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Pharmacology of "atypicality" of antipsychotic drugs: status and perspectives

Adrian Newman-Tancredi, Mark S. Kleven

Summary

"Atypical" antipsychotics are antagonists at serotonin 5-HT2A and dopamine D2 receptors. However, their effects on negative symptoms and cognitive deficits remain modest and they disrupt metabolic function. Recent drugs, such as aripiprazole, perospirone, bifeprunox, lurasidone and cariprazine act as D2 receptor antagonists (or partial agonists) combined with 5-HT1A receptor activation. The latter prevents extrapyramidal symptoms, favors prefrontal cortex dopaminergic neurotransmission, has a beneficial influence on mood and opposes cognitive deficits. Further, recent drugs exhibit little interaction at sites associated with side-effects such as metabolic disorders or autonomic disturbance. However, these drugs differ in their balance of 5-HT1A/D2 receptor properties and this is likely to translate to distinct therapeutic profiles.

5-HT1A receptors/ D2 receptors/ antipsychotic/ schizophrenia

INTRODUCTION

Schizophrenia and psychotic disorders constitute a serious mental health problem and a substantial burden on health care [1]. Although a variety of pharmacological mechanisms have been proposed to underlie antipsychotic activity, dopamine (DA) D2 receptor antagonism remains the cornerstone of the activity of current antipsychotic drugs. Indeed, the "first generation" antipsychotic, haloperidol, exhibits control of positive symptoms of schizophrenia by opposing the excessive stimulation of D2 receptors resulting from hyperactivity of mesolimbic dopaminergic projections. However, it fails to alleviate the hypoactivity of mesocortical dopaminergic neurons (i.e., "hypofrontality"), thought to underlie negative symptoms such as social withdrawal and flattened affect, and cognitive deficits including working memory impairment and loss of cognitive flexibility [2]. Further, selective DA D2 receptor antagonists also block nigrostriatal dopaminergic activity, leading to extrapyramidal symptoms (EPS), and pituitary D2 receptors that control prolactin release, leading to hyperprolactinemia [3]. To overcome these limitations, a variety of "second generation" or "atypical" antipsychotics have been developed that act at other receptors as well as antagonising D2 receptors. The "gold standard" among these antipsychotics is clozapine, which is considered to possess superior therapeutic efficacy whilst inducing negligible EPS. Molecular targets of clozapine's activity have been extensively investigated, with a particular focus on blockade of serotonin 5-HT2A/2C receptors and of DA D3 and D4 receptors. Whilst selective ligands at these receptors have not been shown to produce antipsychotic activity in clinical trials, combinations

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of these pharmacological activities diminish EPS liability and improve negative and cognitive symptoms. Indeed 5-HT2A receptor antagonism favors dopaminergic neurotransmission when associated with D2 receptor antagonism. Increasing cortical DA release is expected to alleviate hypofrontality in schizophrenic patients [4, 5] and a variety of "atypical" antipsychotics that combine 5-HT2A receptor antagonism with D2 receptor antagonism have therefore been developed (e.g., risperidone, olanzapine and ziprasidone) [6]. Nevertheless, the ability of these drugs to control negative symptoms and cognitive deficits remains modest and serious problems of metabolic dysfunction are elicited by olanzapine and clozapine, likely via antagonism of histamine H1 (H1R) and 5-HT2C receptors. Further, antagonism of muscarinic M1 receptors can impair cognitive function.

A pharmacological cocktail strategy for improved antipsychotics: focus on 5-HT1A receptor agonism

