POSSIBLE CLINICAL APPLICATIONS OF SERENICS AND SOME IMPLICATIONS OF THEIR PRECLINICAL PROFILE FOR THEIR CLINICAL USE IN PSYCHIATRIC DISORDERS

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I. INTRODUCTION

Agonistic behaviour is the subset of social behaviours which comes into play in interactions characterised by conflict. This repertoire includes both offensive behaviours (more commonly labelled as "aggressive") and defensive behaviours. While the complexity and diversity of behavioural options vary, most species, including man, possess an agonistic behavioural repertoire.

Neither in man nor in other animals is agonistic behaviour pathological. In the framework of evolutionary theory, these behaviours are understood to encourage survival of the fittest, to disperse populations, to aid adaptation to threatening environments, and generally to improve the probability of both individual and species survival.

In human terms, we tend to understand such behaviour as "competitive" or "defensive" in ourselves and, perhaps, "aggressive" or "hostile" in others. In social terms, however, we differentiate between those agonistic behaviours which are acceptable on the one hand and those which are unacceptable on the other and we censure the latter in a variety of ways. While we find no difficulty in discriminating between the ends of this behavioural spectrum, we often find considerable difficulty in agreeing where to draw the line in the middle.

In deciding how to deal with unacceptable behaviour, we often tend to try to understand its "motivation". At least in modern Western societies, we tend to excuse the behaviour of individuals who are considered mentally incompetent by reason of great stress, mental disease, retardation, or the like.

While we know that "aggressive" behaviour is associated with a number of disease states (both somatic and psychiatric), and while such behaviour may be considered in establishing a diagnosis, there is no diagnostic category of "aggressive disease" or "offensive syndrome" *per se.* In the clinical literature, such behaviours may be referred to as "violent", "hostile", "agitated", "impulsive" or (indeed) "aggressive", and often become a primary focus of therapy, as they may threaten the safety of clinical staff or other patients and thus interfere with other therapeutic efforts.

For the purposes of this discussion, these problems are best referred to as "destructive behaviours" which may be defined (after Eichelman) as "behaviour which threatens or actually results in partial or complete injury to the physical, psychological or sociological integrity of a person, object or environment".

In this sense, destructive behaviours are often encountered in association with neuropsychiatric disorders, and patients will be

found in a variety of settings, including psychiatric hospitals, neurologic and neurosurgical wards, rehabilitation facilities, nursing homes, community residences and institutions for the mentally retarded.

Destructive behaviours often precipitate admission to psychiatric units. For example, Tardiff and Sweillam /1/, in a survey of state hospitals in New York, found about 10% of patients had manifested assaultive behaviour in the two weeks before admission. Binder and McNiel /2/ reported 15% of patients admitted to a university-based hospital locked unit had assaulted another person within two weeks of admission. Rossi *et al.* /3/ reported that about 40% of patients admitted to an acute psychiatric unit in a general hospital had exhibited violent or fear-inducing behaviour immediately before hospitalisation.

Destructive behaviours are also common in patients after hospitalisation. In the New York state hospital system, about 7% of patients were assaultive within a three-month period /4/. In a one-year period, about 12,000 assaults were reported in this hospital system (New York State Senate Select Committee on Mental and Physical Handicap, 1977).

Destructive behaviour is often a problem in the management of patients with primary degenerative dementias (either Alzheimer's SDAT, or multi-infarct, MID) and has been well documented. One way to determine the magnitude of the problem is to survey nursing home populations for the frequency of such behaviour.

Twenty-five per cent of a group of elderly patients in nursing homes in London were found to have at least weekly episodes of destructive behaviour /5/. This increased to 41% of those who had mild to moderate dementia and depression.

In a random sample of residents in a large intermediate-care nursing home in the U.S., 25% exhibited active aggression, 26% showed verbal aggression and 14% were self-destructive /6/. In a survey of 1,139 nursing home patients, Zimmer *et al.* /7/ found that 8.3% were physically aggressive, 4.3% were self-destructive and 12.6% were verbally disruptive.

Using comprehensive rating scales to assess agitated behaviours in 66 nursing home patients, Cohen-Mansfield /8/ documented verbal aggression more than once daily for 36.8% of subjects and hitting or kicking for 21.2%. Chandler and Chandler /9/, who assessed the prevalence of neuropsychiatric disorders in 65 nursing home residents, found 72% had a dementia syndrome. Among these patients, the most common behavioural problems were agitation and aggression in almost half (48%) of the sample.

There have been studies focused on the behaviour of patients

with Alzheimer's dementia. For example, Reisberg *et al.* /10/ studied 57 out-patients. Of the 33 (58%) with significant behavioural problems, 16 were agitated, 10 were violent and 12 had motor restlessness. Rubin *et al.* /11/ studied 44 patients with mild Alzheimer's dementia and found irritability in 23% and hyperactivity in 9% of these patients.

