SERENICS: AN INTRODUCTION

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I. INTRODUCTION

The development of drugs, specifically aimed at reduction of pathological destructive behaviour in psychiatric patients, was started by our company halfway through the seventies. It was conceived, and this idea has been reinforced over the years, that pathologically destructive behaviour, sometimes called "aggressive", "violent", "agitated" or "dysfunctional", presents a delicate problem in psychiatry. Such behaviour, which is often a secondary complication of an underlying organic disorder such as dementia, traumatic brain injury, or profound mental retardation, is very often severely troublesome to family care-givers and leads to their unwilling commitment of their loved ones to institutional care. After these patients are institutionalized, their behaviour often continues to pose serious management problems. In some cases various behavioural modification techniques may facilitate functional integration within the institutional community. However, these techniques are labour intensive and not invariably successful. In most institutions, a residue of patients exhibiting significant destructive behaviour remains. These individuals demand a disproportionate measure of staff time, may require isolation and even physical or chemical restraint to protect other patients, the staff or themselves from undue risk of injury.

A striking variety of drugs has been tried in these patients /1/, but historically, neuroleptics or hypnotics, used for their sedative properties, and benzodiazepines (BDZ) have been most commonly used. The sedatives, of course, in doses adequate to control behaviour, often obliterate virtually all active behaviour, leading to a semi-vegetative state and BDZ may even lead to paradoxical increases in destructive behaviour /2-4/. More recently, lithium, beta-blockers and anticonvulsants have been tried. However, there are few well-controlled studies and, indeed, the actual modes of treatment, essential characteristics of the treated patients, or clear outcome measures are often missing in published reports. In any event, the drugs used have no specific effects upon behaviour (e.g., the neuroleptics) or are associated with significant adverse effects (e.g., neuroleptics and tardive dyskinesias; beta-blockers and hypotension; lithium and renal problems), or both. Therefore, we recognized in the early 1980s that there was a real need for compounds which might specifically inhibit destructive behaviour without other significant behavioural, psychiatric or somatic side effects. However, when addressing ourselves to the problems of synthesis, qualification and development of such compounds, we were immediately faced with limitations of the pharmacological

models many of which (if not most) had been developed empirically based upon the activity of known psychotropics.

To progress beyond the state-of-the-art at the time, therefore, we had to develop a set of animal models which would be functionally feasible to apply to a large number of candidate drugs; which might define the pharmacologic characteristics of classes of compounds yet unknown; and which could provide a credible basis for eventual trials in man. Section 2 has been devoted to a description of the animal models used.

In the remainder of this volume, the results of that effort are outlined and the characteristics of the series of such compounds called "serenics", which answer to a pharmacologic profile apparently unique in specific inhibition of offensive aggression, are described (section 3).

Moreover, the putative mechanism of action is described (section 4). In sections 5 - 8 the pharmacokinetic behaviour of eltoprazine in some species is examined. Section 5 describes the distribution of eltoprazine in rat and dog; section 6 the metabolite patterns in man, dog, rat and rabbit; section 7 focuses on the pharmacokinetics in the dog and section 8 the pharmacokinetics in healthy subjects. The final section discusses some of the therapeutical implications and existing pharmacotherapeutic options.

II. ANIMAL MODELS

Through the sixties and seventies, psychopharmacology laboratories often used simple and somewhat unnatural models involving agonistic behaviours (generically, if somewhat nonspecifically termed aggressive behaviours) in animals to detect putative psychoactivity of newly synthesized compounds. Generally, these models were focused upon a single response variable, such as isolation-induced fighting among male mice, to indicate psychoactivity essentially unrelated to the observed behaviour, in this case to indicate neuroleptic activity /5/. While such models are functionally simple to run and score and, therefore, suitable for screening, they do not reveal the mechanism of action and, therefore, can predict little if anything about the specificity of the observed effect and, excepting relative potency, nothing which might distinguish the compound under test from existing neuroleptics.

