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Effects of beclamide on isolation-induced aggression and locomotor activity in mice

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Abstract—The anti-aggressive effects of orally administered beclamide (N-Benzyl-β-chloropropionamide) have been studied in male albino mice which were individually isolated for a 28-day period. Beclamide (50–250 mg kg^{-1} p.o.) caused an overall dose-dependent increase in the attack onset latency, a reduction in the percentage of animals attacking and the mean number of attacks/animal for this model of aggression. In addition, the highest dose of beclamide (250 mg kg^{-1} p.o.) did not significantly modify locomotor activity in mice. It was concluded that beclamide induced anti-aggressive effects at non-sedative doses. This anti-aggressive action was thought be at least partially mediated, through a beclamide-induced release of 5-HT from presynaptic sites.

Though originally employed as an anticonvulsant agent, beclamide (N-Benzyl-β-chloropropionamide (Nyrane)) has more recently been used in the treatment of behavioural disorders (Sime & Easby 1974). In clinical studies the drug has been found to be of benefit in stabilizing mood, reducing anxiety (Pavulans et al 1975), ameliorating aggressive and destructive antisocial conduct, and in improving impulsive and demanding behaviour in mentally handicapped patients with epilepsy (Delay et al 1958).

Several studies have provided evidence that biogenic monoamines are involved in aggressive behaviour in animals. In particular both noradrenaline and 5-hydroxytryptamine (5-HT) appear to play an important role in aggression (Garattini et al 1969) whereby a drug-induced reduction in central noradrenergic activity (Ross & Ögren 1976; Lassen 1978), or an increase in 5-HT function (Yen et al 1959), give rise to anti-aggressive effects. It has previously been reported (Darmani et al 1986) that beclamide in a single dose reduces 5-HT and dopamine levels in the rat striatum by increasing pre-synaptic release and turnover. Similar effects have been found in the rat frontal cortex (unpublished observations).

Since no substantial clinical or experimental work has been reported on the anti-aggressive properties of beclamide, the present investigation was undertaken to determine its effects on extended isolation-induced aggression in mice. Additionally, any possibility of beclamide sedation at anti-aggressive doses was explored using a locomotor activity model.

Materials and methods

Male albino mice of the ICI GB1 strain, bred in the animal facility of the Welsh School of Pharmacy, were used. After

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weaning (at 19–21 days), mice were grouped in tens in opaque polypropylene cages measuring 45 × 30 × 12 cm with wire tops containing freely available supply of food and water, and under a 12 h light/dark cycle.

Isolation-induced aggression. The isolation programme was similar to that described by Benton (1981), Benton et al (1983, 1984). Briefly, after 7 days of grouped-housing, half the animals were housed individually in wire-topped polypropylene cages (30 × 12 × 11 cm) for a further 28 days. These animals were then randomly assigned to one of four treatment categories receiving either an oral (p.o.) dose of vehicle (0·75% carboxymethylcellulose), or 50, 100 or 250 mg kg^{-1} beclamide (p.o.) (Rona Labs, Hitchin, UK) suspended in vehicle. The remaining group-housed mice were designated as "standard opponents". These were not inherently aggressive and were rendered anosmic by nasal perfusion with 4% ZnSO$_4$ solution under light ether anaesthesia 72 and 24 h before testing. The tests were carried out under subdued red light during the dark phase (21.00–24.00 h). Isolated animals were pretreated with drug or vehicle 45 min before an experiment and each test involved the introduction of a standard opponent in to the home cage of an isolated individual for 10 min. Home cages were not cleaned for at least 24 h before the test to partially standardize olfactory conditions within the test arena.

During the 10 min test, the following behaviours were noted: episodes of direct attack aggression characterized by biting or kicking often accompanied by vocalization (see Benton et al 1984), interspersed with normal exploratory and self-grooming behaviour. The aggressive behaviour was evaluated by a single observer using the following individual measures described by Benton (1981): latency(s) to onset of initial attack, percentage of animals attacking and the total incidence of attacks per animal. There was a negligible incidence of initiated attacks by standard opponents and in such rare cases these episodes were excluded from the assessment.

Locomotor activity. Locomotor activity was measured during the dark phase in non-isolated animals using paired photocell cages fitted with three light beams. Single animals (treated and vehicle-treated controls) were tested simultaneously following 1 h habituation to the cages and cumulative locomotor activity (beam interruptions) was counted electronically at 20 min intervals for a 100 min after oral dosing with beclamide.

Statistical comparisons between mean values in the experiments were made using the Mann-Whitney U test.