Families of patients with dementia reported a 47% incidence of physical violence /12/. This behaviour was problematic for virtually all (94%) of the families and was the most serious problem for the patient. For many families, these behavioural disturbances rather than cognitive deficits were the major source of concern leading to institutionalisation.

Severely or profoundly retarded patients who require institutional care often exhibit destructive behaviour. Reid *et al.* /13/ reported in such a group that 33% were irritable and 20% were injurious to themselves. In a survey of patients in community residences or institutions for the mentally retarded, 30% to 40% of the residents exhibited disruptive behaviour or injury to self, others or property /14/. Administration of antipsychotics was significantly associated with these behaviours. In a survey of mentally handicapped patients over age 40, Day /15/ found destructive behaviours, especially verbal abusiveness or aggression towards self, others or objects, were the most common problems and, moreover, were of long-standing duration.

Traumatic brain injury, especially frontal lobe damage, may result in a frontal lobe syndrome characterised by inability to control angry impulses /16/ and the resulting behaviour interferes with rehabilitation and resocialisation.

In many of these situations, it is necessary to control the destructive tendencies before therapy can be effectively applied to the underlying condition. In other cases, such as the demented or retarded, the underlying condition is essentially untreatable and moderation of the destructive behaviours is a prerequisite to reasonable and humane care in minimally restrictive settings.

II. CURRENT MANAGEMENT OPTIONS

At present, there are no drugs clinically available which specifically inhibit destructive behaviours /17-19/, and pharmacologic therapy aimed specifically at destructive behaviours has been reported relatively infrequently. Although lithium, propranolol or anticonvulsants have been reported to be effective for specific management of such behaviours in some cases, in general the treatment

of human destructive behaviour has been only marginally successful. However, the advent of more sophisticated behavioural methodologies, the apparent, if limited, success of specific therapies, and an increasing understanding of the biological correlates have renewed optimism toward pharmacologic intervention in those individuals whose destructive behaviours represent one of the primary objectives of clinical management.

There is a clinical lore which holds that certain types of patients respond better to particular pharmacologic interventions. For example, Elliott /20/ has suggested that destructive individuals with traumatic CNS injury or ruptured aneurysm respond most favourably to beta-adrenergic antagonists. Monroe /21-23/ suggests that individuals with "episodic dyscontrol" (which he links to an epileptoid-like EEG) respond well to anticonvulsants or benzodiazepines.

Yudofsky *et al.* /24/ have reviewed the pharmacologic treatment of destructive disorders. They conclude that antipsychotics have been most widely used for management of such behaviours, but with little evidence to suggest that they are specifically effective beyond their sedative effects in acutely agitated or violent patients or those whose behaviour is due to active psychosis /19,25-27/.

Yudofsky *et al.* /24/ consider benzodiazepines to be ineffective in chronic destructive behaviour and, indeed, that they may aggravate the behaviour or precipitate rage attacks (the "paradoxical" response observed both in animals and man) /28/. They consider carbamazepine effective in management of behaviour related to temporal lobe epilepsy and review preliminary data suggesting its utility in other cases as well.

Lithium has proved effective in destructive behaviour related to manic excitement and, although controlled studies are contradictory, there is evidence suggesting it may also be useful in management of destructive behaviour. Finally, they review studies which suggest that beta-blockers, particularly propranolol, may have specific value in the management of destructive behaviour related to organic brain syndromes. However, it should be noted that propranolol may have a latency period of four to six weeks and is contraindicated in a variety of conditions which are relatively common in patients with organic brain syndromes.

A few experimental drugs have been tested clinically, e.g. the benzazepine derivative Sch 12679 /27/ and the indenopyridine YG-19-256 /29,30/. These studies suggested for the latter an anti-aggressive effect without overt sedation. Since no such specificity has been found in animal studies /31-33/, claims for a specific anti-aggressive profile must at present be accepted with some reservations.

Overall, it may be concluded that destructive behaviours are frequently encountered in clinical practice, that they present a significant management problem, that a variety of pharmacologic interventions have been (and are) used, and that there is much room for improvement. On this basis, it seems reasonable to search for pharmacologic agents which might specifically inhibit aggressive behaviours in animals and, therefore, might specifically inhibit destructive behaviours in man.

Such a search necessarily depends upon our crude understanding of CNS exciting and inhibiting systems; their relationship with various neurotransmitter systems; their relationship, in turn, with various *in vitro* and *in vivo* models; and finally, our own limited ability to identify from the results of such models compounds with promising effects. It is hardly surprising if this process is not especially efficient.

