ETHOPHARMACOLOGY: A CREATIVE APPROACH TO IDENTIFICATION AND CHARACTERISATION OF NOVEL PSYCHOTROPICS

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SUMMARY

The present contribution describes the basic fundamentals of animal models in ethopharmacology. After defining the role of ethopharmacology in the development of animal models of relevant human diseases, this methodology is used to classify different categories of aggression. Furthermore, the behavioural aspects of agonistic (aggressive) modelling are outlined and the various models used to describe offensive and defensive behaviours, and some miscellaneous models are summarized. Finally, some remarks on the new class of psychoactive drugs, serenics, are given.

I. INTRODUCTION

A wide variety of animal models has for many years been extensively used to characterise the activity of drugs and, from the results, to anticipate their activity in man. The techniques, if recognised as imperfect, are generally well accepted in toxicology, pharmacokinetics and pharmacology, to predict the safety of compounds and, to a lesser degree, the tolerance and efficacy in man. However, the value of animal models which purport to predict the potential therapeutic value of new drugs is often accepted only with considerable reservation and, when the therapeutic objective involves psychiatric disease, is perhaps viewed with outright suspicion.

While the threads of logic connecting human behaviour with that of fighting fish, pecking pigeons or any sort of rodent may seem tenuous at best, it is still the case, apart from serendipity, that discovery and development of novel drugs, such as the serenics, for psychiatric (or other) disorders, depends upon the integrity of the connection. Consequently, it seems worthwhile to outline very briefly some of the roots and rationale for such models and, hopefully, to suggest in the process why these models in their fully elaborated form provide the best available basis for discovery and evaluation of novel drugs with significant potential for therapeutic gain. For brevity, we will focus on rodent models of behaviour, in part because they are reasonable examples, but mainly because they were fundamental to the development of the serenics, including eltoprazine.

Brady and Sodetz /1/ have succinctly pointed out that the roots of behavioural pharmacology as now understood are coincident with those of modern behaviourism. The first of these is that

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knowledge is derived from experience rather than innate ideas, divine revelation or other obscure sources. The second holds that action is governed by consequences rather than instinct, reason, will, beliefs or other such fictions created by the magic of human language. Taken together, these two constructs about human nature defined the behaviourists' social optimism which maintains that environmental circumstances can be arranged to elicit whatever behaviour is desired (and, conversely, that undesirable behaviour emanates from improper environment). Parenthetically, the seminal importance of "nurture" (as opposed to "nature") in determining human behaviour in the behaviourists' view has aroused fierce debate and still polarises discussion although it is now common to accept the importance of both.

The best known of the early workers, and arguably the father of modern behavioural pharmacology, was Pavlov, whose work provides a foundation which conceives behavioural interactions within the framework of an orderly and systematic body of scientific knowledge based upon experimental *observation* as opposed to conjecture concerning invisible "mental" processes. While the scope of behavioural pharmacology now extends well beyond conditioned reflexes, the foundation of such research remains solidly based upon an orderly and systematic evaluation of observable events occurring under defined conditions.

In general, the animal models most readily accepted as a basis for predicting responses in man are those which are homologous; i.e., in which both the condition being observed and its aetiology are demonstrably similar to that in man. Examples might include suppression of bacterial infections by antibiotics or hypertension in monkeys. Needless to say, few, if any animal models of psychiatric dysfunction can be considered homologous if only because the aetiology of these conditions in man is unknown.

Lacking homologous models, isomorphic models (in which the observed condition is apparently similar even if the aetiology is not) may be fairly readily accepted. An example might be amphetamine psychosis as a model for paranoid schizophrenia.

Finally, there are many models in which neither the condition nor the aetiology can be clearly linked with the disease being modelled, but in which there is empirical evidence of some predictive value either for the disease or some aspect of its therapy. In psychopharmacology, the evidence is usually the discovery that agents with known therapeutic activity in man consistently co-vary with some response in an animal model.