Table 1. Dose-dependent increase in latency to onset of initial attack by the isolated aggressive mice. The Mann-Whitney U test was used to compared controls to each dose of beclamide.

| | Vehicle control | Beclamide dose (mg kg⁻¹ p.o.) | | |
		50	100	250
Attack onset latency (s)	37 ± 13.4	111 ± 36.7	115 ± 41	594.2 ± 5.5
Significance		< 0.03	< 0.02	< 0.0001

Results

In the isolated animals, beclamide increased the latency to onset of attack in a dose-dependent manner. Thus at the 50 mg kg⁻¹ dose there was a significant $(P < 0.02)$ three-fold increase in attack onset latency compared with vehicle-treated controls and this was further increased to such an extent by the 250 mg kg⁻¹ dose that it was very highly significant (see Table 1).
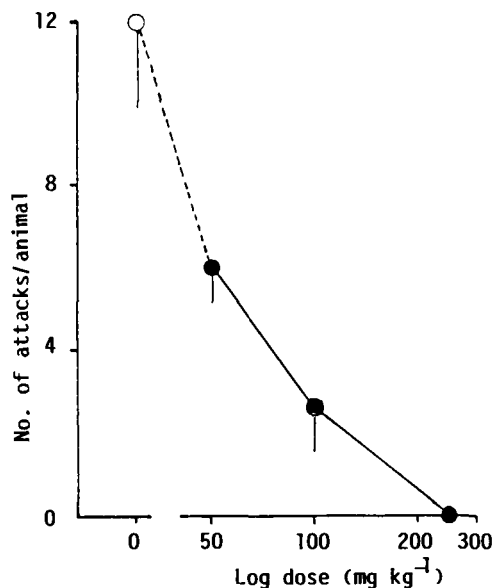

FIG. 1. Log dose-response curve for orally administered becalmide-induced (●) inhibition of aggressive behaviour (group mean number of attacks per animal in 10 min) compared with vehicle-treated control mice (O). The vertical bars represent s.e.m. (n = 10).
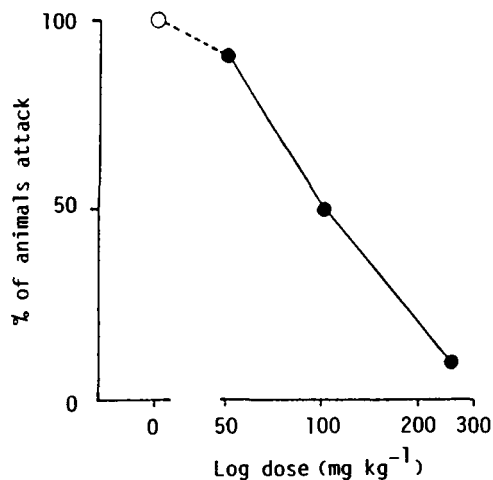

FIG. 2. Log dose-response curve for orally administered becalmide-induced (●) inhibition of aggressive behaviour (% of animal attacks in 10 min) compared with vehicle-treated control mice (O) (n = 10).

In accord with the above observation, the mean number of attacks per animal in 10 min was significantly $(P < 0.001)$ decreased dose-dependently down to a mean of 0.1 attack/animal (i.e. one attack in 10 animals) at the 250 mg kg⁻¹ dose of beclamide (Fig. 1). Similarly, the percentage of animals displaying attack behaviour was decreased linearly (r = 0.961 Fig. 2) by beclamide, there being a 90% reduction in number of animals attacking after 250 mg kg⁻¹ compared with vehicle-treated controls. There were no overt changes in the normal pattern of exploratory or self-grooming behaviour seen at any of the beclamide dose levels studied. Beclamide (250 mg kg⁻¹ p.o.) did not produce any effect on locomotor activity, there being no significant differences $(P > 0.05)$ between cumulative counts in treated or control animals at any of the readings up to 100 min after drug administration (Fig. 3). This lack of difference from control values was most notable between 45 and 55 min after dosing since this corresponded to the period of evaluation of beclamide's anti-aggressive activity in the isolated animals (Figs 1, 2, Table 1).
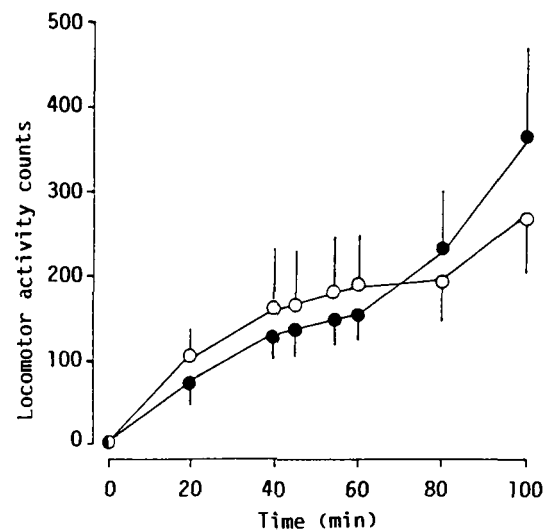

FIG. 3. Effect of beclamide (250 mg kg⁻¹ p.o. ●) compared with vehicle treated controls (O) on cumulative locomotor activity counts in mice (n = 5). Treatments were given at 0 min and each point is a group mean value, the verticle bars representing s.e.m.

