BEHAVIORAL INDICES IN ANTIPSYCHOTIC DRUG DISCOVERY

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ABSTRACT

Schizophrenia is characterized by three major symptom classes: positive symptoms, negative symptoms and cognitive deficits. Classical antipsychotics (phenothiazines, thioxanthines, butyrophonones) are effective against positive symptoms but induce major side-effects, in particular extrapyramidal symptoms (EPS). The discovery of clozapine, which does not induce EPS and is thought effective against all three classes of symptom, has driven research for novel antipsychotics with a wider activity spectrum and lower EPS liability. To increase predictiveness, current efforts aim to develop translational models, where direct parallels can be drawn between the processes studied in animals and in man. The present paper reviews existing procedures in animals for their ability to predict compound efficacy and EPS liability in relation to their translational validity. Rodent models of positive symptoms include procedures related to dysfunction in central dopamine (DA), glutamatergic (N-methyl-D-aspartate, NMDA) and serotonin (5-hydroxytryptamine, 5-HT) neurotransmission. Procedures for evaluating negative symptoms include rodent models of anhedonia, affective flattening and diminished social interaction. Cognitive deficits can be assessed in rodent models of attention (prepulse inhibition) and of learning/memory (object and social recognition, Morris water maze and operant delayed alternation). The relevance of the conditioned avoidance response (CAR) is also discussed. A final section reviews procedures for assessing EPS liability, in particular parkinsonism (catalepsy in rodents), acute dystonia (purposeless chewing in rodents, dystonia in monkeys), akathisia (defecation in rodents) and tardive dyskinesia (long-term antipsychotic treatment in rodents and monkeys). It is concluded that, with notable exceptions (attention, learning /memory, EPS liability), current predictive models for antipsychotics fall short of clear translational validity.
INTRODUCTION

Schizophrenia is characterized by three major classes of symptom: positive symptoms (delusions, hallucinations, bizarre speech and thought, paranoia), negative symptoms (anhedonia, affective flattening, impoverishment of speech and thought, social withdrawal) and cognitive deficits (impairments in attention, learning and memory).

Despite intensive research, the etiology of schizophrenia remains far from understood. Most hypotheses have evolved from the actions of drugs in clinical use or as a result of similarities between the symptoms of schizophrenia and the effects of certain drugs of abuse, notably the indirect dopamine (DA) receptor agonist amphetamine, the glutamate receptor antagonist phencyclidine (PCP) and the 5-HT2 receptor agonist lysergic acid diethylamide (LSD). The major hypothesis has centered around central DA neurotransmission because all classical antipsychotics (phenothiazines, thioxanthenes, butyrophenones) have as principal mechanism the blockade of central DA receptors (Carlsson, 1988).

The introduction of the atypical antipsychotic clozapine in the early 1970s and its revival in the late 1980s (Meltzer, 1989) has stimulated the search for other hypotheses because clozapine is clearly active as an antipsychotic, does not induce EPS, and has been claimed effective even against negative symptoms and cognitive deficits (Meltzer, 1989). Clozapine is less potent than classical antipsychotics in blocking central D2 receptors but has affinity for a wide range of other receptors including D1, D4, 5-HT2A, 5-HT6, α1, H1 and M1 (Jones, et al., 2008). Discovery strategies for novel antipsychotics for the past 30 years have therefore been dominated by attempts to reproduce the advantages of clozapine.

Validity is an essential requirement for any animal procedure used in drug discovery and traditionally has been divided into predictive validity, face validity and construct validity (Willner, 1991). For predictive validity, the procedure must be capable of predicting therapeutic effects in humans. For face validity, the procedure must mimic clinical symptomatology. For construct validity, the procedure must reproduce etiological factors of the disease. Drug discovery programs aim principally to achieve predictive validity. Important in this respect are the notions of sensitivity (absence of false negatives) and selectivity (absence of false positives). Decreasing the number of false positives would appear to represent the major challenge for the discovery of antipsychotics.
In recent years, psychopharmacologists have made considerable efforts to develop translational procedures that seek a direct parallelism between the dependent measures used in animals and in human disease, with the aim to increase the pertinence of the animal procedures employed and thereby improve predictions of therapeutic efficacy (Markou, et al., 2009). The prevalence of the translational approach has been highlighted by two recent research initiatives, the NIMH-funded MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) battery and the European Commission initiative NEWMeds (Novel Methods Leading to New Medications in Depression and Schizophrenia).