A typical example is the conditioned avoidance response (CAR) test used to predict the antipsychotic effects of drugs. In the CAR

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paradigm, a rat is trained to avoid an aversive stimulus (foot shock) by taking a pre-emptive action (lever press) in response to a warning stimulus. Antipsychotics, at doses that do not impair the animal's ability to respond, typically abolish this conditioned avoidance response.

Certainly avoidance of foot shock is not isomorphic with the maladaptive behaviour of schizophrenia. Prototypical neuroleptics were certainly not discovered using this paradigm. However, the relationship having been found, CAR has been used to predict the antipsychotic potential of putative neuroleptics. On that basis, it is assumed that some aspects of the CAR model must be isomorphic for some unknown part of the therapeutic activity of neuroleptics in schizophrenia.

However, models such as the CAR carry a serious liability in the quest for novel therapies. While activity in CAR predicts antipsychotic efficacy in man, the *lack* of effect in CAR does not preclude the possibility that a drug would prove effective in schizophrenia. Hence, while the CAR can identify "me-too" candidates, it may not identify drugs with a different mechanism of action which could prove to be superior antipsychotics. Furthermore, these models follow rather than precede discovery and development of a therapy with demonstrated value and, consequently, are not very helpful in discovery of the prototype drug.

Buspirone, for example, although it has proved to have therapeutic value as an anxiolytic, is not at all, or only marginally effective in the anxiolytic models developed around the benzodiazepines. In a similar vein, it may be anticipated that novel pharmacologic agents for psychiatric conditions for which there is no accepted or generally effective therapy may well be rejected on the basis of results in the classical models.

Given that behavioural pharmacology has no homologous models, few isomorphic ones, and that models empirically based upon coincidental covariance will probably fail to identify novel therapeutic agents, how is orderly progress to be made? Until the pathogenesis and mechanisms of psychiatric disorders are much more clearly understood, the best chance seems to lie with ethologically based, behavioural pharmacology; i.e., ethopharmacology. Indeed the serenics have been characterised using such techniques.

II. ETHOPHARMACOLOGY

The roots of ethology lie in evolutionary biology as defined by Darwin and others and, more specifically, to the studies of Lorenz,

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Tinbergen and Von Frisch. Of central concern in ethology are the *functional* aspects of behaviour and its adaptive value in evolutionary terms where it contributes along with genetic and environmental factors to natural selection. Ethologically based behavioural models, therefore, tend to focus upon a species' entire behavioural repertoire, which is divided into clearly identifiable units of behaviour (e.g., walk, eat, sit, groom, explore, fight, flee, etc.). The repertoire is defined in naturalistic settings by comprehensive, systematic observation and recording of the species' behaviour without resort to *a priori* theories or hypotheses which are likely to bias the objectivity of observation. Having exhaustively defined the behavioural repertoire and the environmental circumstances (antecedent, concurrent and consequential) in which it is found, systematic alteration of environmental conditions, including drug administration, can be undertaken. This holistic behavioural approach allows fine discrimination between environmental changes including, for example, subtle effects of drugs which are indistinguishable in less detailed models.

While these models are neither homologous nor isomorphic for specific psychiatric disorders, elements of recorded behaviour are certainly functionally analogous (if not homologous) with elements of normal human behaviour (e.g., eating, care of young, territorial defence).

As it is clear that the specific features (the topography) of behaviour is species dependent, models which concentrate largely upon behavioural topography are likely to have limited discriminative power. Models which include elements of operant conditioning (or other antecedent or consequential events) are somewhat more potent, but are still likely to have quite limited discriminative power.

However, when the focus is widened, as in the ethologic models, to include the interactions of the animal with its environment, both internal and external; when the entire behavioural repertoire of the animal in such interactions is systematically defined and recorded; when the environmental conditions are similarly defined and recorded; and when these elements are systematically manipulated, the power of a model to detect and characterise the effects of environmental alterations (including drugs) is geometrically increased.