The aforementioned "isolation-induced aggression" in male mice was used as a primary screening model to determine a simple

and straightforward effective dose (ED_{50} in mg/kg orally) for the reduction of aggression. This measure, the dose of a drug which reduces aggression by 50%, is not informative as to how a drug reduces aggression and is consequently not predictive about the specificity of its behavioural effect. To describe the behavioural profile of a drug, we developed an ethological screening procedure, social interaction in mice, which is based on extensive ethological observation and recording of the ongoing behavioural items /6/. For this purpose we divided the behaviour into several elements which have been described before in detail /7/. These elements adequately describe the diverse aspects present in the behaviour of an isolated male mouse as offence, defence, social interest, flight exploration and self care. By carefully observing and recording the ongoing behaviour, often assisted by slow-motion video-analysis, it appeared possible to differentiate the behavioural profile of several drugs /6,8-10/. Using this animal model it appeared possible to distinguish specific anti-aggressive drugs from non-, or less-specific drugs.

In several publications /6,9/, we have shown that inhibition of aggression can be accompanied by inhibition of other behaviours (social interest, exploration) leading to a nonspecific profile (e.g. neuroleptics), but it also shows the profile in which social behaviour and exploration remain intact (e.g. fluprazine, eltoprazine). This latter, highly specific anti-aggressive profile has been depicted by us as the SERENIC profile /9/.

This profile has been elaborated in other animal models describing the anti-aggressive profile of drugs, e.g., in rats.

In our laboratory we have tested new putative serenic compounds in what we call a behavioural cascade (Fig. 1).

After a first screening of all newly synthesized compounds in aggressive mice for anti-aggressive activity, in which the only criterion is a certain ED_{50}-value, any compound which has better activity than the preset ED_{50}-value is tested in the Social Interaction test in mice. Compounds are tested in a dose range comprising the ED_{50} to 25 times higher than the ED_{50} for inhibition of aggression. A compound will only proceed through the cascade if the ratio ED_{50} inactivity/ED_{50} aggression is larger than 25, which means that we want at least a factor of 25 between anti-aggressive and non-specific effects like sedation, muscle relaxation, etc. A drug with such a profile will consecutively be tested in the Resident-Intruder, the Hypothalamic Aggression and Maternal Aggression paradigms in rats, in order to judge whether it exerts a behaviourally specific, i.e. serenic, profile. The extensive description of all the models used is given in section 3.