The present paper will review currently used behavioral procedures in animals for their translational validity and their capacity to predict clinical efficacy and side-effect liability, concentrating on the three primary symptom classes in schizophrenia (positive symptoms, negative symptoms, cognitive deficits) and the principal side-effects of antipsychotic drug treatment (EPS). A more detailed treatment can be found in Castagné, et al. (2009).

PROCEDURES FOR EVALUATING POSITIVE SYMPTOMS

Agitation, hallucinations, delusions and paranoia represent the main positive symptoms described in schizophrenic patients. Although delusions, paranoia and hallucinations are difficult to model in rodents, agitation is more easily amenable to behavioral testing. Indeed the majority of tests relevant to agitation use different reagents to reproduce a behavioral abnormality assumed present in psychotic patients (Geyer and Ellenbroek, 2003). Although caution must be used in drawing parallels between animal and human behavior, stereotyped behavior in animals has been generally accepted as modelling the stereotyped behavior observed in psychotic patients, whereas hyperactivity would appear to translate more closely psychotic agitation.

Hyperactivity and stereotypies induced by DA agonists

Direct and indirect DA agonists, such as apomorphine, cocaine and amphetamine, induce hyperactivity at moderate doses and stereotypies at higher doses when administered to rodents. This suggests a certain translational validity since direct or indirect activation of DA receptors can exacerbate florid psychotic symptoms in schizophrenic patients. Activation of dopamine D2 receptors located in the nucleus accumbens induces hyperactivity, whereas stereotypies seem to involve D2
receptors in the striatum (Costall, et al., 1982). Although all classical antipsychotics inhibit amphetamine-induced locomotion and stereotypies, clozapine has been found less effective against stereotypies (O’Neill and Shaw, 1999; Castagné, et al., 2009). This finding could reflect clozapine’s supposed preferential action on D₂ receptors in the limbic system (Leite, et al., 2008). Because EPS are thought to result from decreased DA activity in the striatum, a preferential action of a novel substance against DA-agonist-induced hyperactivity might thus represent a first indicator of a lower propensity to induce EPS in patients.

Behavioral tests using DA-agonists would appear exclusively linked to the DA hypothesis. Nonetheless, other potential antipsychotics with minimal affinity for DA receptors, for example the 5-HT₂ antagonists MDL 100-907 (R-(+)-a-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol) and WAY 163909 (7bR,10aR)-1,2,3,4,8,9,10,1a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1hi]indole), and diverse client substances we have evaluated in our own laboratory, also antagonize DA-agonist effects suggesting that these procedures are not exclusive to the DA system. On the other hand, substances such as lithium and diverse substances used for mood control also attenuate DA agonist-induced hyperactivity but are devoid of antipsychotic activity (false positives).

Hyperactivity and stereotypies induced by NMDA antagonists

Similarly to DA agonists, stereotypies and hyperactivity are induced in rodents by non-competitive antagonists acting at the ion channel associated with the NMDA subtype of the glutamate receptor such as phencyclidine (PCP), ketamine and dizocilpine (MK-801). PCP and ketamine are known to induce psychotic hallucinations and delusions in man (Coyle, et al., 2003).

NMDA antagonist-induced hyperactivity and stereotypies in the rat can be reversed by both classical and atypical antipsychotics. Atypical antipsychotics, such as clozapine, aripiprazole and olanzapine, have been reported more effective than classical antipsychotics (Leite, et al., 2008). The situation is thus different from that observed with DA agonists. On the other hand, the doses required to antagonize NMDA antagonist-induced stereotypies are sometimes considerably higher than those antagonizing DA agonist effects (Castagné, et al., 2009). Interestingly, the efficacy of antipsychotics (haloperidol, clozapine, olanzapine) against PCP-induced hyperactivity has been reported to become
more robust after repeated treatment and testing, whereas their efficacy against amphetamine-induced hyperactivity tends to wane (Sun, et al., 2009).