In this context, attention has increasingly focused on identifying a "pharmacological cocktail" of receptor interactions that accentuate beneficial properties and avoid undesirable side effects [7]. Tab. 1 illustrates this principle with reference to dopaminergic, serotonergic and noradrenergic receptors. Thus, improved antipsychotic effects may be obtained fromcompounds that possess antagonism of mesolimbic D2 receptors (to achieve efficacy against positive symptoms) whilst antagonizing 5-HT2A, alpha2 and D3/D4 receptors (to achieve efficacy against negative and cognitive symptoms). Improved tolerance may be achieved by reducing affinity for sites associated with side effects, such as H1R and muscarinic M1, as mentioned above, as well as 5-HT2C, alpha1 and ion channels implicated in cardiac function [8]. Some side effects, such as hyperprolactinemia and EPS can be reduced by using drugs that possess partial agonist properties at pituitary and nigrostriatal D2 receptors, respectively, thus ensuring that a modest amount of signaling is maintained at these sites. Indeed, partial agonism at D2 receptors is an attractive means of reducing several troubling side-effects, including EPS, hyperprolactinemia and antipsychotic-induced cognitive dysfunction [9]. However, the precise extent of partial agonism that is desirable is unclear. For most of the drugs described (e.g., aripiprazole, cariprazine and PF-217830; see below and Tab. 2), partial agonism at D2 receptors is generally modest, although for bifeprunox it is sufficient to have substantial electrophysiological and behavioural effects [10]. However, bifeprunox failed to show sufficient antipsychotic efficacy in clinical trials to achieve regulatory approval from the U.S. Food and Drug Administration (FDA), illustrating the necessity to ensure that partial agonist levels at D2 receptors remain sufficiently low to maintain adequate antipsychotic efficacy.

Table 1. Desirable and undesirable effects of antipsychotics, some physiological mechanisms and strategies for identifying improved antipsychotic drugs.

Antipsychotic activity	Physiological mechanisms	Strategies for novel antipsychotics
Efficacy against positive symptoms	Antagonism of mesolimbic dopamine D_2 receptors	Reinforce D_2 receptor affinity Decrease D_2 receptor agonism
Efficacy against negative symptoms	Increase frontal cortex monoamine neurotransmission (particularlydopamine release)	$5\text{-}HT_{2A}$ receptor antagonism; $5\text{-}HT_{1A}$ receptor agonism; $Alpha_2$ receptor antagonism; D_3 and D_4 receptor antagonism
Efficacy against cognitive deficits	Increase frontal cortex monoamine neurotransmission (particularly dopamine release)	$5\text{-}HT_{2A}$ receptor antagonism; $5\text{-}HT_{1A}$ receptor agonism; $Alpha_2$ receptor antagonism; Decrease D_2 receptor agonism D_3 and D_4 receptor antagonism

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Undesirable effects	Physiological mechanisms	Strategies for novel antipsychotics
Extrapyramidal symptoms	Antagonism of nigrostriatal dopamine D_2 receptors	Decrease D_2 receptor affinity D_2 receptor partial agonism; 5-HT_{2A} receptor antagonism; 5-HT_{1A} receptor agonism
Antipsychotic-induced sedation and weight gain	Histamine H1R antagonism; Serotonin 5-HT_{2C} receptor antagonism	Avoid H1R receptor affinity Avoid 5-HT_{2C} antagonism
Cardiovascular impact	Noradrenergic Alpha1 receptor antagonism Interaction at cardiacion channels (e.g. hERG)	Avoid $alpha_1$ receptor affinity; Avoid interaction at "off target" sites.
Antipsychotic-induced memory impairment	Muscarinic M1 receptor antagonism; Antagonism of mesocortical dopamine D_2 receptors	Avoid M1 receptor affinity; D_2 receptor partial agonism
Hyperprolactinemia	Antagonism of pituitary dopamine D_2 receptors	D_2 receptor partial agonism

Considerable attention has increasingly been given to agonism at serotonin 5-HT1A receptors [11] in view of compelling evidence that activating these receptors should improve negative and cognitive symptoms of schizophrenia. Indeed, microdialysis experiments have shown that 5-HT1A receptor activation increases dopamine release in frontal cortex [2, 12, 13], suggesting that activation of 5-HT1A receptors alleviates a deficiency in dopaminergic neurotransmission in frontocortical regions of the schizophrenic brain.

Second, 5-HT1A receptors are up-regulated in schizophrenics, as determined by post-mortem investigations of receptor expression in frontal cortex and other brain regions [14, 15]. 5-HT1A receptor expression may increase as a compensation mechanism subsequent to insufficient activation of this site: a deficiency that could be remedied by administration of 5-HT1A receptor agonists. Further, 5-HT1A receptors are expressed on glutamatergic neurons in the frontal cortex [16] and the non-competitive NMDA antagonist, dizocilpine (MK-801), rapidly upregulates 5-HT1A receptors [17]. This suggests that 5-HT1A receptor activation may modulate dysfunctional glutamatergic activity in schizophrenic patients. Accordingly, 5-HT1A receptor activation opposes the increase in glutamate release induced by NMDA receptor blockade [18].