At the same time, the limited relevance of the species-specific behavioural topography is largely eliminated as the functionality of the behaviour (something roughly analogous to its "motivation") may be deduced and this deduction itself can be a potent and

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legitimate source of information. Functional analogies may be identified which have considerable *prima facie* validity for elements of human behaviour which, if disordered, can become the focus of therapeutic attention in psychiatric therapy.

For example, sadness or "the blues" is a commonly accepted part of ordinary life, but such a mood, if excessive in context or unusually persistent, may lead to a diagnosis of "depression". Similarly, agonistic (competitive, conflict) interactions between individuals or groups of people are commonly recognised, understood and accepted in most cultures even if the particular social manifestations are culturally adjusted. There are, however, equally understood limits to such behaviours which, if exceeded, are socially unacceptable and the perpetrator (depending upon circumstances) may be considered to be psychiatrically ill.

To model such disorders, even behaviours which are topographically very different may make a good bit more sense when considered in functional and analogous terms. For example, in characterising the anti-aggressive effects of the serenics, including eltoprazine, a resident/intruder model was used. In this paradigm, a colony of rats is housed together until they have established a normal hierarchy and territory in their cage. If a male intruder is then introduced, the dominant resident male (the so-called α-male) will exhibit a series of behaviours, including vigorous biting attack, to drive the intruder from his territory. The intruder, who cannot flee the confines of the cage, will in turn exhibit a set of quite different behaviours which are essentially submissive and defensive and apparently designed to limit damage. It is worth noting that both rats draw their behaviours from the same total repertoire and, if the environmental situation is reversed, their behaviours will also reverse.

While the topography of these behaviours is quite alien (people usually don't bite each other) and the model is neither homologous nor isomorphic for any psychiatric disorder, it might reasonably be argued that the responses are functionally not very different from those one might expect of a householder who quite unexpectedly found an uninvited stranger dropped into his living room.

There are, of course, some problems with this sort of analogy:

- The functional similitude of such an analogous model, while it may be striking and possess considerable *prima facie* validity, does not make the model homologous. Very significant differences may still exist even if there is something akin to a functional homology.
- Even though some psychiatric disorders appear to be exaggerations, distortions or perversions of normal behaviour

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(e.g., depression or anxiety), this is by no means certain. If they are, they might reasonably be expected to respond to drugs which affect the relevant, underlying, normal behaviour. If they are not, models based upon normal behaviour may have little relevance even when there is good functional analogy.

In essence, ethologically based models in psychopharmacology generally will have superior discriminative (and, hence, descriptive) power. In many cases, the behaviour observed in these models will be quite clearly analogous to some element(s) of human behaviour. However, the relevance of these models to specific psychiatric conditions depends upon a linkage which cannot now be firmly made. Nevertheless, under present circumstances, these models appear to offer the best hope for discovery and development of novel drugs, especially for disorders for which no effective therapy currently exists.

For example, behavioural deterioration is often the problem which leads to institutional care of demented patients. Behavioural problems often complicate the care of profoundly retarded individuals and may prove problematic in a number of other chronic or acute conditions.

Aggressive or agitated behaviour associated with dementia or retardation is often suppressed by administration of neuroleptics, but further CNS depression and other unwanted effects may seriously limit their utility. A variety of other therapies has been attempted, with limited success.

Because there are no drugs effective in such conditions, discovery and pre-clinical development depended upon use of animal models, such as those mentioned, and particularly upon the use of models involving agonistic animal interactions which seem most analogous to the disordered behaviours encountered in conditions such as the primary degenerative dementias.

Such development is more than usually fraught with risk and uncertainty, not only in the definition of the disorder to be treated, but also in the applicability of the models as predictors of potential effect. Some of these issues are outlined in the following sections.