However, because of the accumulating evidence for the association between the serotonin (5-hydroxytryptamine, 5-HT) system and behaviour, both in animals and in man, our search has focused on compounds with probable activity in the serotonin systems. In the remainder of this paper, we will trace very briefly some of the main issues considered in our search for, characterisation of and future plans for the serenics.

III. SEROTONIN AND BEHAVIOUR

The relationship between serotonin and behaviour (e.g., depression, anxiety, obsessive-compulsive disorders, panic) hardly needs noting and has been extensively reviewed (see, for example, /34/). Accumulating evidence suggests more or less clear associations between some behaviours (e.g., depression) and serotonin receptor subtypes /35/. However, for destructive behaviours, few drugs with receptor specificity have yet been clinically tested. Consequently, if an association does exist, as seems likely, it has not yet been elucidated.

In considering our own work, it seems worth while at the outset to discriminate between non-specific and specific suppression of aggressive behaviours (in animals) or destructive behaviours (in man). Many drugs, among them the commonly used neuroleptics, reduce aggressive behaviour in animals, but at the expense of all other behaviours as well, often to the point of general sedation and ataxia /32,36,37/. Because these drugs have similar effects in man, they are used in the management of destructive behaviours, but with similar suppression of other behaviours /38,39/. This non-spe-

cific inhibition of aggression or destructive behaviour can best be understood as "chemical restraint". In contrast, a drug with specific activity should inhibit aggressive or destructive behaviour *without* significant effects upon other behaviours or capabilities.

IV. ANIMAL MODELLING

As is customary in the search for psycho-active drugs, reliance must be placed on the use of animal models. As long as no drugs with demonstrable specificity in the management of human destructive behaviour are available, the relevance of these models is difficult to assess. However, there are several reasons for believing that such animal models should have predictive value for human behaviour.

There are no main differences in behavioural structure between man and animals /40-42/ and it is suggested that man and animals possess a comparable system (or systems) for agonistic interactions (aggression), both on a behavioural and a neuronal level /40,43/.

Animals and man share similar autonomic and physiological reactions during the states of high arousal which are associated with agonistic interactions /44,45/.

In the central nervous system of mammals, including man, comparable neural substrates exist which, certainly in animals and in man, modulate observable, aggressive behaviour /43,46-49/. Studies of these neural substrates do not support any unitary concept of aggression. Adams /46/ and Ursin /50/ postulate that, because different brain structures are involved in defence, offence and predatory aggression, at least these three types of aggression must be recognized.

However, because the brain is organized as a very complex network rather than a system of reflex chains, notions such as "neural substrates of aggression" are, in fact, over-simplified.

In our laboratory, if we are to accept a neural structure as a possible substrate for aggressive behaviour, several criteria should be fulfilled /51/:

- The behaviour must be elicited by electrical or chemical stimulation of the brain structure, at least when the external environment permits the expected behaviour.
- The behaviour evoked has to belong to the ordinary repertoire of the animal in its natural state.
- Units in the brain structure should change their electrical activity (EEG) during the performance of the behaviour.

- The behaviour should change as a result of lesions to the particular neural structure.
- Pharmacological manipulations should elicit, eliminate or jam the particular behaviour.
- The behavioural changes produced must be reasonably specific for the structure and should not result from interfering effects from other brain structures.

Using such criteria, there is evidence that at least the following brain structures are involved in aspects of aggression, certainly in animals and probably in man as well (for most of them):

- Involvement in all three major types of aggression (i.e., offensive, defensive and predatory)
  - Hypothalamus
  - Brain stem
  - Temporal lobe
- Involvement in offensive behaviours
  - Thalamus
- Involvement in defensive behaviours
  - Septum
- Involvement in defensive and predatory behaviours
  - Olfactory bulb

It has been suggested that a number of other brain structures may be involved, e.g., the hippocampus, frontal lobe and cingulate cortex, but these effects can better be attributed to the general response modulation of these structures or through changes in motivational and discriminatory functions.

In conclusion: there are a number of brain structures involved in at least offensive, defensive and predatory aggression, but it is far from clear precisely how these contribute to the behaviour. Moreover, the neurochemistry of these structures, as far as their involvement in aggressive behaviours is concerned, remains anecdotal /52/ and detailed research is in a very early stage.

V. HORMONES AND BEHAVIOUR

It is commonly accepted that hormones modulate agonistic behaviour both in animals and man. Indeed, castration has been proposed for management of some particularly serious cases. In the experimental study of agonistic behaviours it is necessary to consider the complex interplay between circulating hormones and their

target areas, especially in the CNS /53/. Hormones modulate attack and defence in a variety of ways /54/, e.g.:

- early "programming" effects (peri- and post-natal)
- modulation of motivation
- modulation of somatic mechanisms involved in the production or detection of communicative stimuli (body size, form, colouration, vocalisation, pheromones).