Third, numerous laboratories have demonstrated anti-cataleptic properties of 5-HT1A agonists in rodents, indicating that activation of 5-HT1A receptors should reduce EPS induced by dopamine D2 receptor blockade [19, 20]. The extent to which 5-HT1A agonists are able to reverse neuroleptic-induced catalepsy is dependent on the agonist efficacy of the ligand: relatively high efficacy activation, for example by the prototypical agonist, 8-OH-DPAT, is necessary to completely abolish neuroleptic-induced catalepsy [20, 21].

Fourth, clozapine exhibits clearly measurable 5-HT1A receptor agonism in various in vitro models of receptor transduction [22, 23]. 5-HT1A receptor activation is also involved in clozapine-mediated elevation of DA release in frontal cortex and inhibition of haloperidol-induced catalepsy [13, 20, 24].

Finally, pharmacological data indicate that antipsychotics possessing 5-HT1A receptor agonism oppose NMDA receptor hypofunction-induced cognitive deficits [25, 26, 27] and exploratory clinical trials have shown that buspirone and tandospirone, which act as partial agonists at 5-HT1A receptors, substantially ameliorate cognitive and negative symptoms scores and reduce the incidence of extrapyramidal symptoms in schizophrenic patients concurrently treated with first generation antipsychotics such as haloperidol (for Review see [28]).

Taken together, these observations provide a solid rationale to include 5-HT1A receptor agonism as an ingredient in the "pharmacological cocktail" of novel antipsychotics.

5-HT1A / D2 antipsychotics: the search for the right "balance"

In view of the above considerations, a variety of "third generation" antipsychotics that combine partial agonism at 5-HT1A receptors with antagonism (or partial agonism) at D2 receptors have been described. Drugs that have been clinically evaluated include aripiprazole, perospirone, bifeprunox, lurasidone, cariprazine and PF-217830 [11]. Other compounds have been extensively characterised on a pharmacological level, including adoprazine (SLV313), SSR181507 and F15063 [10, 11].

Overall, novel "third generation" antipsychotics are expected to provide therapeutic benefits against a broader range of symptoms of schizophrenia (with particular reference to negative symptoms and cognitive impairment), to be essentially free of EPS and exhibit little or no interaction at sites potentially involved in side-effects such as weight gain, metabolic disorders or autonomic disturbance (see Tab. 2).

However, whilst all these compounds share the general property of interacting at both 5-HT1A and D2 receptors, the "balance" of activity at these sites profoundly influences their pharmacological profile [11, 29]. Thus, insufficient 5-HT1A agonism would yield an antipsychotic that induces EPS and is likely to be less effective against negative and cognitive symptoms (cf. haloperidol). In contrast, insufficient D2 antagonism and excessive 5-HT1A receptor activation would yield a compound that lacks robust antipsychotic action. In the case of the compounds mentioned above, aripiprazole, bifeprunox, cariprazine, PF-217830 and SSR-181507 exhibit varying levels of partial agonism at dopamine D2 receptors [11, 30]. As mentioned, the precise level of partial agonism that is desirable or necessary is unclear but is likely to be very low, in order to avoid compromising antipsychotic efficacy [10, 31].

Recent antipsychotics also exhibit a variety of levels of agonism at 5-HT1A receptors: aripiprazole has modest partial agonist activity at this

Table 2. Therapeutic and side-effects profiles of principal antipsychotics.

The table shows the generic and trade names of principal antipsychotics, their origin (pharmaceutical company), year of commercialisation or development phase, and a qualitative indication of their effectiveness against different symptoms of schizophrenia, based on clinical and pharmacological studies. An indication of side-effect liability is also shown. First generation antipsychotics are D2 receptor antagonists, are generally ineffective against negative and cognitive symptoms and produce substantial EPS. Second generation antipsychotics have the common characteristic of antagonising both 5-HT2A and D2 receptors. They are considered to show modest efficacy against negative symptoms and cognitive impairment, whilst exhibiting less EPS but, in some cases, substantial weight gain. "Third generation" antipsychotics generally display greater activity in tests of negative symptoms and cognitive dysfunction and improved tolerance profiles.