Repeated administration studies of potential antipsychotics against NMDA antagonists might therefore represent a promising approach for the use of NMDA antagonist models for the prediction of antipsychotic efficacy.

Behaviors induced by 5-HT agonists

Hallucinogens acting on 5-HT receptors, e.g., lysergic acid diethylamide (LSD), psilocybin and mescaline, induce visual hallucinations in humans and cause characteristic behavioral signs in animals suggesting an animal marker for 5-HT agonist-induced hallucinations in humans. For example, administration of mescaline to specific strains of mice induces episodes of paroxysmic scratching. Mescaline-induced scratching is inhibited by classical and atypical antipsychotics, in particular those which directly or indirectly antagonize 5-HT$_2$ receptors (Cook, et al., 1992; Castagné, et al., 2009).

On the other hand, a wide range of indirectly or directly acting 5-HT receptor agonists without known hallucinogenic properties also induce clear behavioral effects in rodents, for example the forepaw treading, head twitches and lower lip retraction induced by 5-HT$_{1A}$ agonists, or the head-twitches and wet-dog shakes induced by the 5-HT$_2$ agonist (+/-)-2,5-dimethoxy-4-iodoamphetamine (DOI). These effects are also clearly antagonized by numerous 5-HT antagonists including antipsychotics with affinity for 5-HT$_2$ receptors (Gardell, et al., 2007).

It is not therefore clearly established that tests using 5-HT agonists are predictors of antipsychotic activity. Indeed, they might reflect more the anti-5-HT activity of some of the substances tested. Furthermore, whereas 5-HT agonist-induced hallucinations in man are primarily visual, hallucinations occurring in schizophrenia are usually auditory.

PROCEDURES FOR EVALUATING NEGATIVE SYMPTOMS

Negative symptoms include anhedonia, emotional blunting, affective flattening, impoverishment of speech and thought, and social withdrawal. Even in clinical terms these symptoms are more difficult to characterize than the more florid positive symptoms discussed above and, furthermore, are not specific to schizophrenia. Some of them (impoverished speech and thought) are uniquely human and
therefore not amenable to modelling in animals. Other symptoms lend themselves more readily to animal testing and are discussed below.

**Anhedonia**

Anhedonia refers to a decrease in the capacity to feel pleasure and, in addition to representing a negative symptom in schizophrenia, is a core symptom of depression. Anhedonia in animals is usually assessed through measures of sucrose consumption or preference.

In normal rats, classical and atypical antipsychotics decrease sucrose consumption and preference (Muscat and Willner, 1989) suggesting that given alone they induce anhedonia. In contrast, the atypical antipsychotics olanzapine and quetiapine, but not the classical agent haloperidol, reverse stress-induced anhedonia (Orsetti, et al., 2007), suggesting the possible relevance of this procedure for assessing novel antipsychotics.

**Affective flattening**

Affective flattening refers to apathy in various situations, including those involving stress. Although there is no animal model for affective flattening, the immobility induced by forced swimming has been suggested to reflect a lowered affective state in the rodent (Porsolt, et al., 1977). PCP increases immobility in the forced swim test in the mouse, particularly after repeated treatment (Corbett, et al., 1999). PCP-enhanced immobility is attenuated by the atypical antipsychotics clozapine, risperidone, olanzapine and quetiapine, but not by the classical antipsychotics haloperidol, pimozide or chlorpromazine (Nagai, et al., 2003). The above data suggest that enhanced immobility in the forced swim test induced by PCP might represent a promising model of affective flattening in schizophrenia. In terms of the behaviors involved, forced swimming does not present any clear translational characteristics.

**Social interaction**

Social interaction in the rat has been widely used as a procedure to evaluate anxiety, but has also been proposed as a model for antipsychotic activity using acute or repeated administration of NMDA antagonists to decrease social investigation (Sams-Dodd, 1999).

