Perspectives in Pharmacology

Nonhuman Primates: Translational Models for Predicting Antipsychotic-Induced Movement Disorders

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ABSTRACT
Repeated haloperidol treatment administered to nonhuman primates (NHPs) over several months or even years leads to the gradual appearance of drug-induced dystonic reactions in the orofacial region (mouth opening, tongue protrusion or retraction, bar biting) and in the whole body (writhing of the limbs and trunk, bar grasping). The propensity of antipsychotics to induce dystonia in NHPs is not correlated with their propensity to induce catalepsy in rodents, suggesting that the two types of effects are dissociated and may represent distinct aspects of the extrapyramidal symptoms induced by antipsychotics. In view of the clear homology to clinically observed phenomena, antipsychotic-induced dystonias in antipsychotic-primed NHPs would appear to possess a high degree of translational validity. These NHP phenomena could therefore serve as a useful model for predicting the occurrence of similar abnormal movements with novel substances developed for the treatment of schizophrenia or other psychotic disorders. Moreover, the NHP dystonia model could possibly serve as a biomarker for substances that will eventually cause tardive dyskinesia in patients.

Introduction
A major side effect of first-generation antipsychotics (chlorpromazine, haloperidol, fluphenazine) is the occurrence of extrapyramidal symptoms (EPS) that occur either early in the course of treatment (Parkinsonism, akathisia, acute dystonia) or at a much later stage (tardive dyskinesia). The early phenomena are a direct consequence of drug administration, decrease when drug administration ceases, and can be attenuated by anticholinergic agents. Tardive dyskinesia occurs during sustained antipsychotic therapy or on reduction or cessation of treatment, can be suppressed by reinstatement of treatment, and is generally exacerbated by anticholinergic agents. For a more comprehensive review of EPS induced by antipsychotics in patients, see Casey (2004). EPS were initially considered to be intrinsic to antipsychotic action (Haase, 1978). The discovery of the antipsychotic activity of clozapine challenged this notion because clozapine was shown to be an effective antipsychotic without inducing EPS (Hippius, 1989; Meltzer, 1989).

Since the discovery of clozapine, the pharmaceutical industry has invested heavily in the research for novel substances, frequently termed atypical antipsychotics or second- and third-generation antipsychotics, which like clozapine were intended to be clinically more effective than first-generation antipsychotics but have a lower incidence of EPS.

The results have been generally disappointing. With the possible exception of olanzapine, none of the more recently developed antipsychotics have been shown to be superior to first-generation antipsychotics or even to attain the level of clinical efficacy achieved with clozapine (Attard and Taylor, 2012; Hartling et al., 2012). The results are also equivocal concerning the incidence of EPS in which, apart from clozapine itself, no clear improvement in EPS profiles with newer antipsychotics has been demonstrated (Bakker et al., 2011; Pringsheim et al., 2011; Gurevich et al., 2012; Haddad et al., 2012; Peluso et al., 2012). This failure is perhaps not surprising given the lack of clarity/validity of the distinction between typical versus atypical antipsychotics, or the distinction between first-, second-, and third-generation antipsychotics. Sophisticated biochemical/molecular approaches based on these classifications [e.g., Maheux et al. (2005)] may not facilitate the discovery of more efficacious or safer antipsychotic treatments unless the clinical endpoints are taken more clearly into account. Indeed, one can ask whether classifying antipsychotics in this manner really represents an adequate way of distinguishing between the clinical effects of the numerous available antipsychotics, even those of the first generation.

The quest for more efficacious antipsychotic drugs with a lower incidence of EPS therefore remains highly topical and
represents an unmet research need in the discovery of novel treatments not only for schizophrenia, but also for other disorders in which psychosis constitutes an important feature, such as Huntington’s disease (Alpay and Koroshetz, 2006; Johnston, 2011).