III. CLASSIFICATION OF AGGRESSION

Despite many attempts, a generally acceptable definition of "aggression", particularly as it applies to individual human behaviour, has not yet been achieved. This arises in part from the varying theoretical or philosophic persuasion of those offering

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definitions; in part from the inherent difficulty in capturing the essence of a multi-faceted behaviour; in part from the attempt to include within the definitions (especially, but not exclusively, as regards human aggressive behaviour) elements of motivation which cannot readily be observed or elicited; and other, similar problems. Consequently, there remains considerable scope for contention and confusion (cf. /2-4/).

However, in research into animal behaviour and model building, a generally acceptable working definition is somewhat easier to obtain as the egocentric difficulties in defining our own behaviour become agreeably irrelevant. Consequently, an utilitarian definition of aggression among animals is "any overt behaviour which produces aversive or noxious stimuli or harm to another organism". In this definition, the generally arcane "motivation" of the behaviour is not an essential element, but may be deduced directly from the environmental situations which elicit the behaviour and from the overt behaviour itself.

Indeed, types of animal aggression may be distinguished based upon the environmental situations which generally elicit the behaviour. One of the first and, consequently, most influential of such classifications was that of Moyer /5/, which includes the following categories:

- *Predatory aggression*
  An animal kills (and often consumes) another animal, usually of another species. An example used as a laboratory model is the mouse-killing (muricidal) behaviour of rats. As this type of aggression is influenced by hunger, it may properly be considered to be related to feeding behaviour.

- *Intermale aggression*
  This involves fighting between two male conspecifics.

- *Fear-induced aggression*
  Fighting is always preceded by attempts to escape.

- *Territorial aggression*
  Fighting when a strange male intrudes into the territory of another.

- *Irritable aggression*
  Fighting evoked by such factors as fatigue or pain in the presence of an attackable organism or object. For example, a paradigm often used in the laboratory is shock-induced attacks.

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- *Sex-related aggression*
  Fighting in a sexual context, i.e., which is evoked by the same stimuli which elicit sexual behaviour.

- *Maternal aggression*
  Attacks induced, usually in females, by apparent threat to her young, nesting site, or eggs.

- *Instrumental aggression*
  Fighting elicited somewhat unnaturally by training. For example, an animal is repeatedly exposed to an attackable object in a situation where attack is rewarded.

Because there are a number of problems associated with this classification, as may be seen even from the brief description given, other authors have proposed alternatives; e.g., Huntingford /6/ and Brain /3,7/. The latter author suggested:

- *Self-defensive behaviours*, including
  "escape-directed"
  "proximity-related"
  "pain-induced"

- *Parental defensive behaviours*, including attack on intruders who apparently threaten young or nesting sites.

- *Reproduction termination,* including for example, pup-killing in rodents

- *Predatory attack*; i.e., attack on potential prey

- *Social conflict,* including:
  territorial aggression
  intermale aggression
  conflicts between females

It is apparent from these classifications that some of these behaviours do not comfortably fit within the rubric "aggression" with its connotations of initiated offensive action or attack. For that reason, among others, the class of behaviours involving conflict between members of the same species is more usefully subsumed under the term "agonistic behaviour" /8/. This cognomen is derived from ethologic terminology and refers to all elements of behaviour present in situations of intra-species conflict. It includes attack,

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defence and flight behaviours. It does *not* include inter-species interactions such as predatory behaviour.

It is also clear that classification of aggression, even in animals, is at best difficult. More important, however, is the consensus that agonistic behaviour (aggression) is not an homogeneous set of activities. A number of different types may be distinguished based upon the kinds of stimuli which elicit them, the topography of the behavioural response, the sex of the animals involved, or the reinforcing properties and interactions with other behavioural tendencies.

There is also evidence (e.g., /4,9,10/) that these different kinds of aggressive behaviour have different underlying physiological mechanisms, both in neuronal circuitry and in hormonal responses. Moreover, different types of aggressive behaviour may be differentially influenced by learning or situational determinants.