Classical antipsychotics such as haloperidol do not reverse acute NMDA antagonist-induced deficits in social investigation (Boulay, et al., 2004). Conflicting data exist for clozapine, which is either inactive (Boulay, et al., 2004) or reverses social investigation deficits (Becker and Grecksch, 2004).
Repeated administration of PCP or MK-801 also decreases social investigation in the rat (Geyer and Ellenbroek, 2003). Acute treatment with the atypical agents ziprasidone and aripiprazole has been reported to reverse sub-chronic PCP-induced deficits in social investigation, whereas similar treatment with haloperidol or clozapine was without effect (Snigdha and Neill, 2008).

The fact that social interaction is clearly diminished in schizophrenia and by NMDA glutamate antagonists in rodents, and improved in the latter by some atypical antipsychotics, suggests that NMDA antagonist-reduced social interaction in rodents might represent an interesting translational model for evaluating novel antipsychotics.
PROCEDURES FOR EVALUATING COGNITIVE DEFICITS

Cognitive deficits in schizophrenic patients encompass attentional processes and memory/learning. Both aspects can be investigated in animal models with varying degrees of translational validity.

**Attentional processes**

Cognitive function relies on adequate processes for the treatment of incoming information. The main behavioral paradigm used in pre-clinical and clinical research is prepulse inhibition (PPI) (Geyer and Ellenbroek, 2003). PPI refers to the decrease in startle reaction to a sudden stimulus by pre-exposure to a weak non-startling stimulus. The weak and the strong stimuli are termed prepulse and pulse, respectively. PPI is observed in normal humans and is considered an index of sensori-motor gating, i.e. the capacity to filter incoming information. Schizophrenia and several other brain disorders involve PPI deficits that can be modelled in animals with clear translational validity.

The DA agonists, apomorphine and amphetamine are widely used to disrupt PPI in the rat. Apomorphine-induced PPI deficits can be reversed by haloperidol (Auclair, et al., 2006). Some reports describe reversal of apomorphine-induced PPI deficits by clozapine although its effects are often limited to a narrow dose-range (Martin, et al., 2003). Amphetamine-induced PPI deficits are reversed by classical and some atypical antipsychotics (Marquis, et al., 2007). Nonetheless, conflicting data exist regarding clozapine (Martin, et al., 2003).

Antagonists of NMDA glutamate receptors also disrupt PPI in the rat (Martinez, et al., 2000). PCP-induced PPI deficits are resistant to classical and atypical antipsychotics (Pouzet, et al., 2002) although reversal by clozapine has been reported (Suemaru, et al., 2004). Similarly, deficits in PPI induced by MK-801 are resistant to classical and atypical antipsychotics (Bast, et al., 2000), although positive effects have been described for olanzapine and clozapine (see Castagné et al., 2009).

The demonstration of PPI in humans and rodents and the fact that PPI is impaired in schizophrenics and can be disrupted by various means in normal humans and rodents suggest that PPI possesses clear translational validity. On the other hand, the data obtained so far with classical and atypical antipsychotics, although sometimes encouraging, have not yet confirmed its utility for predicting antipsychotic activity.
Learning and memory

Learning and memory impairments are present in schizophrenic patients but are difficult to differentiate from symptoms occurring in other CNS pathologies. Ketamine, in addition to its hallucinogenic properties, induces clear learning/memory deficits in humans (Morgan and Curran, 2006) suggesting translational relevance of animal models for cognitive deficits induced by glutamate antagonists.

There are a multitude of procedures in animals for investigating learning and memory. The following section will focus on procedures which have been used for developing drugs in schizophrenia and will not attempt to cover the whole range of available procedures in the learning and memory domain.

Object and social recognition

Object recognition is impaired in schizophrenic patients (Gabrovska, et al., 2003). This has led to the use of object recognition for evaluating substances aimed to improve cognitive deficits in schizophrenia. The object recognition test, generally performed in the rat, is a two-session procedure where recognition at the second session is indicated by a decrease in investigation of a familiar object as compared with a new object. The atypical antipsychotics clozapine and risperidone, but not haloperidol, have been reported to reverse the deficits in object recognition induced by PCP (Grayson, et al., 2007). Other substances with different molecular mechanisms intended for the treatment of cognitive deficits in schizophrenia have also been reported active against NMDA antagonist-induced deficits in object recognition (see Castagné, et al., 2009).