While several hormones modulate to some degree effects in any model of animal aggression, androgens (testosterone) are clearly the most important /55,56/. The effects of androgens occur both during early development and thereafter concurrently.

The early effect (early programming) occurs during pre- and post-natal development and induces permanent changes in latent (potential) behaviour. On the other hand, the concurrent effects of androgens involve activation of ongoing behaviour. The mechanism by which androgens exert their concurrent effects involves alterations in the way in which the brain processes sensory information.

A number of animal models are androgen-dependent, a number are not. In general, offensive behaviours are testosterone-dependent, while defensive and predatory behaviours are not. Thus, for example, to induce fighting in males, testosterone should be present (but, under certain conditions, is not necessary). Animals exposed to testosterone early in life require much less androgen exposure in adulthood to activate fighting, as compared with animals without such early exposure.

In conclusion, androgens are important modulators of some agonistic behaviours, especially offensive ones in males, whereas in others no effect is found. However, it is clear that hormones do not directly induce or inhibit behaviour, but do affect activational potentials. It is, therefore, unlikely that direct behavioural effects of psychotropic drugs are mediated by effects upon androgens.

Other hormones also play a role in agonistic behaviours (as well as in other behaviours), e.g., corticosteroids, prolactin, oestrogens and progestins. Their roles, however, are far from elucidated but, as with the androgens, there is no evidence of direct effects.

In the present study, various aggression models are grouped in classes representing predominantly offensive or defensive/flight aspects of agonistic behaviour. This classification does not suggest specificity for types of human aggression; rather it reflects a division now much used in animal research /46,57-60/. Offensive behaviour is always characterised by initiative and active attempts (attacks) to

remove the attack-releasing stimulus from the environment (e.g., the territory or nesting place).

There may be some similarities in this respect between human and animal behaviours in that the offensive (animal) aggression may reflect some affective or appetitive behaviour or angry aggression /41/. It could be assumed in many situations of human conflict that offensive or affective aggression is present in the behaviour of the attacker /61/. Blanchard and Blanchard /41/ postulate that the defence/flight modality in animals may be related to fear-based attack in man. Although hard evidence delineating offensive and defensive types of aggression in humans is still scarce, the face validity of the distinction is considerable and the existing evidence is not inconsistent with such an hypothesis.

Without further belabouring such issues, it seems intuitively reasonable from a biological perspective to assume that a drug, which has anti-offensive properties in animal models, may also influence some types of agonistic behaviour in man. Defensive behaviour, the other side of an animal's agonistic interactions considered in this report, probably also has its similarities in human behaviour (self-defence, flight; /61/). It seems possible, therefore, that drugs which are active in animal models of agonistic behaviour, whether in offensive or in defensive ones, may also prove effective in certain situations of human conflict.

Assuming, then, that animal models may have predictive value for human use, we shall discuss the properties of eltoprazine in the animal models used and compare them with those of some other putative "anti-aggressive" drugs and some other reference compounds.

VI. SEROTONIN AND BEHAVIOUR IN ANIMALS

In animals, there is general agreement that serotonin inhibits aggressive behaviours /62/. For example, in rats, general serotonin depletions by PCPA increase offensive aggression, but leave defensive behaviours intact /63,64/. Localised 5-HT depletions, obtained by injections of the neurotoxin 5,7-DHT into the hypothalamus, also lead to increases in aggression. Such manipulations affect predatory aggression in a similar fashion although the biological significance of these behaviours differs. Studies in mice lead to similar conclusions about the relation between 5-HT and aggressive behaviours.

In other studies, decreased serotonergic function achieved by reducing tryptophan in the diet of rats induced predatory aggression which could be inhibited by supplying tryptophan /65/. In-

creased serotonergic function achieved by injection of the immediate precursor 5-HTP reduced predatory aggression after either systemic or intraventricular application /66-69/.

In another approach to the study of serotonin and aggression, the correlation between serotonin turnover in various areas of the brain and aggression within and between strains was evaluated /70/. In particular, the hypothalamus seems to be involved since low serotonin turnover appeared to be associated with increased aggression. To a lesser extent, the hippocampus and amygdala were involved, but no correlations were found between behaviour and cortical serotonin.

In monkeys, a more complex picture emerges. Dominant and subordinate males differ in 5-HIAA and HVA levels in cerebrospinal fluid (CSF) /71/ as well as in whole blood serotonin /72/. These status-dependent effects indicate involvement of serotonin in aggression. Although reduction of serotonin by PCPA increased aggression, various drugs which increase serotonin did not show a significant effect /72,73/. However, eltoprazine, which has predominantly serotonergic activity, has proved effective in vervet monkeys.