Finally, as already noted, many of these behaviours are functionally analogous (if not homologous) across many species including the primates and man. Therefore, in the search for drugs which may prove useful in management of behavioural disorders, models based upon agonistic interactions of various animal species offer the best option currently available for discovery and preclinical characterisation of new compounds.

A general overview of the techniques used in our laboratory and the factors which most influence our use and interpretation of these models are outlined below. Like most laboratories, we emphasize rodent models as these are, for a number of logistical reasons, the more attractive.

IV. BEHAVIOURAL ASPECTS OF AGONISTIC (AGGRESSIVE) MODELLING

Because we rely in our search for new drugs with serenic potential upon ethological paradigms (models) involving the behaviour of animals, careful observation and recording of all ongoing behaviour is required to quantify agonistic components within their natural context. Agonistic behaviour, as we found in a variety of models, includes a number of behavioural components which have complex functions and which have been organised in certain patterns and sequences. The species-specific behavioural patterns, taken together, can be viewed as that species' agonistic behavioural repertoire. The diversity of the repertoire, i.e., the number and subtlety of behavioural options available, is smaller in more primitive species and becomes apparently larger and more

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complex in the higher orders. This is one practical reason for modelling these behaviours, at least initially, in rodent species.

Depending upon the model used, as defined by the specific environmental situation constructed, a particular frequential and temporal distribution of the species' behavioural repertoire can be elicited. In that regard, it is important to note that the *distinction* between different *types* of agonistic behaviour occurring in different models is based mainly upon:

- the frequency of occurrence (incidence) of behavioural elements employed by each participating animal.
- the relative timing of the elements
- the specific environmental stimuli (experimental situation).

For example, in a territorial model of agonistic behaviour in rats, the resident α-male ordinarily takes the offensive role, and the intruder the defensive role. Clearly, each rat has available to him the same behavioural repertoire. However, the two rats show a very different frequency and sequence of behavioural elements. On the basis of these different distributions, the overall behaviour of each can be classified either as offensive or defensive.

The initial, appetitive phase of agonistic behaviour consists of approach of one (or both) combatants and commencement of introductory behaviours (investigation). Thereafter, a clear distinction evolves between offensive behaviour on the part of one and defensive behaviour on the part of the other. One animal exhibits the elements belonging to the offensive subset of the agonistic repertoire, the other exhibits elements from the defensive subset. This division of agonistic behaviours is observed in a wide variety of species from low to very high in the evolutionary scale.

Remarkably, an animal which behaves defensively in one situation (e.g., in the territory of a stranger) may behave very offensively in another situation (e.g., in its own territory). This underlines the hypothesis that offensive, defensive, submissive and flight behaviours belong to a single repertoire of agonistic behaviours. On one extreme is pure offence (attack); at the other extreme is pure defence with flight as the first option. This behavioural continuum, present in a variety of animal models, is one of the key elements exploited in animal models of agonistic behaviour (specifically in rodents /11/).

Thus, the situation (environment) in which the animal finds itself determines to a large degree its behavioural strategy. In addition to the obvious, external environment, of course, is the animal's

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internal environment which includes such factors as, for example, sex, hormones, previous experience, or drugs.

Through systematic manipulation of these variables and careful observation and recording of the resulting changes in behaviour, it is possible to construct models which discriminate quite subtle differences in the activity profiles of various drugs. The models most often used in our laboratory are outlined below.

V. MODELS OF OFFENSIVE BEHAVIOURS

Several models focus (although not exclusively) upon the "offensive" components of agonistic interactions. "Offensive" behaviour in this context is always characterised by initiative on the part of the offensive animal and injury (inflicted wounds) to the opponent /12-14/. The offensive nature of these behavioural models has been substantiated by measuring the *wound pattern* inflicted upon the defenders. The same measure can be used as a crude index of the anti-aggressive effects of compounds, although, in isolation, this measure does not discriminate, for example, between sedative, motor-relaxing or more specific anti-aggressive compounds.

