). Headshakes induced by DOI were significantly decreased in AS oligonucleotide-injected animals compared with control mice (Fig. 2C). Although the decreased headshake response cannot be attributed to a specific pool of receptors, it nevertheless demonstrated a functional 5-HT2A receptor deficit in the brain of AS oligonucleotide-injected mice.

Taken together, these results demonstrated that repeated intracerebroventricular injection of AS oligonucleotide can selectively decrease 5-HT2A receptor binding, mostly in the cortex, leading to the attenuation of receptor function.

**Receptor down-regulation increases mobility in FST.** FST is an animal model of depression that is used routinely for preclinical testing of antidepressants (14). FST is sensitive to tricyclic antidepressants, monoamine oxidase
inhibitors, and atypical antidepressants. FST is also sensitive to SSRIs in both mice and rats (22); however, some SSRIs are less active and sometimes even inactive in rats (23). The test is based on the observation that when forced to swim in a restricted space from which there is no escape, mice will gradually cease attempts to escape and become immobile. It was suggested that immobility reflects a state of despair that can be reduced by a variety of drugs and treatments that are therapeutically effective in depression (22).

As Fig. 3A shows, immobility of AS oligonucleotide-injected animals was reduced significantly compared with control animals (aCSF and MS oligonucleotide-injected animals). The test was validated by using the atypical antidepressant mianserin at the highest nonsedative dose of 3 mg/kg. As expected, mianserin had an anti-immobility effect in FST comparable to that induced by AS oligonucleotide injection (Fig. 3B). However, mianserin can block both the 5-HT2A and 5-HT2C receptors. On the other hand, the selective 5-HT2A

Fig. 3. Behavioral characterization of mice with a deficit in cortical 5-HT2A receptor. A, FST. Animals exposed to swim stress show an intense escape-directed behavior in the first block of the test. aCSF and MS oligonucleotide-injected animals subsequently display a gradually diminishing mobility throughout the second and third blocks of the test. AS oligonucleotide-injected animals showed less immobility. Values (mean ± standard error) are shown for aCSF (13 animals), MS (20 animals), and AS (22 animals) oligonucleotide-injected animals. B, Mianserin (3 mg/kg; 10 animals) and MDL 100907 (0.15 mg/kg; 7 animals) reproduce the AS oligonucleotide-induced behavioral effect in FST. Control animals were injected with saline (10 animals). C, Locomotor activity of AS oligonucleotide-injected animals is not altered in the open field (noninjected, 8 animals; aCSF, 8 animals; MS, 8 animals; AS, 9 animals). D, Elevated maze. AS-treated animals did not differ from control groups in percentage of time and entries in the open arms as well as in total number of entries in all arms of the maze (aCSF, 14 animals; MS, 17 animals; AS, 19 animals).
receptor antagonist MDL 100,907 (24) was also effective in FST, demonstrating that blockade of the 5-HT$_{2A}$ receptor can lead to an anti-immobility effect (Fig. 3B).

The anti-immobility effect in AS oligonucleotide-injected animals was not due to increased basal locomotion because activity of these animals in open field was similar to that of control mice (Fig. 3C). In addition, receptor down-regulation had no detectable effect in the elevated maze (Fig. 3D). We conclude that a reduction in 5-HT$_{2A}$ receptor level is sufficient to increase mobility in FST.

**Increased c-Fos response of AS oligonucleotide-injected animals in the piriform cortex.** FST induces the expression of the immediate-early gene c-fos, indicating an extensive neuronal activation during swimming (25). Using immunohistochemistry directed toward the c-Fos protein and related antigens, we observed no difference between AS and MS oligonucleotide-injected animals in subcortical nuclei (lateral septal nucleus, bed nucleus of the stria terminalis, MS oligonucleotide-injected animals in subcortical nuclei and hypothalamic and thalamic paraventricular nuclei; data not shown). However, a greater increase in immunoreactivity was found in the piriform cortex of AS oligonucleotide-injected animals compared with control animals [150 ± 11.7% of control (mean ± standard error), p < 0.005] (Fig. 4). The FST-induced c-Fos response was not significantly increased in other cortical regions of AS oligonucleotide-injected animals compared with control (MS- and aCSF-injected) mice (data not shown).

The increased c-Fos response in AS oligonucleotide-injected animals after the forced swim raised the possibility of a general hyperexcitability as a consequence of down-regulation of the 5-HT$_{2A}$ receptor. The overall excitability of the brain of AS oligonucleotide-injected mice was measured by using the seizure-inducing agent PTZ. PTZ seems to decrease the potency of GABA-mediated inhibition in brain (26) and, depending on the dosage, can produce myoclonic jerks, clonic convulsions, tonic seizures, and death in animals. The 85 mg/kg dose of PTZ used in this experiment was equally potent to produce myoclonic jerks and clonic convulsions in both AS and MS oligonucleotide-injected animals (Table 1). However, there was a tendency for more lethality among AS oligonucleotide-injected mice, albeit the difference between AS oligonucleotide-injected and control animals did not reach statistical significance. These results argue for no increased excitability in AS oligonucleotide-injected animals, at least not in brain regions involved in initiating PTZ seizures, such as the reticular formation and the anterior thalamus (27, 28). These data also suggest that increased neuronal activation in AS oligonucleotide-injected animals is restricted to certain regions that may correspond to areas rich in 5-HT$_{2A}$ receptor.