This article reviews EPS models in rodents and nonhuman primates (NHPs). Although there are clear differences between early EPS (Parkinsonism, akathisia, acute dystonia) and tardive dyskinesia, the literature and experimental data reviewed below suggest that even the early EPS phenomena can be dissociated in animal models and likely clinically as well. For example, there is an absence of correlation between the propensity of novel substances to induce catalepsy in rats, a putative predictor of antipsychotic-induced Parkinsonism in patients, and their propensity to induce dystonic signs in NHPs, a highly probable predictor of antipsychotic-induced acute dystonia in patients (Table 1). We argue that the antipsychotic-induced dystonia model in NHPs has higher translational validity to humans than any available procedure in rodents (Porsolt, 2013), and should thereby be best able to predict the occurrence of at least this type of antipsychotic-induced movement disorder in humans. Moreover, this review suggests that data obtained in the NHP dystonia model could possibly serve as a biomarker for substances that will eventually cause tardive dyskinesia in patients.

**Animal Models of Antipsychotic-Induced Parkinsonism**

Parkinsonism, both antipsychotic-induced and idiopathic, is characterized in patients by a triad of symptoms: tremor in the extremities, rigidity, and akinesia [see Casey (2004) for a review]. None of these phenomena can be clearly identified in rodent behavior. On the other hand, most first-generation antipsychotics, but not clozapine or several second-generation antipsychotics (remoxipride,quetiapine, or aripiprazole), induce catalepsy in rodents as indicated by the time an animal will remain in an unusual position imposed by the experimenter (Arnt and Skarsfeldt, 1998). Although catalepsy bears only a superficial resemblance to Parkinsonism, thereby decreasing its translational validity, available data suggest that catalepsy in rodents represents a reasonable predictor of antipsychotic-induced Parkinsonism in patients (Castagné et al., 2009; Porsolt et al., 2010).

Antipsychotics generally reduce locomotor activity in animals. This type of effect in NHPs includes static posture and crouching, which have been assimilated to Parkinsonian-like akinesia (Auclair et al., 2009). The muscular rigidity observed in NHPs after antipsychotic treatment has also been assimilated to that observed in patients (Casey, 1996). The literature is less clear concerning tremor. Although some reports suggest the occurrence of antipsychotic-induced tremor in some species of NHP, as described for example by Lieberman and Neale (1980) in squirrel monkeys or by Peacock et al. (1999) in cebus monkeys, no Parkinsonian-like tremors were observed in rhesus monkeys (Porsolt and Jalfre, 1981) and none were clearly described by Auclair et al. (2009) in cynomolgus monkeys. In most of the publications concerning cebus monkeys, the EPS-like signs observed were grouped under the heading of dystonia (see below).

**Animal Models of Antipsychotic-Induced Akathisia**

Akathisia, which involves subjective feelings of unrest accompanied by signs of motor agitation [see Casey (2004) for a review], does not appear to have any clear parallel in rodent or NHP behavior. The major problem is that most, if not all, antipsychotics do not induce behavioral agitation but in fact decrease spontaneous activity. It has been suggested that antipsychotic-induced increases in defecation in rats parallel the incidence of akathisia in patients with the same drugs (Sachdev and Brüne, 2000). On the other hand, this type of observation does not take into account the effects of these substances on gastrointestinal transit. More importantly, enhanced defecation in rats has no obvious translational link to humans.

**Animal Models of Antipsychotic-Induced Dystonia**

Acute dystonia is characterized by involuntary muscle spasms, accompanied by briefly sustained or fixed abnormal postures including bizarre positions of the limbs and trunk, oculogyric crises, tongue protrusion, and torticollis [see Casey (2004) for a review].

Early-onset vacuous chewing movements have been reported in rats after repeated treatment with certain antipsychotics (haloperidol, cis-flupenthixol, trifluoperazine, fluphenazine, and clozapine) that could be dissociated from both catalepsy and tardive dyskinesia. However, Park and colleagues (2009) reported that antipsychotic-induced increases in defecation in rats parallel the incidence of akathisia in patients with the same drugs (Sachdev and Brüne, 2000). On the other hand, this type of observation does not take into account the effects of these substances on gastrointestinal transit. More importantly, enhanced defecation in rats has no obvious translational link to humans.