The social recognition test can be considered a “social version” of the object recognition test. Social recognition at the second session is indicated by a decrease in investigation of an intruder rat previously introduced as compared with a new animal. Using the social recognition test, it has been shown that increasing activity of NMDA receptors via blockade of the glycine transporter with the potential antipsychotic SSR 504734 (2-Chloro-N-(S-phenyl 2S-piperidin-2-yl methyl)-3-trifluoromethyl benzamide, monohydrochloride) attenuates the long-term deficits induced by neonatal PCP (Depoortere, et al., 2005).

Thus both object and social recognition represent memory models in rodents with potential translational validity to schizophrenia.
Morris water maze

The procedure most commonly used for evaluating test substances on learning and memory is the Morris water maze. Rats or mice are placed in a circular water tank and left to find the escape platform just beneath the surface of the water and therefore not visible to the animal. On repeated exposure to the test situation, animals learn to find the escape platform more rapidly. Acute PCP treatment impairs performance in the Morris maze in the rat, and this effect can be reversed by clozapine and other atypical antipsychotics but not by haloperidol (Didriksen, et al., 2007). Likewise, acute MK-801-induced impairment of spatial learning in the Morris maze is attenuated by the $\alpha_7$ receptor agonist SSR 180711 (4-bromophenyl 1,4diazabicyclo(3.2.é) nonane-4-carboxylate, monohydrochloride) (Pichat, et al., 2007).

These data are encouraging for the use of the Morris maze as a predictive procedure. On the other hand, the behaviors investigated possess no clear translational validity for schizophrenia.

Operant delayed alternation

Another procedure useful for evaluating drug effects on cognition, in particular short-term memory, is the operant delayed alternation procedure (delayed non-matching to sample). Previously trained rats are presented with a lever, either on the right or the left side of the food dispenser. The rat presses on the lever and the lever is withdrawn. After a delay, two levers are presented and the rat has to press on the lever opposite to that presented previously to obtain a food reward. Data obtained in our laboratory (Castagné, et al., 2009) suggest that clozapine can partially correct PCP-induced short-term memory deficits in this task, whereas haloperidol is without effect or even exacerbates them.

Although not frequently used in antipsychotic research, the delayed alternation procedure possesses clear translational validity in that analogous procedures can be employed in rodents, primates and man.

Conditioned Avoidance Behavior

Blockade of the conditioned avoidance response (CAR) has long been considered a selective and sensitive indicator of antipsychotic activity (Wadenberg and Hicks, 1999). Animals can be trained to prevent the occurrence of an aversive stimulation, usually electric shock, by performing a specific behavior.
In antipsychotic testing, three paradigms have traditionally been used, the pole jump procedure, the shuttle box procedure, both with auditory or visual warning signals (discriminated avoidance), and the Sidman continuous avoidance procedure without any warning signal (non-discriminated avoidance). The results obtained, however, have been very different. In an early publication on the effects of antipsychotics on the CAR using the pole jump procedure (Cook and Weidley, 1957), the authors reported a specific blockade of avoidance responding (response to the warning signal) at doses which were without effect on escape responding (response to the shock). These early findings have led to the persistent belief that selective blockade of avoidance behavior is an identifier of antipsychotic activity (Wadenberg and Hicks, 1999). Unfortunately, this principle appears to be procedure-specific. In another early publication, Heise and Boff (1962), showed that neuroleptics blocked escape behavior in a Sidman procedure at doses very close to those blocking the CAR whereas with benzodiazepines the dose-ratio between escape and avoidance responding was considerably larger, i.e. the opposite of what was described by Cook and Weidley (1957). Using the Sidman procedure in our own laboratory, we have reported observations similar to Heise and Boff (1962) with classical antipsychotics (chlorpromazine, thioridazine, haloperidol), newer agents (sultopride, α-flupenthixol) and the atypical antipsychotic, clozapine (see Castagné, et al., 2009). All substances inhibited the CAR at doses also impairing escape behavior. Thus, although drug potency in CAR procedures is clearly correlated both with anti-DA activity and with clinical potency, the notion of selective blockade of the CAR as a specific predictor of antipsychotic efficacy is not generally true, or at best is dependent on the procedures employed. Furthermore, the CAR has no apparent translational validity.
PROCEDURES FOR EVALUATING EXTRAPYRAMIDAL SYMPTOMS