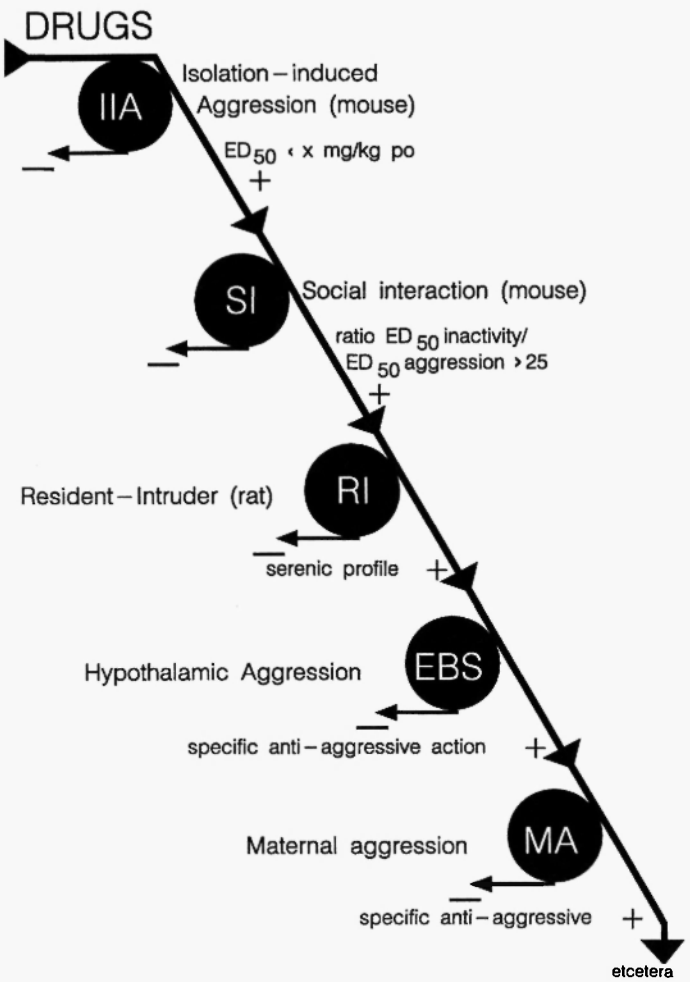


Fig. 1: Behavioural cascade to detect serenics.
The primary test is isolation-induced aggression in mice. When a certain ED_{50} value (mg/kg p.o.) is found, a social interaction test in mice is performed. When a large ratio (>25) between the ED_{50} for enhancement of inactivity (sedation) and the ED_{50} for inhibition of aggression is found, the drug proceeds to the resident-intruder paradigm in rats where a specific anti-aggressive profile is needed before continuation occurs along the cascade towards hypothalamic aggression and maternal aggression.

III. CHEMISTRY

In this part we summarize the chemical development of the serenics. In a combined lead-finding and screening operation in the mid-seventies, about 2,000 chemical structures, selected from different chemical classes, were screened for potential anti-aggressive activity in the isolation-induced aggression test in mice. In 1975 we detected some phenylpiperazine-analogues which fulfilled our primary pharmacological criteria for a non-sedative anti-aggressive structure. These compounds were the starting point for further chemical optimalisation. During the following exploration and optimalisation period, about 50 new phenylpiperazine analogues were synthesized /11/. In 1980, one of them (DU 27716; fluprazine) was, based on its promising anti-aggressive and pharmacological profile, selected for further development. This development was stopped in 1982 because of toxic problems in animals. Meanwhile, the optimalisation strategy, directed by increasing knowledge of the structure-activity relationships of this chemical class, shifted to a new class of up to then unknown bicyclic-heteroaryl-piperazines (Fig. 2).

This was based on our findings that 2- and 3-methoxy-phenylpiperazines (Fig. 2A2 and 2A3) were both active in isolation-induced aggression, whereas anti-aggressive activity was largely lost in the 2,3-dimethoxyphenyl compound (Fig. 2A1). Combination of these two substituents into a benzodioxan structure (Fig. 2C1) resulted in a remarkable anti-aggressive activity. This finding was further explored by designing an extensive series of analogues, using structure-activity relation studies (SAR). All these compounds were tested for anti-aggressive activity in the isolation-induced aggression test. This resulted in the selection of a number of interesting compounds, of which, in 1984, after the withdrawal of fluprazine, a new serenic (eltoprazine, Fig. 2) was selected for further investigation. Based on the information that it was allowed to combine the substituents on position 2 and 3 in the phenyl ring, we designed a series of bicyclic compounds with the general structure shown in the center of Fig. 2, containing in the annelated ring one or more atoms from the group of carbon, oxygen, sulphur or nitrogen. After the often laborious syntheses of these new heterobicyclic structures, they were screened for anti-aggressive activity, resulting in additional information about the relation between the chemical structure and anti-aggressive activity in mice. It appeared that annelation of a heterocyclic ring was allowed and that there were neither large differences in potency between the compounds with the annelated 5-, 6- or 7-hetero ring analogues,

nor between oxygen, sulphur and/or nitrogen containing rings, as illustrated in Figs. 2B, C, D. Moving the piperazine ring from the 1-position to the 6-position (Fig. 2H1) of the phenyl ring resulted in a complete loss of the anti-aggressive activity, indicating that