### Table 1

Effects of different antipsychotics on apomorphine antagonism versus catalepsy in the rat and apomorphine antagonism versus dystonias in the rhesus monkey

<table>
<thead>
<tr>
<th>Test Substance</th>
<th>Rat Minimum Effective Dose</th>
<th>Rhesus Monkey Minimum Effective Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apomorphine Antagonism</td>
<td>Catalepsy</td>
</tr>
<tr>
<td></td>
<td>mg/kg i.p.</td>
<td>mg/kg i.m.</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.31</td>
<td>3.3</td>
</tr>
<tr>
<td>Clozapine</td>
<td>2</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>9.7</td>
<td>15.4</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>Sulpapride</td>
<td>20.4</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Tropapride</td>
<td>0.44</td>
<td>27.1</td>
</tr>
</tbody>
</table>

*Unpublished data from Delalande (now Sanofi).

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**Data from Porsolt and Jalfre (1981), Porsolt et al. (1982), Jalfre et al. (1983), and Castagné et al. (2009).**
sulpiride), but not clozapine. They are attenuated by centrally active, but not peripherally active, anticholinergic agents. These data parallel the clinical profiles of these substances (Stewart et al., 1988; Waddington, 1990; Egan et al., 1996). Vacuous chewing in rodents appears, nonetheless, remote from the above-described clinical phenomena.

More encouraging data have been obtained in NHPs. Dystonia-like phenomena have been observed in a wide range of NHP species, including squirrel monkeys (Weiss et al., 1977; Liebman and Neale, 1980, Neale et al., 1982), cebus monkeys (Gunne and Bárány, 1976, 1979; Häggström, 1984; Gerlach and Casey, 1990; Casey, 1996; Peacock and Gerlach, 1999; Peacock et al., 1999; Casey et al., 2001; Shibig et al., 2003; Andersen et al., 2003; Brandt-Christensen et al., 2006; Madsen et al., 2011), rhesus monkeys (Porsolt and Jalfre, 1981; Porsolt, 1984), cynomolgus monkeys (Gunne and Bárány, 1976; Auclair et al., 2009), green monkeys (Casey et al., 1980), marmosets (Fukuoka et al., 1997), and baboons (Meldrum et al., 1977).

Of particular interest is the recent article by Auclair et al. (2009) that describes the evaluation of a whole range of first-, second-, and third-generation antipsychotics on a variety of symptoms in the cynomolgus monkey. Among the various signs observed were static posture (halting and then pausing before initiating another movement, crouching) and the occurrence of unusual positions or movements (persistent limb extension, twisted torso, tongue protrusion, biting metal grids, or perseverative pushing of the head or body against cage walls). These two types of phenomena would appear to parallel drug-induced Parkinsonism and acute dystonia, respectively. Clearly differential profiles were observed with the drugs investigated. Haloperidol induced unusual movements but surprisingly did not cause any static posture/crouching (see below). Risperidone and olanzapine induced both types of symptoms, whereas only increased static posture/crouching was observed with clozapine. Two more recent substances, quetiapine and aripiprazole, had no effects on the investigated parameters, whereas the substituted benzamide remoxipride induced only abnormal movements and ziprasidone induced only static posture/crouching. If it can be assumed that static posture/crouching could also reflect the hypolocomotor component of drug action, these differential profiles would appear to correspond to the known clinical profiles of these substances (Gerlach, 2002) with the possible exception of haloperidol. Some of these data in cynomolgus monkeys have been replicated in our own laboratory (Hayes et al., 2012; Porsolt, 2013). In contrast to the study by Auclair et al. (2009), we observed both static posture/crouching and unusual positions/movements with haloperidol, a result that is more in accordance with haloperidol’s clinical effects.

The above experiments were carried out in monkeys with little or no prior experience with antipsychotics (nonprimed). In experiments performed many years ago, rhesus monkeys were repeatedly administered different antipsychotics over extended periods (months and even years) (Porsolt and Jalfre, 1981; Porsolt, 1984). In contrast to the marked sedation and catalepsy observed during the early phases of antipsychotic treatment, several of the monkeys gradually developed dystonias in the orofacial region (mouth opening, tongue protrusion or retraction, bar biting) and in the whole body (writhing of the limbs and trunk, bar grasping). The symptoms occurred with two first-generation antipsychotics (haloperidol, fluphenazine) but not with two second-generation antipsychotics (chlorpromazine, thioridazine) or clozapine at doses that were clearly behaviorally active. The dystonias could be attenuated by anticholinergic treatment. Clinical psychiatrists invited to observe these animals confirmed that the behavioral symptoms corresponded closely to what they had seen in patients. Moreover, the differential profiles observed in the monkeys corresponded to the then-described clinical profiles of these drugs (Deniker et al., 1980).