VII. SEROTONIN (5-HT) RECEPTOR SUBTYPES

Research over the past decade has vastly expanded our understanding of the complexity of the serotonin system in animals. Several subtypes may be differentiated on the basis of radioligand binding /74/. Not all the subtypes, for example, the 5-HT_{1B} receptor, are found in all species. Provisional evidence suggests that the 5-HT_{1B} receptor in rodents and the 5-HT_{1D} in primates may serve as a presynaptic autoreceptor. However, both subtypes are also found on postsynaptic neurons.

Specific agonists are available for the 5-HT_{1A} receptor, but not for the 5-HT_{1B}, $_{1C}$ or $_{1D}$ sites; entirely satisfactory antagonists are also generally lacking. Nevertheless, exploration of the functional characteristics of these receptors can be undertaken with some success using the ligands which are available. Many of these serve to underline the importance of the 5-HT receptors in behaviour.

Several non-selective 5-HT receptor agonists (e.g., 5-methoxy N,N-dimethyltryptamine) as well as antagonists (e.g., methysergide) inhibit agonistic interactions in animals, but usually in a behaviourally non-specific fashion /75/. 5-HT_{1A} agonists, such as 8-OH-DPAT, buspirone or ipsapirone, all reduce offensive behaviours of a resident male rat towards an intruder and maternal

aggression in lactating females /76/. However, this inhibition is obtained at the cost of reductions in non-aggressive social activities and exploratory behaviours as well as behavioural inactivity which may reflect sedative properties of these drugs.

Mixed 5-$HT_{1A/B}$ agonists, such as eltoprazine, and more specific 5-HT_{1B} agonists, such as TFMPP (a metabolite of fluprazine, another serenic), inhibit offensive behaviours in several models (Olivier, Mos and Rasmussen, this issue; /77/) as well as in a resident animal confronting an intruder /76-82/. Furthermore, these compounds do not adversely affect social behaviours and may even activate exploratory behaviours.

At present, the lack of specific agonists and antagonists to the 5-$HT_{1C/D}$ receptors prevents effective exploration of their specific functions.

Behaviourally, mixed results have been obtained with 5-HT_2 antagonists. While ketanserine reduces offensive behaviour in isolated mice /83/ and in the resident-intruder paradigm in rats /76/, albeit non-specifically in both cases, ritanserin did not significantly affect aggressive behaviours /76,81/. Lack of selective agonists for the 5-HT_2 site inhibits characterisation of the behavioural importance of the receptor and work with non-selective compounds gives results which are not readily interpreted.

Finally, the 5-HT_3 receptor antagonists MDL 72222 and ondanserine (GR38032F) do not affect aggressive behaviour in male mice or in lactating female rats /84/. More definitive characterisation of the behavioural importance of this site awaits development of specific agonists.

Overall, it is clear that the serotonin subtypes are important in modulation and control of agonistic behavioural interactions and that there is very considerable specificity of effect associated with selective agonists. It seems quite likely that this specificity is likely to be found also in man when suitable compounds are available for clinical use.

VIII. SEROTONIN AND BEHAVIOUR IN MAN

In man, there is a clear, but as yet imprecisely defined, relationship between CNS serotonin function and destructive behaviours. In 1976, Åsberg *et al.* /85/ found in depressed patients a bimodal distribution of 5-HIAA in CSF and noted that low levels were associated with an increased risk of suicide attempts. Tråskman *et al.* /86/ found that suicide attempts were generally more violent in patients with depressed CSF 5-HIAA. Lidberg *et al.* /87/ reported

similar findings in a group of suicidal subjects in whom, compared with controls, CSF 5-HIAA was significantly lower, and the lowest levels were found in those subjects who had used active, violent methods in their suicide attempts.

In a similar vein, Linnoila /88/ and Lidberg *et al.* /87,89/ found CSF 5-HIAA levels significantly lower among impulsive offenders than among those whose behaviour was apparently premeditated. Virkkunen *et al.* /90/ found a similar association for impulsive arsonists.

In a cohort of young men with a diagnosis of personality disorder, Brown *et al.* /91,92/ found a significant negative correlation between CSF 5-HIAA and a life history of aggressive behaviour, suicide attempts and psychopathic deviate scores. Two reports by Bioulac *et al.* /93,94/ on a very small cohort (6) of particularly violent delinquents with the 47 XYY phenotype suggested that normalisation of serotonin metabolism by administration of 5-hydroxytryptophan (5-HTP) attenuated their behavioural symptomatology as effectively as the neuroleptics with which their symptoms had been controlled.