Key: 0 = no effect; 0/+ = weak effects; + or ++ = moderate to substantial effects; ? = uncertainty.

		Therapeutic properties			Side-effects		
		Positive symptoms	Negative symptoms	Cognitive deficits	EPS	Arrhythmia (QT)	Weight gain
First Generation Antipsychotics: D_2 antagonism							
Chlorpromazine	*Thorazine* (RhonePoulenc) 1955	++	-	-	++	+	+
Haloperidol	*Haldol* (Janssen) 1967	++	-	-	++	++	-
Second Generation Antipsychotics: 5-HT_{2A} & D_2 antagonism							
Clozapine	*Clozaril* (Novartis) 1975	++	+	+	0/+	+	++
Risperidone	*Risperdal* (J&J) 1993	++	+	0/+	+	+	0/+
Paliperidone	*Invega* (J&J) 2009	++	+	0/+	+	+	0/+
Olanzapine	*Zyprexa* (Eli Lilly) 1996	++	+	0/+	+	+	++
Sertindole	*Serdolect* (Lundbeck) 1996	++	+	+	0/+	++	0/+
Quetiapine	*Seroquel* (AstraZeneca) 1997	++	+	0/+	0/+	+	+

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Ziprasidone	*Geodon* (Pfizer) 2001	++	+	?	0/+	++	0/+
Iloperidone	*Fanapt* (Vanda) 2009	++	+	0/+	0/+	+	0/+
Asenapine	*Saphris* (Shering-Plough) 2009	++	+	0/+	+	0/+	0/+
Third Generation Antipsychotics: 5-HT_{1A} agonism & D_2 antagonism or partial agonism							
Perospirone	*Lullan* (Dainippon Sumitomo) 2001	++	+	+	0	0/+	0
Aripiprazole	*Abilify* (Otsuka / BMS) 2002	++?	+	+	0/+	0/+	0
Lurasidone	*Latuda* (Dainippon Sumitomo) 2010	++	+	+	0	0	0
Bifeprunox	(Solvay) FDA: non approvable	+?	+	?	0	0	0
Cariprazine	(Richter / Forest) Ph.III	++?			0	0?	0
PF-00217830	(Pfizer) Ph.II	++			0		
Adoprazine	(Solvay) Ph.I disc.	++	+	+	0		
SSR-181507	(Sanofi-Aventis) Ph.I disc.	++	+	+	0		
F15063	(Pierre Fabre) pre-clinical	++	+	+	0		

site whereas bifeprunox, adoprazine, SSR181507 and F15063 have higher efficacy [23]. It is interesting that adoprazine produces signs of "serotonin behavioural syndrome" in rats whereas F15063 does not [32]. This illustrates the fact that the "balance" of 5-HT1A and D2 receptor properties has functional consequences in behavioural models. In neurochemical tests (rat microdialysis studies), the 5-HT1A partial agonism of aripiprazole was insufficient to overcome its D2 partial agonism and elicit increases in frontal cortex DA release [12]. In contrast, adoprazine and F15063, which have a different balance of 5-HT1A and D2 properties (complete antagonism of D2 receptors and efficacious 5-HT1A agonism), did increase DA release [12, 33]. In contrast, in a rodent model of social withdrawal induced by treatment with the non-competitive NMDA receptor antagonist, phencyclidine (PCP), the 5-HT1A agonist properties of aripiprazole mediated a pro-socialising activity [30, 34] whereas other novel antipsychotics, such as adoprazine or bifeprunox, did not show activity, reinforcing the notion that a specific balance of activity at 5-HT1A and D2 receptors is necessary to achieve optimal therapeutic benefit.