5.1. Isolation-induced offensive behaviour

A manipulation often used to induce aggression is isolation of male animals (typically mice) for several weeks. Such isolated animals upon encountering another will reliably exhibit attack behaviour /15/. This isolation-induced aggression model is one of the most frequently used aggression models in behavioural pharmacology /16/.

Because these isolated male mice show a full repertoire of agonistic behaviours /11,17/, ethologic techniques can be used to allow detection of very specific drug effects /18/.

While the model mainly represents offensive aspects of agonistic behaviour, defensive aspects are also present so the model can be used very elegantly to differentiate the activity of drugs which influence agonistic behaviour /19/.

A similar model in both rats and mice uses a relatively short isolation period to increase the probability of attacks in a short test period (e.g., 10 minutes) /14,18/. In this test, a more diverse pattern of activities is exhibited because the situation delivers a mix of offensive-defensive behaviour which allows even more subtle discrimination between the behavioural specificity of drugs /18/.

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The model is very interesting in this respect because it shows properties of compounds which are revealed only partially, or not at all, by common pharmacological test models /11,14,20/.

5.2. Resident-intruder offensive behaviour

This model, used with increasing frequency in pharmacology, depends upon the resident animal's typical response to a conspecific intruder /21/. In this model, a male rat (or mouse) is housed with a female, a situation more closely resembling the natural situation in which animals establish and defend territories /22,23/.

When such territorial males meet a strange intruder in their territory, heavy fighting may occur. This apparently offensive behaviour can be considered quite natural /12,24/.

This paradigm differs both from isolation-induced aggression in mice and intermale aggression in rats, because there is no isolation, which may lead to behavioural pathologies /25/. Moreover, resident-intruder paradigms have a very wide species generality /26,27/, probably including man, whereas isolation-induced aggression is restricted to certain species /11/.

The behavioural topography in the territorial situation resembles to a great extent that seen in intermale aggression (although the latter has more defensive components), and both models discriminate effectively the quality and behavioural mechanisms of action of several drugs with some anti-aggressive properties /14,28,29/.

5.3. Offensive behaviour following electrical stimulation of the brain

Behaviour similar to that of offensive territorial males can be induced by electrical stimulation in the hypothalamus of both male *and* female rats /30,31/. The current threshold required to elicit attack behaviour is used as the index of anti-aggressive potency of a test compound.

Because stimulation of the same electrode can be used to assess the effects of drugs not only upon the aversive qualities of the current, but also upon sedative or stimulating effects (via locomotion), the model allows estimation of the *specificity* of the anti-aggressive effects of test drugs.

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5.4 Maternal offensive behaviour

Although males of a species are generally more apt than females to exhibit attack behaviours in a variety of situations /4/, females will also exhibit offensive behaviours. The maternal aggression model, for example, depends upon the fact that a lactating female rat with young will exhibit offensive behaviours toward a wide variety of intruders. This behaviour is most pronounced during the first part of the lactating period /32,33/.

Because the critical stimulus is clearly the proximity of some threatening object to the female's young, some authors /4/ have suggested the behaviour is essentially defensive. However, these behaviours can be considered as offensive /34/. We concur with this view because female behaviour in this model is clearly self-initiated, pro-active and not necessarily in reaction to any threat initiated by the intruder.

5.5 Offensive play-fighting among juvenile rats

Another model considered to belong to the offensive agonistic repertoire considers play-fighting among juvenile rats. The juvenile behaviour is considered to be an analogue of later adult agonistic behaviour.

5.6 Offensive behaviour among piglets

When piglets from different litters are mixed, fierce fighting generally occurs until an hierarchy is established within the overall group. As with other offensive behaviours, attacks are pro-active rather than defensive in nature.