Extrapyramidal symptoms (EPS) were originally viewed as inextricably linked to the therapeutic efficacy of antipsychotics. Classical antipsychotics before clozapine induced a variety of symptoms generally grouped under the heading of EPS that occur at different times during antipsychotic treatment. Acute EPS (parkinsonism, dystonia, akathisia) develop early in the course of treatment, whereas tardive dyskinesia occurs only after prolonged antipsychotic therapy (Casey, 1993). Although generally considered to represent different forms of the same underlying drug-induced pathophysiology, EPS syndromes are clinically distinct from one another and may therefore require different animal procedures to assess the liability of novel substances to induce them.

Parkinsonism

Both antipsychotic-induced parkinsonism and idiopathic parkinsonism are characterized by a triad of symptoms: tremor, rigidity and akinesia (Casey, 1993). None of these phenomena can be clearly identified in rodent behavior. On the other hand, most classical antipsychotics but not clozapine induce catalepsy in rodents. Despite the many different procedures used to assess catalepsy, all involve measures of the time an animal will remain in an unusual position imposed by the experimenter. In contrast to the early days of antipsychotic screening, where catalepsy in rats was used as an identifier of antipsychotic activity, modern antipsychotic research seeks to demonstrate a wide difference between the doses showing potential therapeutic activity and those inducing catalepsy. Although catalepsy bears only a superficial resemblance to parkinsonism thereby decreasing its translational validity, available data suggest that catalepsy is a good predictor of antipsychotic-induced parkinsonism.

Dystonia

Antipsychotic-induced 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 torticolis (Casey, 1993). Nothing resembling the above has been reported in rodents. On the other hand, purposeless chewing movements have been reported in rats that are increased by administration of certain antipsychotics, e.g., haloperidol, cis-flupenthixol, trifluoperazine, fluphenazine and sulpiride (Stewart, et al., 1988), all
of which induce dystonia in humans. Clozapine, which is devoid of such effects in clinical use, does not alter chewing behavior even after chronic administration (Stewart, et al., 1988). Furthermore, as in patients, the antipsychotic-induced chewing movements can be attenuated by centrally acting anticholinergic agents such as scopolamine or atropine, but not by the peripherally acting anticholinergic, methylscopolamine, suggesting the central cholinergic origins of the effect. Although purposeless chewing in rats bears no resemblance to the spasmic nature of dystonia described in patients, pharmacologically the model would appear to possess predictive validity.

Clear dystonic phenomena have, however, been reported in different primate species (for details see Castagné et al., 2009). These phenomena are observed with the classical antipsychotics haloperidol and fluphenazine but not with chlorpromazine, thioridazine and in particular clozapine, thereby resembling the clinical profiles of these substances (Deniker, et al., 1980).

The data available suggest that primate dystonia, in contrast to purposeless chewing in the rat, is directly homologous to clinical observations in man, and can thus be considered to possess clear translational validity.

Akathisia

Another EPS syndrome associated with antipsychotics is akathisia, where subjective feelings of unrest are accompanied by objective signs of restlessness: pacing, rocking, marching on the spot, crossing and uncrossing the legs and other repetitive non-purposeful actions (Casey, 1993).

The motor aspect of restlessness would appear difficult to model in the sense that most antipsychotics reduce spontaneous activity. It has, however, been suggested that antipsychotic-induced increases in defecation in rats habituated to the test environment may represent a model of the subjective component of akathisia (Sachdev and Brune, 2000). Indeed haloperidol and risperidone induce more fecal boli in habituated rats than those treated with clozapine, thioridazine or chlorpromazine, which would correspond to their clinical profiles. On the other hand, drug-induced anxiety or more local drug effects on gastrointestinal transit could also explain such findings. Indeed, antipsychotic-induced defecation in habituated rats can be attenuated by treatment with anxiolytics that have limited efficacy in treating the subjective restlessness of akathisia.
Overall, the data available are too fragmentary to allow firm conclusions about the usefulness of antipsychotic-induced defecation in rodents for predicting antipsychotic-induced akathisia. In any case, rodent defecation possesses no obvious translational validity.