**Discussion**

The down-regulation of the 5-HT$_{2A}$ receptor by virtually all antidepressants raised the possibility of receptor involvement in drug action. However, antidepressants down-regulate the 5-HT$_{2A}$ receptor by different mechanisms, and it has been difficult to determine whether the receptor down-regulating and therapeutic effect of antidepressants are linked. For example, fluoxetine, a 5-HT transporter blocker and effective antidepressant probably has no direct action on the receptor itself; rather, it is the elevated level of 5-HT that may down-regulate the receptor. In contrast, mianserin, a 5-HT$_{2A}$/2C receptor antagonist and atypical antidepressant presumably acts on the receptor itself (29).

To study whether down-regulation of the receptor leads to an antidepressant-like effect, the level of 5-HT$_{2A}$ receptor was reduced by injecting AS oligonucleotides into the brain of mice. The antisense approach provided down-regulation of the 5-HT$_{2A}$ receptor that was analogous to the reduction in receptor number induced by chronic antidepressant treatment. Even the extent of the down-regulation of the receptor in the frontal cortex by AS oligonucleotide injection (~47%, Figs. 1 and 2) was similar to that achieved by antidepressant treatment (up to 50%) (3, 30). The effect of AS oligonucleotide injection was selective for the 5-HT$_{2A}$ receptor because no attenuation of the 5-HT$_{2C}$ receptor was detectable (Fig. 2A). Receptor down-regulation was accompanied by a functional attenuation because DOI-induced headshakes were significantly decreased in AS oligonucleotide-injected animals (Fig. 2C).

As Fig. 3A demonstrates, down-regulating the level and attenuating the function of the 5-HT$_{2A}$ receptor by intrace-rebroventricular injection of a receptor-specific AS oligonucleotide resulted in a significant change in the behavioral response of mice. Receptor down-regulation inhibited immobility in FST, which is an indication of an antidepressant effect. The extent of anti-immobility effect in receptor-deficient animals was comparable to that induced by the atypical antidepressant mianserin (Fig. 3B). Clinically active antidepressants have an anti-immobility effect in FST without altering locomotor activity in open field. Likewise, no locomotor activation was seen in AS oligonucleotide-injected animals (Fig. 3C). Taken together, experiments involving AS oligonucleotide injections demonstrate that down-regulation of the

![Image](Antisense oligonucleotide.png)

**Antisense oligonucleotide**

![Image](Mismatched oligonucleotide.png)

**Mismatched oligonucleotide**

![Image](Fig. 4. Increased c-Fos response after FST in the piriform cortex of a mouse with a deficit in 5-HT$_{2A}$ receptors (top, AS oligonucleotide-injected animal) compared with a control (bottom, MS oligonucleotide-injected animal). Bar, 40 μm. Number of c-Fos-positive nuclei/0.01 mm$^2$ were 66 ± 5.6 for AS, 44.3 ± 3.4 for MS, and 48 ± 5.0 for aCSF.)
receptor alone is sufficient to achieve an antidepressant-like effect in mice.

How does down-regulation of 5-HT_{2A} receptor inhibit immobility in FST? Although it is attractive to interpret immobility as a sign of despair and compare it with depression, there is no evidence to support this notion. Rather, behavior of mice in FST is more similar to a typical response to stress. Initially, stress activates a number of effector systems within the central nervous system that promote arousal and vigilance. However, when stress becomes chronic, the acute behavioral stress responses are gradually diminished, presumably because excessive stress reactions would be counterproductive (exhaustion to swim). The stress nature of FST is supported by the activation of the hypothalamic-pituitary-adrenal axis and the induction of the early-immediate gene c-fos after swimming (25, 31). Both AS and MS oligonucleotide-injected animals showed an ∼4-fold increase in plasma corticosterone levels 10 min after the initiation of FST (data not shown). Also, the temporal and spatial patterns of c-fos activation were very similar to that induced by stressful stimuli such as restraint (Ref. 25; see also Fig. 4). Therefore, the gradually developing immobility in FST can represent a containment process (32) rather than a despair.

Whether the behavior in FST is a stress response or more of a despair-like reaction, the data presented here unequivocally demonstrate that it can be significantly altered by the 5-HT_{2A} receptor.