A remarkable feature of antipsychotic-induced dystonia in rhesus monkeys was that the sensitivity of antipsychotic-primed rhesus to haloperidol remained unaltered even when the monkeys were left without exposure to antipsychotic treatment of periods of up to 1 year (Porsolt, 1984). Similarly, when the same cebus monkeys were used repeatedly [e.g., by Gunne and Bárány (1976, 1979), Gerlach and Casey (1990), or Casey (1996)], there were no reports of tolerance. In contrast, Neale et al. (1982) reported that squirrel monkeys showed clear signs of tolerance to these effects after repeated treatment. There are, however, too few published data to determine whether the occurrence of tolerance depends on the type of NHP species used.

Catalepsy in Rats versus Dystonia in NHPs

Because catalepsy in rats has traditionally been the behavioral sign taken to evaluate the EPS liability of putative antipsychotics during the drug discovery phase, it is instructive to compare the cataleptogenic potential of different substances in rats with their capacity to induce dystonias in rhesus monkeys. Table 1 shows results obtained many years ago with the first-generation antipsychotics haloperidol, chlorpromazine, and thioridazine, the atypical antipsychotic clozapine, and the substituted benzamides sulotropride and tropapride [(exo)-2,3 dimethoxy-N-[8-(phenylmethyl)-8-aza-bicyclo [3.2.1] oct-3-yl] (MD 790501), the latter being an experimental substance that was subsequently dropped from development.

The data indicate that haloperidol antagonized apomorphine in both species and induced clear catalepsy in rats and dystonias in monkeys. Clozapine weakly antagonized apomorphine in the two species but induced neither catalepsy nor dystonias. The two phenothiazines (chlorpromazine, thioridazine) were clearly cataleptogenic in rats at doses close to those that antagonized apomorphine but induced no signs of dystonia in monkeys at doses well above those that antagonized apomorphine. The two substituted benzamides (sulotropride, tropapride) were only weakly cataleptogenic in rats, but induced clear dystonias in monkeys at doses close to those that antagonized apomorphine. These data suggest a dissociation between two indices of EPS as assessed in the two species in a manner that would appear to reflect the clinical profiles of the drugs investigated, in which Parkinsonism is associated with most phenothiazines but less so with benzamides, dystonias are associated with most benzamides but not with all phenothiazines, and haloperidol clearly induces both types of EPS, whereas clozapine induces neither Parkinsonism nor dystonia (Deniker et al., 1980; Gerlach, 2002).
Animal Models of Antipsychotic-Induced Tardive Dyskinesia

Tardive dyskinesia is a syndrome of involuntary abnormal movements that occur during sustained antipsychotic therapy or on reduction or cessation of treatment. The movements include chewing, tongue protrusion, lip smacking, puckering, paroxysms of rapid eye blinking, and choreoathetoid movements of the limbs and trunk. Some of the features, such as orofacial movements, may resemble or even occur simultaneously with acute dystonia, making differential diagnosis difficult. Tardive dyskinesia is characterized by the fact that once manifest, it appears irreversible. It can be reduced by reinstatement of antipsychotic treatment but appears to be exacerbated by anticholinergic treatment [see Casey (2004) for a review].

Vacuous chewing movements have been observed in rats after cessation of long-term haloperidol administration for periods of up to 1 year (Waddington, 1990; Egan et al., 1996; Turrone et al., 2002). On the hypothesis that long-term antipsychotic treatment induces supersensitivity of postsynaptic dopamine (DA) receptors, some authors described an increased behavioral response to DA agonists after long-term neuroleptic treatment (Clow et al., 1979), whereas others related the phenomena to continued DA D2 receptor occupancy (Turrone et al., 2002). However, in contrast to the clinical syndrome, the vacuous chewing movements or the increased response to DA agonists in the rodent disappear spontaneously over a few days or weeks (Clow et al., 1979; Waddington, 1990; Egan et al., 1996; Turrone et al., 2002).