O'Neil *et al.* /95/ report treatment of a 22-year-old retarded man with Cornelia de Lange syndrome whose destructive behaviour was significantly moderated by treatment with trazadone and tryptophan, which markedly increased his abnormally low peripheral serotonin levels. They suggest that his aggressive behaviours may have been linked to his abnormal serotonin metabolism and that patients with similar deficits may benefit from treatment which improves serotonin function.

Finally, several drugs, including lithium and propranolol, which have been reported to moderate destructive behaviours in some patients, are known or thought to have effects which increase serotonin turnover.

Although such associations are far from elucidating the specific association between deficits in CNS serotonin function and destructive behaviour, they clearly suggest that depressed CSF 5-HIAA levels, and presumably therefore CNS 5-HT turnover, is associated with impulsiveness perhaps manifested by destructive behaviour. It also suggests that pharmacologic modulation of CNS serotonin function may specifically attenuate destructive behaviours in some patients.

IX. CLINICAL MANAGEMENT OF DESTRUCTIVE BEHAVIOUR

It is not within the scope of this paper to contribute to the debate concerning the causes or social management of aggressive behaviours in man. Clearly, these are complex and even a consensus concerning definition of the terms used, including "aggression" itself, is often the subject of conflicting opinions arising from the enormous amount of methodological, cultural and political approaches to aggression (see, for example, /96/).

In biologically oriented research into destructive behaviours in man (by whatever name they are called), it is evident that they are associated with and present a significant clinical problem in a number of mental disorders and syndromes. For example, such behaviours are not infrequently associated with schizophrenic psychosis /97/, epileptic seizures, mania, depression, organic brain syndrome and mental retardation /18,38,61/.

There is, in addition, violent human behaviour associated with psychiatric disorders less clearly recognised as "diseases": e.g., the personality or character disorders /18,98,99/ in adults and conduct disorders in children /100,101/.

When these problems become the focus of clinical attention, treatment of the underlying disorder will always be the therapy of first choice. However, in a number of cases, such primary therapy will be inhibited or impossible until the gross destructive tendencies are adequately controlled /39/.

At present, there are no drugs clinically available which specifically suppress aggression /17,18,38/. Consequently, reliance has generally been placed on neuroleptics and minor tranquillizers.

The taming effects of neuroleptics are closely linked with their general inhibition of all behaviours /19,25-27/.

The use of minor tranquillizers, such as chlordiazepoxide, based upon their "taming" properties, has been criticized because *increased* aggressiveness (paradoxical aggression) has been observed following its use both in animals and man /19,28,102-104/.

Eltoprazine is very active in several models of offensive aggression, e.g., isolation-induced and inter-male aggression in male mice, territorial aggression (resident-intruder) and colony aggression in male rats and hypothalamically-induced aggression in male rats (this volume: Olivier, Mos and Rasmussen). The results, obtained with very extensive ethological observation and recording techniques /105/, point to very specific decreases in the offensive components of the behaviour.

Animals treated with eltoprazine (about 0.5 to 10 mg/kg by oral or parenteral route) are fully capable of normal social interactions

with members of the same species, but do not display the final consummatory parts of the offensive behavioural repertoire. These changes in offensive behaviour are not secondary to any general depressant or sedative effect of eltoprazine as there is no indication at behaviourally effective doses of sedation (sitting, lying, immobility), muscle relaxation, or sensory or motor disturbances.

In fact, the inhibition of offensive behaviour was accompanied by increases in social interest and exploratory behaviour. The latter finding cannot be ascribed to psychostimulant activity such as that found with d-amphetamine. Detailed behavioural analyses /33/ showed dramatic differences in the structure of the behaviour between eltoprazine- and d-amphetamine-treated animals /105/, indicating that eltoprazine did not induce stereotypies. Eltoprazine has, however, some limited stimulating effects on locomotor behaviour when animals were measured in exploratory situations as, for example, in hypothalamus-stimulated locomotion, photocell activity or open-field activity. It is possible that this stimulation is also present during social interactions, but is implemented as normal behaviours without interrupting them as does d-amphetamine or scopolamine. Therefore, it can be concluded that the potent anti-aggressive action of eltoprazine and other serenics is not caused by response incompatibility between locomotor stimulation and aggression.

Eltoprazine was active in play-fighting among juvenile rats. This behaviour is considered to be a form of agonistic behaviour which is a juvenile representation of later adult agonistic behaviour. Eltoprazine was active in the same dose ranges as in adult rats and showed a similar behavioural profile; i.e., the decrease in aggression was not accompanied by a decrease in activity. Eltoprazine was also active in an aggression paradigm evoked by mixing groups of piglets unknown to each other. Unlike azaperone, a neuroleptic which sedated the animals and only postponed aggression, eltoprazine inhibited fighting without sedation or other apparent side-effects.