CONCLUSIONS

Accumulating evidence from molecular, neurochemical, rodent behavioural and clinical studies has provided compelling evidence that compounds possessing a balanced combination of 5-HT1A receptor agonism together with D2 antagonism (or weak partial agonism) yield robust activity in a broad range of rodent pharmacological models and have a lower propensity to elicit adverse side effects such as EPS or metabolic dysfunction. These observations suggest that such compounds may be effective in treating a broader range of symptoms of schizophrenia and be better tolerated than existing antipsychotics. Accordingly, a variety of novel compounds are undergoing pharmacological and clinical evaluation and will likely provide new therapeutic options for the management of schizophrenia. Nevertheless, these compounds exhibit widely differing agonist or antagonist properties at 5-HT1A and D2 receptors. These differences translate to clearly divergent profiles in pharmacological tests and may be reflected in differing clinical efficacy. It is therefore necessary, when testing novel antipsychotic candidates, to consider their balance of 5-HT1A and D2 properties.

REFERENCES

1. Rossler W, et al. Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol. 2005; 15(4): 399–409.
2. Meltzer HY, and Huang M. In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. Prog Brain Res. 2008; 172: 177–97.
3. Goff DC, and Shader RI. Non-neurological side-effects of antipsychotic drugs. In: Hirsch SR, Weinberger D. edi-

tors. Schizophrenia. Oxford: Blackwell Publishing; 2003. 573–588.

