Journal of Pharmacological and Toxicological Methods 68 (2013) 23–29

Contents lists available at SciVerse ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Original article

The usefulness of non-human primates in central nervous system safety pharmacology

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ARTICLE INFO

Article history:
Received 3 January 2013
Accepted 6 March 2013

Keywords:
Biting
Cognition
Delayed matching/non-matching-to-sample
Dystonia
Executive function
Extrapyramidal symptoms (EPS)
Frustration-aggression
Methods
Non-human primates (NHP)
Object retrieval

ABSTRACT

Introduction: The present paper will suggest, on the basis of experimental evidence, that several non-human primate (NHP) procedures can be uniquely useful and relevant for central nervous system (CNS) safety pharmacology purposes. **Methods and results:** Classical antipsychotics (e.g. haloperidol) but not atypical antipsychotics (e.g. clozapine), in contrast to rodents, induce behavioral signs in NHP which are clearly homologous to those observed in humans and thus have high translational value. Operant techniques (delayed matching/non-matching-to-sample) and non-operant techniques (object retrieval) can be used in NHP to assess the facilitating and impairing effects of drugs on cognition. Brain structures sub-serving these functions are closer to humans in NHP than in rodents suggesting that drug data from NHP translate better to humans. Biting into a rubber tube can be induced in squirrel monkeys by exposure to non-reinforcement (frustration). This model is close to human notions of frustration/aggression, and is ethically more acceptable than methods using shock or animal fighting. It could therefore serve as a model of drug-induced irritability with potentially high translational value. **Conclusion:** There are cogent scientific reasons for selecting NHP in CNS and other safety pharmacology areas.

1. Introduction

The following paper summarizes a talk I gave at the Safety Pharmacology Society Meeting in Phoenix (Arizona) in October 2012 on the occasion of my being presented a Distinguished Service Award by the Society. The talk and the paper uphold a position I have held since the beginning of my professional career, namely that NHP studies constitute an important step in the drug development process, particularly when a candidate quality substance is about to be tested in humans (Phase 1). Despite extensive reports justifying the use of NHP in pharmaceutical research (e.g. Weatherall, 2006), the use of NHP continues to be challenged, even by regulatory authorities which have urged that rodents be preferred unless there are specific reasons for using NHP (Anon, 2006). Often cited are the three Rs (replacement, reduction, refinement), which is a program aimed at reducing the use of animals in experimental biology (Balls et al., 1995) (www.nc3rs.org.uk).

It is not the intention of this paper to engage in polemics with the protectors of animal rights or concerning the desirability of reducing the use of animals, in particular NHP. Even without ethical issues, the cost of experiments in NHP is a driver towards selecting models in smaller animals when possible. On the other hand, the aim of safety pharmacology is to assess the risk of novel medications to humans. As a consequence, the principal justification for the selection of any experimental model should be how well the procedure or species selected can translate to the human situation.

Many arguments can be advanced which *a priori* suggest the pertinence of NHP. Perhaps the most important is pharmacokinetics which are more similar between NHP and humans than rodents (Ward & Smith, 2004a, 2004b). The affinity or selectivity of the test substance for different target sites is also likely to be closer to humans in NHP than in rodents (Weerts, Fantegrossi, & Goodwin, 2007). Drug-induced behavioral symptoms, for example sedation, drowsiness, excitation, aggressiveness or motor incoordination, are readily recognized as being similar between NHP and humans, whereas this is not the case with rodents. Finally, several biological factors show greater similarity between NHP and humans than rodents. For example, humans and NHP, both being diurnal species, have generally similar sleep/wake cycles, whereas diurnal rhythms are reversed in rodents. Another example is vomiting, which occurs both in humans and NHP but is absent in rodents.

Instead of arguing the *pros* and *cons* of NHP in safety pharmacology, I shall attempt here to demonstrate, by means of specific examples, how certain procedures in NHP translate more readily to humans and are thence more suitable than rodent procedures for safety pharmacology. The examples I shall use are limited to my own research experience

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http://dx.doi.org/10.1016/j.vascn.2013.03.004

Drug	Static posture/crouching	Unusual positions/movements
Haloperidol	-	X
Clozapine	X	-
Risperidone	X	X
Olanzapine	X	X
Remoxipride	-	X
Quetiapine	-	-
Ziprasidone	X	-
Aripiprazole	-	-

Fig. 1. Extrapyramidal symptoms (static posture/crouching, unusual positions/movements) induced in non-primed cynomolgus monkeys by diverse antipsychotics. Figure generated from data described by Auclair et al. (2009).

in neuropharmacology and do not cover the whole spectrum of possibilities.