Eltoprazine was also very active in a model involving aggression of a lactating female rat confronting an intruder to her nesting area. In this model, eltoprazine, like fluprazine, exhibits a different behavioural profile than that found in most male models. In particular, the stimulation of social interest and exploration is absent /106-108/. On the other hand, treated females are clearly not incapacitated as they exhibit typical maternal behaviours such as pup retrieving, burrowing of pups and pup care (suckling). The behavioural structure certainly does not point to the sedative effects characteristic of several other compounds /37,109/.

Eltoprazine effectively suppresses mouse-killing behaviour (muricide) in rats, a model which involves both predatory and feeding elements.

However, for a proper perspective, effects of eltoprazine in these models of agonistic behaviour in animals should be compared with other putative "anti-aggressive" drugs or other reference compounds. For this reason, a very short summary is given of the effects of representatives of the main pharmacological classes of psychotropic drugs in these models.

It is clear upon reviewing the literature /110/ that a considerable number of psychotropic drugs, representing various pharmacological classes, do influence aggressive behaviour in animals. Because of the different types of aggression in animals, interpretation of drug effects is often difficult, and generalisation from one type to another has to be treated with special caution.

In the past decade, several influential reviews have more or less comprehensively summarised the known effects of psychotropic drugs on aggression in animals /66,110-112/. In general, drugs may inhibit or facilitate aggressive behaviours, and the following paragraphs briefly outline the major effects.

9.1 CNS-stimulants

High doses of stimulants (e.g. amphetamine) suppress all kinds of aggressive behaviour, probably due to the stereotypy induced, leading to response incompatibility /113,114/. At low or moderate doses, a confusing picture emerges, as both enhancing and inhibiting effects have been reported /110/. These complex effects depend upon the stimulus situation, the species, the previous behavioural experience, the dose and the type of aggression invoked.

9.2 Antidepressants

There is a wide variation in the effects of antidepressants on agonistic behaviours and it is, consequently, difficult to generalise /110/. After acute administration of tricyclics, aggression is generally inhibited, but this is always accompanied by non-specific side effects /32/. On the other hand, after chronic dosing, the effects of antidepressants are often opposite to those after acute administration /110,115/. Lithium has anti-aggressive properties /116/, but its use is very limited due to its toxicity.

9.3 Neuroleptics (antipsychotics)

Neuroleptics have anti-aggressive activity, but these effects are behaviourally non-specific, being secondary to the heavy sedation

and severe motor debility which occur at the same dosages /32,33,110/.

9.4 Alcohol

Low doses of alcohol may facilitate certain kinds of aggression, while higher doses inhibit agonistic behaviours /110,116,117/ associated with non-specific motor and sensory depression /37,118/.

9.5 Barbiturates

Low doses may exacerbate aggressive behaviours, while higher doses inhibit these behaviours, due mainly to non-specific motor debility /110/.

9.6 Benzodiazepines

Again, low doses may increase aggression /78,103,104,106-108/, whereas high doses decrease aggression secondary to muscle relaxation. The taming effects described after benzodiazepine administration in animals and humans are mainly obtained after high doses. At lower doses, conflicting effects have been reported, including the known paradoxical increases in aggression.

9.7 Hallucinogens

Compounds such as LSD exhibit conflicting effects in animal agonistic behaviours /111/. There is no consistent effect and those which have been found are generally attributed to alterations in responsiveness rather than in the agonistic behaviour itself. Marijuana (Δ^9-THC) reduces all kinds of aggression in most animal species, but it also hampers the defensive capabilities of animals, which suggests that its anti-aggressive effects are non-specific /33,111/.

9.8 Anticonvulsants

Leaving aside such drugs as the barbiturates and benzodiazepines, the remaining anticonvulsants (e.g., diphenylhydantoin, primidone and carbamazepine) show contradictory effects on aggressive behaviour in both animals and man. In particular, the suggestion that anticonvulsants in man decrease episodic violent behaviour due to a dyscontrol syndrome (temporal lobe epilepsy) has not been conclusively answered as most data are derived from single case reports /22/.

9.9 Other drugs

Recently, there have been suggestions that centrally acting β-adrenergic antagonists may have specific anti-aggressive effects in some clinical situations and in animals as well /110/. This area of research clearly needs much more attention, but it may be pointed out that beta-blockers may have serious side-effects /38/.

X. OUR RESULTS

When we compare results obtained in our laboratory using other "anti-aggressive" compounds, a very similar picture emerges. We tested some of the compounds used clinically (e.g., Sch 12679, YG-19-256, chlordiazepoxide, haloperidol and chlorpromazine). It appeared that YG-19-256, Sch 12679, haloperidol and chlorpromazine all have anti-aggressive effects, but certainly coincident with and probably secondary to behaviourally non-specific effects, such as sedation (sitting, lying, immobility). Moreover, these compounds all inhibited the entire social repertoire (e.g., introductory social behaviour and avoidance in male rats) suggesting that the anti-aggressive effects were caused by highly non-specific behavioural effects /32,105/.