Discussion

Along with the advent of new and more powerful anticonvulsant drugs, the clinical use of beclamide (Nydrane) as an antiepileptic agent has declined. However, in conditions where epilepsy is part of the diagnosis such as those occurring in mentally retarded patients, behavioural disorders and temporal lobe epilepsy, its use has continued (Delay et al 1958; Melin 1970; Sime & Easby 1974; Pavulans 1975). In those clinical reports, aggressive behaviour was a part of the diagnosis and it was significantly reduced by beclamide.

The present study shows that beclamide reduces aggressive behaviour in isolated male mice dose-dependently and over a dose-range in which it causes no sedation (Darmani et al 1987). The acute dose required to reduce aggressive attacks by 50% (50 mg kg⁻¹) is eight times less than the dose required to reduce the convulsive score by 50% in mice in the maximal electroshock and leptazol seizure tests (Sehmbhi 1981). The daily dosage of beclamide as an antiepileptic agent recommended by the British National Formulary (1987) is between 3 and 4 g daily for adults. Thus it is reasonable to assume that much lower doses are required to produce its anti-aggressive effects.

One approach to the management of behavioural disorders with aggression is treatment with neuroleptics. Since their effective clinical value is restricted by side-effects (Peuch et al 1962), beclamide provides an approach attended by few side-effects and a wide margin of safety (Hawkes 1952).

A further advantage of the drug is that in acute doses (250 mg kg^{-1}) it causes no reduction of motor activity (Darmani et al 1987) and thus appears to produce its anti-aggressive action without major effects on other behaviours. Since drugs with anti-aggressive properties invariably induce an increase in 5-HT or a decrease in noradrenaline function, it may be hypothesized that beclamide produces its anti-aggressive effects, at least partially, through 5-HT release from presynaptic sites (Darmani et al 1986).

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The influence of urotensin II on calcium flux in rat aorta

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Abstract—The fish neuropeptide urotensin II (UII, 10 nM) caused a 51% increase in uptake of ^{45}Ca by segments of rat aorta; this increase was abolished by the Ca channel blocking drug nitrendipine (200 nM). ^{45}Ca efflux was unchanged in the presence of UII, but was significantly increased following washout of the peptide; again, this increase was not observed in the presence of nitrendipine. The results provide direct evidence that the nitrendipine-sensitive component of the contractile response of rat aorta to UII involves mobilization of extracellular Ca, with subsequent activation of a Ca-induced, Ca-release process intracellularly. The mechanisms responsible for the nitrendipine-resistant component of the contractile response to UII remain to be established.

Urotensin II (UII) is a dodecapeptide neurohormone which was first detected in the caudal neurosecretory system of teleost fish (Bern et al 1985). It has been known for some time that UII produces smooth muscle contraction and osmoregulatory changes in fish (Bern et al 1985), but it is only in recent years that clear biological effects have been demonstrated in mammalian species (Larson et al 1985). Of particular interest, in terms of

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pharmacology, has been the demonstration of potent effects of UII on cardiovascular function in rats (Gibson et al 1986). Most recently, two studies have shown that UII produces complex changes in tone of rat aorta in-vitro, causing endothelium-dependent relaxations (Gibson 1987) and more predominant, endothelium-independent contractions (Itoh et al 1987; Gibson 1987). Both studies reported preliminary investigations into the role of calcium ions (Ca) in the contractile response to UII. Gibson (1987) found that the contraction consisted of two components, phasic and tonic. The phasic response was dependent on extracellular Ca and was blocked by the Ca channel blocking drug nitrendipine; the tonic contraction was also dependent on extracellular Ca, but was more resistant to Ca depletion and was not blocked by nitrendipine. Itoh et al (1987) also found that a large component of the UII-induced contraction (about 50%) was inhibited by Ca channel blocking drugs, and that most of the residual response was dependent on extracellular Ca. However, these workers found a small component (about 10% of the original, full contraction) that persisted in the absence of extracellular Ca, and suggested that this might be due to Ca released from intracellular stores. Thus, the results