Given that many species, including primates, engage in offensive agonistic behaviours while establishing and maintaining hierarchies, it is our view that a reasonable predictor of generalised inter-species activity will be the ability of a drug to abolish or moderate these behaviours without material effects upon other elements of the behavioural repertoire.

VI. MODELS OF DEFENSIVE AGONISTIC BEHAVIOUR

While offensive agonistic behaviour is characterised by the initiative of the aggressor and damage to the opponent /35-38/, defensive behaviour, in contrast, lacks active approach (initiative) and no wounds (or incidental ones only) are inflicted by the defensive animal.

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6.1 Pain-induced defensive agonistic behaviour

A widely used "aggression model" in pharmacology is foot-shock or pain-induced aggression, in which agonistic behaviour is elicited typically by delivering an electrical shock to the hind paws of a pair of rats or mice. While either or both animals may attack, the behaviour is now conceived as defensive /35,36,39/, in part because the animals mutually exhibit typical, upright defensive postures and squealing. These reactions are well integrated, but no complete sequences of fighting and no offensive threat displays are present.

Although this model has been extensively used to assess anti-aggressive activity of drugs, a confounding factor in the model is that the behaviour-releasing stimulus (pain) can be masked by the analgesic properties of psychoactive drugs. This fact, together with the very restricted behavioural repertoire in this paradigm, limits the utility of this defensive model in characterising the anti-aggressive properties of drugs.

6.2 The intruder model of defensive behaviour

A more natural model of defensive behaviour is that which considers the behaviour of the intruder in the resident-intruder or maternal aggression models discussed above /33/. Study of this defensive behaviour reveals that defending rats have special tactics to protect the more vulnerable parts of their bodies.

In unconstrained situations, animals on the defensive usually flee from the territory of the residential male or lactating female /22/, but when this is impossible, as is often the case in laboratory settings, they defend themselves by flight, crouching, upright defensive postures, emission of ultrasonic sounds and submissive postures. Generally these behaviours seem to be aimed at protecting the back, the area where most wounds are inflicted by attacking rats /38/.

Although this model involves at least two rats, an offensive and a defensive one, it gives the opportunity to measure the capacities of the defending animal when it is treated with a drug. When the behaviour of the defender is assessed by ethological methods, this model gives a very powerful and subtle way to describe the effects of drugs. Despite its obvious advantages, however, this defensive model has found only limited use in psychopharmacological research in aggression /40/.

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VII. MISCELLANEOUS MODELS

Muricidal (mouse killing) behaviour of some rats has often been used as a model to characterise the anti-aggressive properties of drugs, perhaps as much for its logistic simplicity and dramatic impact as for its predictive value.

Considering the behaviour of the rat, the model is perhaps best conceived as a predatory attack on prey, whereas the behaviour of the mouse can be considered as defence against a predator. In fact, there is much dispute concerning the motivation of the rat /41/.

Moreover, muricide differs from intra-species aggression with regard to the neuroanatomical, physiological and hormonal mechanisms /4/. The behavioural elements typical of this predatory model involve chasing, seizing and biting the mouse at the level of the cervical spine. The agonistic displays (sounds, threats or pilo-erection) typical of intra-species offensive behaviour in rats do not occur, which strongly suggests that this behaviour should not be considered agonistic as defined earlier.

Nevertheless, the model gives some clues to activities of drugs and may be used for comparative purposes as an addition to the more credible models of agonistic behaviour /42/.

VIII. THE SERENICS

The serenics are one of the first products of systematic application of ethological pharmacology to drug development. Almost certainly they could not have been discovered without the contributions of the ethologic models in which they have been characterised. It is reasonable to expect that as their development proceeds, especially in the clinic, the strengths and limitations of the models of ethological pharmacology will become much more sharply focused. It would not be surprising, and would certainly be no tragedy, should we discover that our behaviour is in fundamental ways not so far removed from the "lesser" species as we might, in our egocentric way, have wished.

Acknowledgements: We thank Marijke Mulder for her excellent assistance.

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