The anti-immobility effect of receptor down-regulation may be explained by the specific localization of the receptors in the central nervous system. 5-HT is present at the terminal area of fine 5-HT immunoreactive axons in the cortex that arise from the dorsal raphe nucleus (33). In these areas, 5-HT_{2A} receptors are frequently found on interneurons. Based on morphology and electrophysiological properties, 5-HT_{2A} receptor-bearing interneurons are likely GABAergic cells (34–36). 5-HT_{2A} receptor-bearing interneurons form a dense band on layer III in the piriform cortex (34) and could provide an inhibitory cortical input. Low 5-HT_{2A} receptor levels in AS oligonucleotide-injected animals may lead to increased pyramidal activity due to less activation of the inhibitory GABAergic interneurons during FST. In turn, the increased neuronal activity could result in an anti-immobility effect by augmenting neuronal pathways that mediate the behavioral stress responses such as the escape-directed behavior.

Although GABAergic interneurons expressing 5-HT_{2A} receptors are also localized in the frontal/parietal cortex, the overall number of these cells represents a relatively small portion of the total cell number in these regions (35). Moreover, the 5-HT_{2A} receptor is also expressed in pyramidal cells in the frontal/parietal cortex, which could counteract the effect on GABAergic function by activating pyramidal cells directly. Therefore, AS down-regulation of the receptor in neocortex could have less impact on the overall neuronal activity, and this situation would render it undetectable by c-Fos immunostaining. The localized nature of increased neuronal activity is also supported by the lack of overall brain hyperexcitability shown in the PTZ test (Table 1). Although not revealed by our immunostaining experiments, a 5-HT_{2A} receptor-mediated tonic inhibition may exist in the medial prefrontal cortex. Schmidt et al. (24) showed that blocking 5-HT_{2A} receptors by the selective antagonist MDL 100,907 results in an increase in dopamine efflux in rats. These results raise the possibility that the behavioral effects of the AS oligonucleotide injection may also be due to an increased dopamine release during forced swim. Taken together, the data presented here support the hypothesis that down-regulation of 5-HT_{2A} receptors disinhibits piriform cortex and perhaps other receptor-rich cortical areas in mice that could lead to a state of increased psychomotor activity, visible as anti-immobility effect in FST.

The antidepressant-like effect induced by AS oligonucleotide injection in mice is consistent with the beneficial effect of pharmacological blockade of the 5-HT_{2A} receptor in dysthmic disorders. Studies with ritanserin, a 5-HT_{2A/2C} receptor antagonist, showed that a group of patients with anxiety syndrome felt less tired and more energetic after treatment (37). This observation prompted further studies that showed a benefit of ritanserin in patients with dysthmic disorder characterized by anergy, lack of motivation, and depressive mood (37). It is tempting to speculate that block of 5-HT_{2A} receptors would increase psychomotor activity that could counterbalance the psychomotor retardation present in these patients. However, antidepressant action is certainly more complex than producing a state of psychomotor activation. Nevertheless, psychomotor activation could be an important part of antidepressant drug action. Indeed, sympathomimetic stimulants, such as amphetamine and amphetamine surrogates, are occasionally used as antidepressants.

Another disease characterized by psychomotor retardation is schizophrenia, which may also respond to the manipulation of the 5-HT_{2A} Receptor (38). Indeed, the 5-HT_{2A/2C} receptor antagonist ritanserin and the 5-HT_{2A/D2} receptor antagonist clozapine showed a benefit in schizophrenia, in particular by ameliorating negative symptoms (39, 40).

Taken together, we propose that down-regulation of the 5-HT_{2A} receptor contributes to the beneficial effect of antidepressants by producing a state of increased psychomotor activity. Drugs with selectivity to the 5-HT_{2A} receptor could be used to relieve certain symptoms of depression. Recently,

### Table 1

Susceptibility of AS oligonucleotide-injected and control animals to PTZ-induced seizures

<table>
<thead>
<tr>
<th></th>
<th>aCSF (n = 8)</th>
<th>MS (n = 8)</th>
<th>AS (n = 8)</th>
</tr>
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<tr>
<td>Animals displaying jerks (n)</td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Time spent in jerks in 20 min (sec)</td>
<td>50 ± 10</td>
<td>57 ± 2</td>
<td>47.4 ± 9.9</td>
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<tr>
<td>Animals displaying clonus (n)</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Mean number of clonus in 20 min</td>
<td>8 ± 0.5</td>
<td>2 ± 0.5</td>
<td>1.4 ± 0.9</td>
</tr>
<tr>
<td>Animals displaying tonic seizures (n)</td>
<td>1</td>
<td>2</td>
<td>4^a,b</td>
</tr>
<tr>
<td>Animals that died (n)</td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Time spent in clonus in 20 min (sec)</td>
<td>15.3 ± 4.6</td>
<td>15.3 ± 4</td>
<td>13.4 ± 5.7</td>
</tr>
</tbody>
</table>

^a p < 0.01 versus aCSF; ^b p < 0.3 versus MS, χ² test.
MDL 100,907, a selective 5-HT_{2A} receptor antagonist, has been developed (40). MDL 100,907, is currently in clinical trial for schizophrenia, but it would be interesting to test this compound in depression, too.

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References