More convincing signs of tardive dyskinesia have been shown in NHPs. These studies were recently reviewed by Blanchet et al. (2012). An early publication by Gunne and Bárány (1976) reported the occurrence of dyskinetic movements persisting for up to 6 years in two of three cebus monkeys after cessation of 3 or 12 months of once-daily oral treatment with haloperidol (doses escalating from 0.5 to 8 mg/kg per day). All three cebus monkeys showed signs of acute dystonia after each haloperidol administration as did two cynomolgus monkeys, also included in the study, which did not develop tardive dyskinesia. The anticholinergic biperiden reduced the dystonia but reinstated the signs of tardive dyskinesia. In a later study with the same two cebus monkeys, the same authors reported that chlorpromazine, thioridazine, clozapine, melperone, and fluphenazine attenuated the signs of tardive dyskinesia (Gunne and Bárány, 1979). In subsequent studies, the same group of authors showed that acute treatment with two putative antipsychotics, the DA autoreceptor agonist 3-(3-hydroxyphenyl)-N-(1-propyl) piperidine (3-PPP) (Häggström et al., 1983) and the benzamide sulpiride (Häggström, 1984), suppressed these signs. Other findings by these authors suggested the effectiveness of the GABA agonist 4,5,6,7-tetrahydroisoxazolo[5,4-c]epyrindine-3-ol (THIP) (Andersson and Häggström, 1988). Similar findings were reported for 3-PPP in cebus monkeys in which tardive dyskinesia was induced by long-term treatment with fluphenazine enanthate (Kovacic et al., 1988). Another study included a total of 24 cebus monkeys that had been previously primed with antipsychotics for periods of up to 2 years (Casey, 1996). Among these animals, there were seven that could be considered very aged (23–29 years), four of which showed signs of spontaneous tongue protrusions in the absence of antipsychotic treatment. These phenomena seemed assimilable to tardive dyskinesia, which is clearly more prevalent in older human populations (Jeste et al., 1995). The spontaneous tongue protrusions were attenuated by acute administration of sertindole, risperidone, and haloperidol.

Conclusions

The above-reviewed findings suggest that catalepsy in rodents may represent a good predictor for the propensity of novel substances to induce Parkinsonism in patients. On the other hand, antipsychotic-induced Parkinsonism in NHPs is not a clear occurrence. There are no convincing models of akathisia in rodents or in NHPs.

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With regard to tardive dyskinesia in NHPs, the available data suggest their translational validity. Such models, however, do not lend themselves readily for drug development purposes because they are extremely time-consuming and the numbers of animals eventually manifesting signs of tardive dyskinesia appear limited in relation to the numbers of animals initially included in the programs.

The situation is different for NHP models of dystonia. Although chronic antipsychotic priming appears necessary to induce reliable and clearly identifiable dystonic signs, once established in rhesus or cebus monkeys, the phenomena appear stable and can be reinvoked on demand even in animals that have not received antipsychotics for longer periods. Available findings suggest that antipsychotic-induced dystonia in NHPs represents a direct homology of the acute dystonias observed with the same drugs in patients. Moreover, although antipsychotic-induced dystonia is distinct from tardive dyskinesia, it seems plausible that the capacity to induce dystonia in NHPs could possibly serve as a biomarker for substances that will eventually cause tardive dyskinesia in patients after long-term treatment.

Despite the number of years since most of the work on antipsychotic-induced dystonias in NHPs was performed, recent clinical and preclinical publications suggest that such disorders remain high on the antipsychotic research agenda. It is suggested that the NHP dystonia model would be of interest to any pharmaceutical company, research foundation, or public agency wishing to develop new treatments for schizophrenia or other psychotic disorders, whether for positive symptoms, negative symptoms, or both. The techniques do not depend on any assumptions concerning the neuroanatomical substrates of acute or tardive EPS (nigrostriatal, limbic, or cortical pathways) or on any notions concerning the neurochemical mechanisms whereby antipsychotic agents exert their therapeutic effects (antagonism of DA D1 or D2 receptors, modulation of noradrenergic and/or serotonergic 5-HT2 transmission). On the contrary, they concern evaluation of behavioral phenomena in NHPs that are clearly homologous to symptoms observed in human patients and thereby possess a high degree of translational validity.

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