In our aggression paradigms, chlordiazepoxide had no anti-aggressive effect; rather it appeared even to be pro-aggressive in some models, a result which corresponds with the paradoxical increase in aggression previously observed both in animals and in man /19,66,102/.

Comparison of eltoprazine with the other compounds tested shows that *only* eltoprazine and other serenics have a demonstrably specific anti-aggressive profile in all the offensive models. This specificity should include a dose-dependent decrease in aggression, no impairment of social behaviour, no unwanted side-effects such as sedation, motor impairment, sensory incapacity or muscle relaxation. This profile underlines the unique properties of eltoprazine which, to our knowledge, is the most specific anti-aggressive compound found so far. The anti-aggressive qualities of eltoprazine are very pronounced in offensive aggression models (isolation-induced, inter-male aggression in mice and rats, territorial aggression and brain-stimulation-induced aggression in rats), but are also present in some other models (pig, maternal and predatory aggression).

Although aggression in males is more common than in females, females can behave quite aggressively. The fact that eltoprazine reduces female aggression, strongly indicates that eltoprazine does not exert its influence via testosterone, the male hormone which

has been closely coupled to the expression of certain kinds of aggression (inter-male; hypothalamic induced; territorial /119-121/). In addition, fluprazine (another serenic) inhibited muricide in castrated rats, which, we believe, suggests that the behavioural effect is not mediated by any central, testosterone-dependent mechanism /122/.

Finally, it should be noted that several investigators have confirmed the specific anti-aggressive effects of the first serenic, fluprazine, in both rats and mice /123-128/.

In general, eltoprazine has a reasonable-to-good duration of action with results somewhat dependent upon the species and paradigm used. After subchronic administration in mice and rats, either no (mice) or some (rats) minor tolerance has been noted. This indicates that the compound remains quite active after chronic use.

Eltoprazine had no significant influence upon defensive or flight capabilities. It had no activity in a defensive behaviour model in mice or on foot-shock-induced defensive behaviour. Fluprazine, on the other hand, had considerable activity in the latter model, possibly due to its analgesic properties which can interfere with the evoking stimulus, i.e., pain.

In a more ethologically valid paradigm, assessing the intruder's behavioural response to attack, eltoprazine was tested after both acute and chronic treatment to the intruders. Although acute dosing with eltoprazine shifted defensive and flight strategies from more active towards more passive forms, the absence of effects on other behaviours strongly indicates that the increase in inactive behaviours after eltoprazine has not been caused by incapacitating effects such as sedation or muscle relaxation. The unchanged aggressive behaviour of the attacker towards eltoprazine-treated intruders also suggests that the behaviour of the latter is not dramatically changed. Such an indirect drug effect on the behaviour of the attackers can be clearly observed after intruder treatment with haloperidol or d-amphetamine /37/. After seven days pre-treatment, and one wash-out day, intruders were not distinguishable from vehicle treated ones, suggesting that no rebound effects occur in defence/flight behaviour.

The pattern observed in defence/flight after eltoprazine is comparable to that observed after fluprazine /37/. The decrease in offence, concomitant with intact retention of social interest and defence behaviour, implies that serenics may be good candidates for the effective control of destructive behaviours in some clinical situations.

In summary, it can be suggested that the typical profile of the

specific anti-aggressive drugs, serenics, is an inhibition of the offensive components of agonistic behaviours without interference with the social or defensive capacities of the animals. While offensive behaviours are inhibited, they engage in all kinds of social interactions, including following, sniffing, approaching, and the like. This pattern typically differs from drugs belonging to other drug classes including those most often used in attempts to manage pathological destructive behaviour in the clinic /18,38,39,129,130/. The drugs used in these destructive states are largely chosen upon empirical grounds (and sedative effects) rather than by extrapolation from animal data or coherent study in patients. The non-specific effects of these drugs are clearly seen also in animal models of agonistic behaviour /109,114,131/.

In general, by characterising the effects of drugs in several paradigms of offensive and defensive agonistic interactions and by using ethological methodology, we believe it may prove possible to develop drugs which may specifically inhibit certain destructive behaviours, such as those which may be found associated with schizophrenia, mania, primary dementias, profound retardation and similar disorders /38/. The need for such drugs is further supported by some clinicians, who suggest that "the optimal pharmacologic agent has yet to be discovered" /23/. Therefore, serenics, on the basis of their specific behavioural profile in animal models of agonistic behaviour, will be tested in several states associated with destructive behaviours in patients.

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XI. REFERENCES

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