4. Ichikawa J, Meltzer HY. Relationship between dopaminergic and serotonergic neuronal activity in the frontal cortex and the action of typical and atypical antipsychotic drugs. Eur Arch Psychiatry Clin Neurosci. 1999; 249(Suppl 4): 90–8.
5. Lahti AC, et al. Functional effects of antipsychotic drugs: comparing clozapine with haloperidol. Biol Psychiatry. 2003; 53(7): 601–8.
6. Richtand NM, et al. Role of serotonin and dopamine receptor binding in antipsychotic efficacy. Prog Brain Res. 2008; 172: 155–75.
7. Roth BL, Sheffler DJ, Kroeze WK. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov. 2004; 3(4): 353–9.
8. Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment-pharmacological mechanisms. Pharmacol Ther. 2010; 125(1): 169–79.
9. Tamminga CA, Carlsson A. Partial dopamine agonists and dopaminergic stabilizers, in the treatment of psychosis. Curr Drug Targets CNS Neurol Disord. 2002; 1(2): 141–7.
10. Newman-Tancredi A, Cussac D, Depoortere R. Neuropharmacological profile of bifeprunox: merits and limitations in comparison with other third-generation antipsychotics. Curr Opin Investig Drugs. 2007; 8(7): 539–54.
11. Newman-Tancredi A. The importance of 5-HT1A receptor agonism in antipsychotic drug action: rationale and perspectives. Curr Opin Investig Drugs. 2010; 11(7): 802–12.
12. Assie MB, et al. Contrasting contribution of 5-hydroxytryptamine 1A receptor activation to neurochemical profile of novel antipsychotics: frontocortical dopamine and hippocampal serotonin release in rat brain. J Pharmacol Exp Ther. 2005; 315(1): 265–72.
13. Rollema H, et al. Clozapine increases dopamine release in prefrontal cortex by 5-HT1A receptor activation. Eur J Pharmacol. 1997; 338(2): 3–5.
14. Burnet PW, Eastwood SL, Harrison PJ. [3H]WAY-100635 for 5-HT1A receptor autoradiography in human brain: a comparison with [3H]8-OH-DPAT and demonstration of increased binding in the frontal cortex in schizophrenia. Neurochem Int. 1997; 30(6): 565–74.
15. Tauscher J, et al. Brain serotonin 5-HT(1A) receptor binding in schizophrenia measured by positron emission tomography and [11C]WAY-100635. Arch Gen Psychiatry. 2002; 59(6): 514–20.
16. Czyrak A, et al. Serotonin 5-HT1A receptors might control the output of cortical glutamatergic neurons in rat cingulate cortex. Brain Res. 2003; 989(1): 42–51.
17. Wedzony K, et al. Single doses of MK-801, a non-competitive antagonist of NMDA receptors, increase the number of 5-HT1A serotonin receptors in the rat brain. Brain Res. 1997; 756(1-2): 84–91.
18. Calcagno E, Carli M, Invernizzi RW. The 5-HT(1A) receptor agonist 8-OH-DPAT prevents prefrontocortical glutamate and serotonin release in response to blockade of cortical NMDA receptors. J Neurochem. 2006; 96(3): 853–60.
19. Invernizzi RW, Cervo L, Samanin R. 8-Hydroxy-2-(di-n-propylamino) tetralin, a selective serotonin1A receptor agonist, blocks haloperidol-induced catalepsy by an action on raphe nuclei medianus and dorsalis. Neuropharmacology. 1988; 27(5): 515–8.
20. Kleven MS, et al. Novel antipsychotic agents with 5-HT(1A) agonist properties: role of 5-HT(1A) receptor activation in attenuation of catalepsy induction in rats. Neuropharmacology. 2005; 49(2): 135–43.
21. Prinssen EP, Colpaert FC, Koek W. 5-HT1A receptor activation and anti-cataleptic effects: high-efficacy agonists maximally inhibit haloperidol-induced catalepsy. Eur J Pharmacol. 2002; 453(2-3): 217–21.
22. Heusler P, et al. Antipsychotics differ in their ability to internalise human dopamine D2S and human serotonin 5-HT1A receptors in HEK293 cells. Eur J Pharmacol. 2008; 581(1-2): 37–46.
23. Newman-Tancredi A, et al. Novel antipsychotics activate recombinant human and native rat serotonin 5-HT1A receptors: affinity, efficacy and potential implications for treatment of schizophrenia. Int J Neuropsychopharmacol. 2005; 8(3): 341–56.
24. Millan MJ, et al. S 16924 ((R)-2-[1-[2-(2,3-dihydro-benzo[1,4] dioxin-5-yloxy)-ethyl]-pyrrolidin-3yl]-1-(4-fluoro-phenyl)-ethanone), a novel, potential antipsychotic with marked serotonin (5-HT)1A agonist properties: II. Functional profile in comparison to clozapine and haloperidol. J Pharmacol Exp Ther. 1998; 286(3): 1356–73.
25. Depoortere R, et al. F15063, a compound with D2/D3 antagonist, 5-HT 1A agonist and D4 partial agonist properties. III. Activity in models of cognition and negative symptoms. Br J Pharmacol. 2007; 151(2): 266–77.
26. Hagiwara H, et al. Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the antipsychotic drug perospirone: role of serotonin 5-HT1A receptors. Eur Neuropsychopharmacol. 2008; 18(6): 448–54.
27. Nagai T, et al. Aripiprazole ameliorates phencyclidine-induced impairment of recognition memory through dopamine D1 and serotonin 5-HT1A receptors. Psychopharmacology. 2009; 202(1-3): 315–28.
28. Meltzer HY, Sumiyoshi T. Does stimulation of 5-HT(1A) receptors improve cognition in schizophrenia? Behav Brain Res. 2008; 195(1): 98–102.
29. Lawrence AJ. Optimisation of anti-psychotic therapeutics: a balancing act? Br J Pharmacol. 2007; 151(2): 161–2.

30. Bruins Slot LA, Kleven MS, Newman-Tancredi A. Effects of novel antipsychotics with mixed D(2) antagonist/5-HT(1A) agonist properties on PCP-induced social interaction deficits in the rat. Neuropharmacology. 2005; 49(7): 996–1006.
31. Benkert O, Muller-Siecheneder F, Wetzel H. Dopamine agonists in schizophrenia: a review. Eur Neuropsychopharmacol. 1995; 5 Suppl: 43–53.
32. Cuisiat S, et al. Towards a new generation of potential antipsychotic agents combining D2 and 5-HT1A receptor activities. J Med Chem. 2007; 50(4): 865–76.
33. Assie MB, et al. F15063, a potential antipsychotic with dopamine D2/D3 receptor antagonist, 5-HT1A receptor agonist and dopamine D4 receptor partial agonist properties: influence on neuronal firing and neurotransmitter release. Eur J Pharmacol. 2009; 607(1-3): 74–83.
34. Snigdha S, Neill JC. Improvement of phencyclidine-induced social behaviour deficits in rats: involvement of 5-HT1A receptors. Behav Brain Res. 2008; 191(1): 26–31.

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