2. Extrapyramidal symptoms (EPS) and antipsychotics

A major side effect of classical antipsychotics (chlorpromazine, haloperidol, fluphenazine) is the occurrence of extrapyramidal symptoms (EPS) which occur either early in the course of treatment (Parkinsonism, acute dystonia, akathisia) or at a much later stage (tardive dyskinesia). The early phenomena are a direct consequence of drug treatment, decrease when drug administration ceases and can be attenuated by anticholinergics. Tardive dyskinesia occurs on drug discontinuation or dose reduction after long-term treatment, can be suppressed by reinstatement of treatment and is generally exacerbated by anticholinergics - for review see Casey (1993). EPS were initially considered to be intrinsic to antipsychotic action (Haase, 1978). The discovery of clozapine challenged this notion because clozapine was shown to be an effective antipsychotic without inducing EPS (Meltzer, 1989).

We have recently reviewed animal models for EPS (Porsolt, Moser, & Castagné, 2010). While drug-induced catalepsy in rats appears to represent an adequate model of drug-induced Parkinsonism, there are few phenomena in rodents which clearly model the acute dystonia (abnormal limb and body postures, muscular spasms, orofacial dyskinesias) observed in psychotic patients. As for akathisia and tardive dyskinesia, no convincing rodent models have yet been described.

More encouraging data have been obtained in NHP. A recent publication by Auclair et al. (2009) reported a variety of symptoms induced by acute administration of antipsychotics to cynomolgus monkeys. Amongst 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 respectively drug-induced Parkinsonism and acute dystonia.

The authors reported results obtained with a variety of conventional and atypical antipsychotics. The data are summarized in Fig. 1. Clearly different profiles were observed with the different drugs investigated. Haloperidol induced unusual movements but surprisingly did not cause any static posture/crouching (see below). Risperidone and olanzapine induced both kinds of symptom, 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 hypo-locomotor component of drug action, these differential profiles would appear to correspond to the known clinical profiles of these substances with the possible exception of haloperidol.

We have replicated some of these data in cynomolgus monkeys in our own laboratories (Hayes et al., 2012) and the results for haloperidol are shown in Fig. 2. In contrast to Auclair et al. (2009), we observed both static posture/crouching and unusual positions/movements with haloperidol thereby substantiating our remarks above.

The above experiments were carried out in monkeys which had had little or no prior experience of antipsychotics. Many years ago, I conducted experiments in rhesus monkeys where the animals were repeatedly administered different antipsychotics over extended periods (months or even years) (Porsolt & Jalfre, 1981). In contrast to the marked sedation and catalepsy observed during the early phases of antipsychotic treatment, several of the monkeys gradually developed clear dystonias in the oro-facial region (mouth opening, tongue protrusion or retraction, bar biting) and in the whole body (writhing of the limbs and trunk, bar grasping). Photographs of these symptoms are shown in Fig. 3. The symptoms occurred with classical neuroleptics of that time (haloperidol, fluphenazine) but not with chlorpromazine, thioridazine or clozapine at doses which were clearly behaviorally active (Fig. 4). The dystonias could be attenuated by anticholinergic treatment (Fig. 5). 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

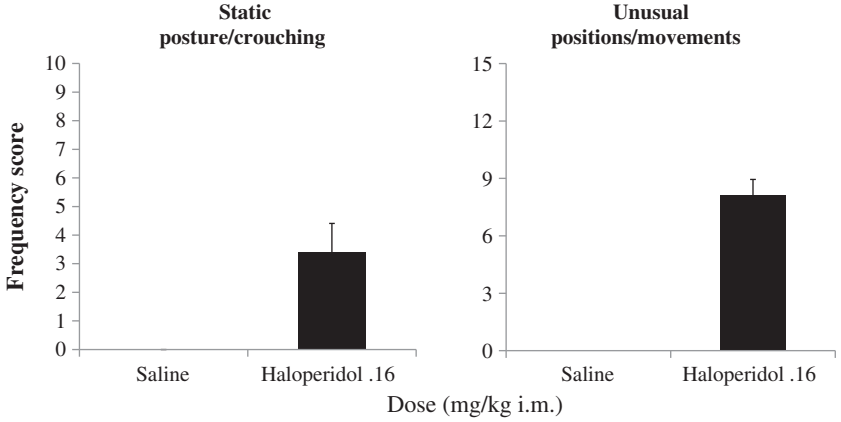

Fig. 2. Extrapyramidal symptoms (static posture/crouching, unusual positions/movements) induced in non-primed cynomolgus monkeys by haloperidol. $N = 10$. Data from Hayes et al. (2012).