**Tardive dyskinesia**

Tardive dyskinesia is a syndrome of involuntary abnormal movements that occur on reduction or cessation of long-term antipsychotic therapy. The movements include chewing, tongue protrusion, lip smacking, puckering, paroxysms of rapid eye blinking and choreoathetoid movements of the limbs and trunk (Casey, 1993). Some of the features, for example the orofacial movements, may resemble or even occur simultaneously with dystonia making differential diagnosis difficult.

Animal tests for tardive dyskinesia are hindered by the fact that antipsychotic treatment must be continued over considerable periods to model the slowly developing nature of the syndrome. Thus, in the rodent, periods of up to one year of antipsychotic treatment have been required to demonstrate an increased behavioral response to DA agonists thought to result from hypersensitivity of central DA receptors (Clow, et al., 1979). In contrast to the clinical syndrome which is thought to be irreversible, these behavioral changes in the rodent disappear spontaneously within a brief period.

More convincing signs of tardive dyskinesia have been induced in monkeys. An early publication (Gunne and Barany, 1976) reported the occurrence of dyskinetic movements persisting for 1 to 6 years in cebus monkeys after cessation of years of haloperidol treatment. Acute treatment with two putative antipsychotics, the DA autoreceptor receptor agonist 3-PPP (3-(3-hydroxyphenyl)-N-(1-propyl)piperidine) and the benzamide sulpiride suppressed these signs (for details see Castagné et al., 2009).

Although the primate procedures would appear to possess translational validity, they do not lend themselves readily for drug development programs because they are extremely time-consuming. There remains the intriguing possibility that the occurrence of dystonia in man or monkeys might represent a marker for the propensity of a novel substance to induce tardive dyskinesia after prolonged therapy.
OTHER ADVERSE EFFECTS OF ANTIPSYCHOTICS

The present paper has concentrated on EPS as the major adverse side-effect of antipsychotics. This could provide a biased impression of the inconveniences of currently available drugs. Other troublesome side-effects include body weight gain, blood dyskrasias, blood pressure changes and QT prolongation. In contrast to EPS, these other side-effects are not specific to schizophrenia and can occur in conjunction with a wide range of drug treatments. Furthermore, they can all be assessed using procedures with no specific relation to models for schizophrenia. For this reason they are not reviewed here.

CONCLUSIONS

The present paper has reviewed the range of behavioral pharmacology procedures for antipsychotics in terms of their predictive and translational validity. The translational approach has received particular attention in recent years in the hope that prediction from animal data will be improved if the processes evaluated are more directly translatable from animals to man.

The major problem with schizophrenia is that the processes involved are still poorly understood. Despite considerable research (not reviewed here), genetic studies have not advanced to the point where a genetically based animal model of schizophrenia could be used for this purpose. Our understanding has to rely on hypothetical disorders in diverse brain neurotransmission systems (DA, NMDA and 5-HT inter alia). In so far as these hypothesized processes account for schizophrenia, procedures based on them will possess construct validity. The closer such procedures approximate the neurobiological substrates of schizophrenic disease or the symptomatology of schizophrenia, the more such approaches will be considered to possess translational validity. In only few instances, for example the induction of dystonia or tardive dyskinesia in monkeys, can the processes be described as homologous to those occurring in man and thereby truly translational. However these processes relate to the side-effects of antipsychotics and not to their therapeutic efficacy.

The translational approach has been more productive in other areas, in particular those related to attention and learning/memory deficits, where direct parallels can be drawn between the processes disturbed in schizophrenia and those investigated in animals. On the other hand, the major question posed by such approaches is whether the disturbances investigated are specific to schizophrenia and,
much more importantly, whether substances found active in correcting them in animals will be useful
in the treatment of schizophrenia. The jury is still out on that question.

ACKNOWLEDGEMENTS

We thank Dr. David Sanger for his invaluable comments on the manuscript and Ms Nathalie de
Cerchio-Dorczynski for expert secretarial assistance.
REFERENCES


FOOTNOTES

A: Financial support statement

All authors (RDP, PM and VC) are full-time salaried staff of Porsolt & Partners Pharmacology and do not receive financial support from any other institution.

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