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Acute Effects of Beclamide on Brain Regional Monoamine Concentrations, their Metabolites and Radioligand Binding Studies

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Abstract—The effects of beclamide on regional brain monoamine levels and radioligand binding have been studied in rats. One hour oral pre-treatment with beclamide (400 mg kg^{-1}) increased rat striatal dopamine turnover by increasing the levels of its major metabolites (DOPAC and HVA) three-fold. Simultaneously the drug reduced the concentration of striatal dopamine by a similar factor, and the concentrations of 5-hydroxytryptamine, (5-HT), 5-hydroxyindoleacetic acid, (5-HIAA) and 3-methoxytyramine in the striatum were reduced below the detection limits of the assay. In the frontal cortex, beclamide depleted the dopamine, 5-HT and 5-HIAA content whilst having no significant effect on the noradrenaline level. The concentrations of bioamines and their metabolites in the hypothalamus were unaffected by such acute beclamide treatment. In radioligand binding studies beclamide lacked affinity and failed to displace radioligands from α_2, β, 5-HT, 5-HT_2 and dopamine D_2 sites in selective loci of the rat brain.

Beclamide [*N*-benzyl-β-chloropropionamide] was originally employed as an antiepileptic agent and has more recently been used in the treatment of behavioural disorders (Sime & Easby 1974; British National Formulary 1987). In conditions where epilepsy is part of the diagnosis, such as behavioural problems in mentally retarded patients, beclamide has also been indicated (Delay et al 1958; Melin 1970; Pavulans et al 1975). In all of the above reports, aggressive behaviour was a component of the clinical diagnosis, and was significantly reduced by beclamide. Moreover, the drug was found to be of benefit in stabilizing mood, reducing anxiety, ameliorating destructive antisocial conduct and improving impulsive and demanding behaviour in mentally handicapped epileptic patients.

Several studies have provided evidence that biogenic monamines are involved in aggressive behaviour in animals. 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; Eichelman 1987), yields antiaggressive activity. Recently, we reported dose-dependent inhibitory properties of beclamide on isolation-induced offensive behaviour in mice (Darmani et al 1988). Since offensive behaviour is associated with changes in monoamine function in the CNS, the present study was undertaken to examine the acute effects of beclamide on levels of monoamines and some metabolites in discrete areas of rat brain. In addition, our preliminary monoamine determination experiments indicated that beclamide may act as a monoamine depletor. Since previous studies in this field have used the frontal cortex, striatum and hypothalamus in monoamine determinations for accepted depletors, (Anden 1967; Pettibone et al 1984; Hong et al 1987a) we have investigated beclamide's effects on the same brain regions.

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Materials and Methods

Determination of monoamine levels

Male Wistar rats, 150–200 g, were housed under a 12/12 h light/dark cycle and had free access to food and water. A pharmacologically active oral dose of either beclamide (400 mg kg^{-1} suspended in 0·75% sodium carboxymethylcellulose) (Darmani 1988) or vehicle was administered. One hour later animals were killed and the striatum, frontal cortex and hypothalamus rapidly removed (Glowinski & Iversen 1966) and frozen in liquid nitrogen. Each tissue sample was homogenized using a Teflon-glass homogenizer in 1 mL ice-cold perchloric acid (PCA, 0·1 M) and centrifuged for 25 min at 3000 *g* to precipitate protein. The supernatant was frozen in liquid nitrogen and subsequently stored at −20°C until analysis within 3 weeks. The protein content of the homogenate was determined using a protein assay kit reagent. HPLC was used for separation and detection of monoamines and their metabolites (Darmani 1988). In brief, a Hichrom column (25 cm × 4·9 mm i.d. ODS C_{18}) was connected to an LDC Constametric pump and an LKB 2143 electrochemical detector. It was possible to separate simultaneously dopamine, 5-hydroxytryptamine (5-HT) and four of their major metabolites, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxytyramine (3-MT) and 5-hydroxyindoleacetic acid (5-HIAA), in the following mobile phase: 5% methanol, 5 mM butylamine, 0·5 mM sodium octane sulphonic acid, 0·15 mM EDTA in 0·1 M citrate/acetate buffer, pH 5·0. A second mobile phase containing 2% methanol, 2 mM sodium octane sulphonic acid, 0·15 mM EDTA in 0·1 M acetate/citrate buffer solution, pH 5·0 was used to separate noradrenaline.