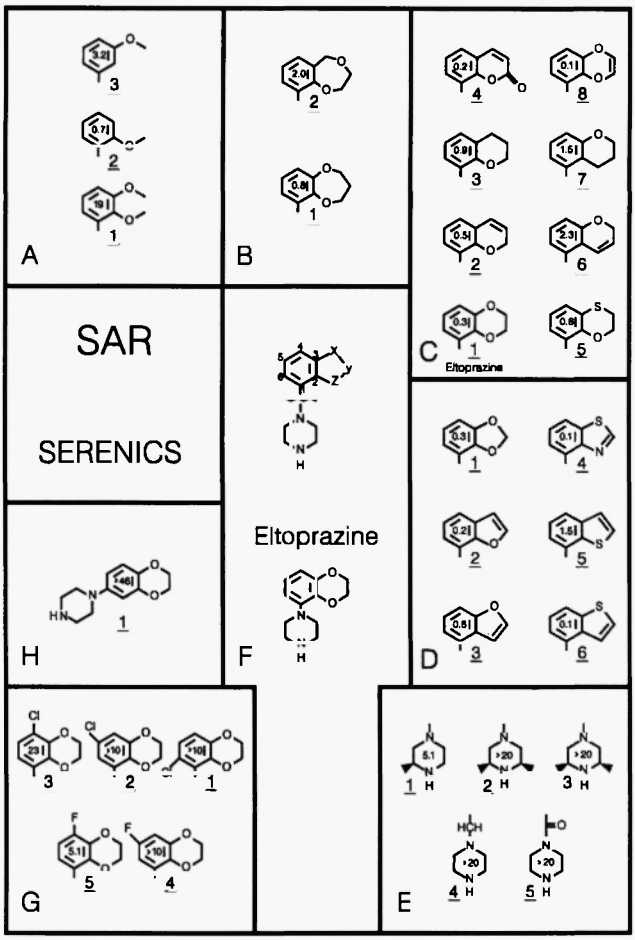


Fig. 2: Structure activity relation (SAR) of serenics.
The central part shows the mother molecule basic to several chemical modifications of different parts of this basic molecule. The figures in either the phenyl ring or the piperazine ring depict the oral ED_{50}-values to inhibit aggression in mice.

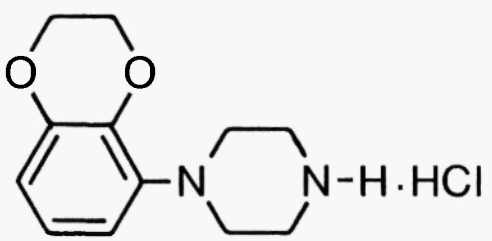
substitution of the para-position (opposite to the piperazine nitrogen) is not allowed. This may be explained by alterations in physical-chemical properties and/or steric factors. Additional substitution in the phenyl ring, for instance by chlorine or fluorine (as illustrated in Fig. 2G 1-5), resulted in a strong decrease of anti-aggressive activity when compared to the unsubstituted compound (eltoprazine). Relatively small variations in the piperazine ring, or insertion of a carbonyl- or methylene function between the phenyl and the piperazine ring (Fig. 2E; 1-5) also strongly diminished the anti-aggressive potency compared with the parent compound. Besides an ED_{50} for inhibition of isolation-induced aggression, the compounds were also screened for *in vitro* serotonergic (5-HT_1) receptor affinity.

High affinities for serotonin receptors were found for all derivatives with anti-aggressive properties. Correlation of the latter with serotonin 1A, 1B or 1C receptor affinity strongly suggests that the anti-aggressive activity is mediated by a 5-HT_1-like activity.

IV. ELTOPRAZINE: PHYSICAL AND CHEMICAL PROPERTIES

The chemical structure of eltoprazine hydrochloride (in all the following articles named "eltoprazine") is shown in Fig. 3.

Eltoprazine (DU 28853)



1-(2,3-dihydro-1,4-benzodioxin-5-yl)-piperazine hydrochloride

Fig. 3: Chemical structure of eltoprazine hydrochloride.

The chemical name for eltoprazine hydrochloride is 1-(2,3-dihydro-1,4-benzodioxin-5-yl)piperazine hydrochloride ([CAS-98206-09-8]). Its melting point is 263.1 - 263.6°C and its molecular weight 256.7.

Eltoprazine hydrochloride has an excellent solubility (19 g/100 ml water at room temperature).

In all the animal experiments described, eltoprazine hydrochloride has been used as the active drug substance and doses are always given in mg of the HCl salt per kg body weight.

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