In-vitro radioligand binding studies

Rats were decapitated and brains were removed rapidly and dissected on a cold petri-dish on ice. Different brain regions (frontal cortex, hippocampus, striatum or temporal cortex) were removed and homogenized in 30 vol (w/v) of ice-cold Tris HCl buffer in an Ultraturrux rotor homogenizer (setting

Table 1. Summary of radioligand binding parameters.

Brain region	D_2[a] Striatum	5-HT_1[b] Hippocampus	5-HT_2[b] Frontal cortex	α_2[c] Temporal cortex	β[c] Temporal cortex
Buffer	Tri-HCl 50 mM	Tris-HCl (50 mM) 4 mM $CaCl_2$	Tris-HCl 50 mM	Tris-HCl 50 mM	Tris-HCl 50 mM
pH	7·6	7·4	7·4	7·7	7·4
Incubation temp.	37°C	37°C	37°C	25°C	37°C
Time	15 min	15 min	15 min	15 min	15 min
Non-labelled displacer and concentration	Butaclamol (1 μM)	5-HT (1 μM)	5-HT (100 μM)	Noradrenaline (2 μM)	Propranolol (2 μM)
Tritiated ligands concentration	Spiperone (0·1–10 nM)	5-HT (0·1–5 nM)	Spiperone (0·1–5 nM)	Clonidine (0·5–6 nM)	Dihydroalprenolol (0·25–4 nM)

[a]O'Boyle & Waddington (1984), [b]Stolz et al (1983), [c]Wong et al (1985).

5 for 20 s). This crude homogenate was further homogenized using a glass-Teflon homogenizer (700 rev min^{-1}, 10 s, 120 μm clearance). The homogenate was centrifuged in an MSE Europa 65M centrifuge at 48 000 *g* for 20 min at 4°C. The pellet was resuspended in 30 vol of ice cold buffer and further homogenized using the glass-Teflon homogenizer. The homogenate was frozen in liquid nitrogen and was stored at −20°C until use.

Binding incubations

The frozen membrane suspension was thawed and incubated for 15 min at 37°C, followed by the addition of pargyline to give a final concentration of 20 μM. For Scatchard analysis, portions of membrane suspension (200 μL) in triplicate were incubated with various tritiated ligands (100 μL) plus 10 μM beclamide in a final volume of 1 mL. Non-specific binding was defined as that remaining in the presence of appropriate unlabelled displacers (100 μL). All assays were carried out in 5·0 mL disposable plastic test-tubes. Assay conditions for measuring D_2-, 5-HT_1-, 5-HT_2-, α_2- and β-receptor binding are summarized in Table 1 according to the stated published methods. In displacement studies a fixed concentration of tritiated ligand (1 nM) was incubated with increasing concentrations of beclamide.

Incubations were terminated by the addition of 4 mL ice-cold buffer, followed by filtration and washing the tissue twice through Whatman GF/B filters. The filtered membranes were added to 4 mL Cocktail T scintillation fluid and counted 24 h later.

Drugs

The following drugs were obtained from Sigma, UK: dopamine hydrochloride, DOPA, DOPAC, 5-HIAA, 5-HT creatinine sulphate, HVA, 3-MT hydrochloride, noradrenaline hydrochloride and propranolol. Butaclamol was from Ayerst and butylamine from Aldrich. Beclamide was a gift from Rona Labs (UK). [^{3}H]Dihydroalprenolol (specific activity 73 Ci $mmol^{-1}$), [^{3}H]clonidine (s.a. = 24·1 Ci $mmol^{-1}$); [^{3}H]5-hydroxytryptamine creatinine sulphate (s.a. = 31·3 Ci $mmol^{-1}$) and [^{3}H]spiperone (s.a. = 64·4 Ci $mmol^{-1}$) were obtained from Amersham. Other materials were bought from BDH. For in-vitro radioligand binding studies, beclamide and its metabolites were dissolved in 100 μL DMSO and then diluted with buffer.

Results

Effects of beclamide on the levels of monoamines and metabolites in discrete rat brain areas

One hour beclamide pre-treatment at a dose (400 mg kg^{-1} p.o.) which produces both anticonvulsant and anti-aggressive activity without sedation (Sehmbhi 1981), evoked a 3·2-fold decrease (176 ± 40 pmol (mg prot.)$^{-1}$, $P < 0.05$) in the striatal dopamine level and two differing effects on its free metabolites. The levels of DOPAC and HVA (103.2 ± 9 and 23.0 ± 1.8 pmol (mg prot.)$^{-1}$, respectively, were increased to 3 times the pretreatment concentrations (i.e. 399.4 ± 43 and 67.5 ± 11, respectively) and that of 3-MT fell below the detection limit of the assay (250 pg). Similar to the changes in 3-MT levels, the striatal 5-HT and 5-HIAA concentrations (23.6 ± 2.7 and 28.4 ± 3 pmol (mg prot.)$^{-1}$, respectively) were reduced below the detection limits of the assay (75 pg) (Table 2).

In rat frontal cortex, beclamide reduced the concentrations of dopamine, 5-HT and 5-HIAA (5.95 ± 2.1, 38.3 ± 2.4 and 18.8 ± 1.7 pmol (mg prot.)$^{-1}$, respectively) below the detection limits of the assay. No free DOPAC, HVA or 3-MT could be detected in either control or treated frontal cortices. Furthermore, beclamide had no significant effect ($P > 0.05$) on the levels of noradrenaline in this region (Table 2). It was not possible to measure the levels of the principal noradrenaline metabolites because 3,4-dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG) are mainly present as sulphated conjugates in rat brain. Sulphated agents are not detectable using HPLC-ECD and even hydrolysis of these sulphated metabolites causes co-elution of unknown substances with DHPG and MHPG. In the hypothalamus, beclamide did not induce a significant change in the concentrations of noradrenaline, dopamine, 5-HT, DOPAC, HVA or 5-HIAA (Table 2). No 3-MT was detected in either control or treated hypothalamic supernatant.

In-vitro effects of beclamide and its metabolites on monoamine-ligand binding sites

Regression analysis of the Scatchard plots for [^{3}H]spiperone binding to rat striatal D_2-sites, [^{3}H]5-HT to hippocampal 5-HT_1-sites, [^{3}H]spiperone to 5-HT_2-sites in frontal cortex, [^{3}H]clonidine to cortical α_2-adrenergic sites and [^{3}H]dihydro-

Table 2. The acute (400 mg kg^{-1} p.o., 1 h) effects of beclamide on the steady state levels of noradrenaline, dopamine, 5-HT and some of their major metabolites in discrete regions of the rat brain.

		Noradrenaline	Dopamine	DOPAC	HVA	5-HT	5-HIAA
Striatum (n=6)	Control		565±35·0	103±9·0	23·0±1·8	23·6±2·7	28·4±3
	Beclamide		176±40·0***	399·4±43***	67·5±11	ND***	ND***
Hypothalamus (n=6)	Control	135·7±31·9	49·5±9	5·5±0·23	2·3±0·2	63·9±9	20·4±3·8
	Beclamide	181·2±27	54·5±13·9	4·8±0·39	2·1±0·18	78·0±9·8	31·6±6·1
Frontal cortex (n=6)	Control	27·4±2·3	5·95±2·1	ND	ND	38·3±2·4	18·8±1·7
	Beclamide	22·0±1·4	ND***	ND	ND	ND***	ND***

Concentrations expressed as mean pmol (mg prot.)$^{-1}$ (±s.e.m.) obtained from 4–6 animals. Group differences between controls and beclamide pretreated animals were assessed using Student's *t*-test. *** $P<0·01$, ND = not detected (i.e. below limits of assay where the lowest detectable monoamine level was used for statistical comparison).

Table 3. In-vitro effects of beclamide on radioligand binding parameters on α_2, β, D_2, 5-HT and 5-HT_2 receptor sites. Values are means±s.e.m. (n=4, $P>0·05$) (B_{max} = fmol (mg prot.)$^{-1}$).

	5-HT_1		5-HT_2		D_2		α_2		β	
	K_d (nM)	B_{max}	K_d (nM)	(B_{max})	K_d (nM)	B_{max}	K_d (nM)	B_{max}	K_d (nM)	B_{max}
Control	2·64± 0·52	187± 36	1·2± 0·19	270± 7·8	0·32± 0·003	255± 6·4	1·93± 0·17	46± 9	2·8± 0·09	97± 18
Beclamide (10 μM)	2·5± 0·56	188± 42	1·1± 0·12	258± 10·4	0·3± 0·015	247± 0·33	2·0± 0·11	48± 11	2·5± 0·17	89± 17

alprenolol bound to cortical β-adrenoceptor sites showed no significant difference in B_{max} and K_d between control and beclamide (10 μM)-treated brain tissue homogenates (Table 3). Drugs used as positive controls for the above receptor systems (i.e. (+)-butaclamol, propranolol, ketanserin, phentolamine or pindolol) all decreased specific binding of the appropriate radioligand concentration-dependently (Darmani 1988).

Discussion

Aggressive behaviour is sometimes associated with other central disorders such as schizophrenia and temporal lobe epilepsy in mentally subnormal patients and those with hyperkinetic syndromes. In these conditions a variety of drugs such as barbiturates, benzodiazepines, phenothiazines, carbamazepine, diphenylhydantoin, lithium and reserpine has been clinically prescribed (Dostal & Zvolski 1970; Itil & Wadud 1975; Itil & Mukopadhyay 1978; Itil & Reisberg 1979) though their clinical value may be restricted by side effects. Beclamide usage has provided an approach attended by few side effects and a wide margin of safety (Hawkes 1952; British National Formulary 1987). Moreover, beclamide at effective doses lacks sedative effects (common to most anti-aggressive drugs) since it does not depress locomotor activity after continued dosage and enhances this behavioural parameter mildly in the acute situation (Darmani et al 1987); at the same time beclamide has been found to be eight times more effective in reducing offensive behaviour than in decreasing convulsive score in animal studies (Sehmbhi 1981; Darmani et al 1988). Despite the clinical use of beclamide for nearly three decades, there is a dearth of information on its mode of action in the CNS.

The present study reports that beclamide treatment reduced rat striatal dopamine levels 3-fold and increased its turnover (as shown by a similar increase in the levels of its major metabolites DOPAC and HVA). It also depleted striatal 5-HT stores and reduced the level of its major metabolite 5-HIAA below the detection limit of the assay. Furthermore, beclamide selectively reduced the levels of dopamine, 5-HT and 5-HIAA (below detection limits) in the rat frontal cortex, although it had no significant effect on the noradrenaline concentration ($P>0·05$) (neither DOPAC nor HVA could be detected in frontal cortices from control or beclamide-treated rats). Moreover, beclamide caused no significant change in the levels of noradrenaline, dopamine, 5-HT, DOPAC, HVA or 5-HIAA in the rat hypothalamus. Thus the present results indicate that beclamide has induced selective depletion of bioamines in discrete areas of the rat brain. Similar regional differential effects have been reported for tetrabenazine (Pettibone et al 1984). Out of the three monoamines studied, dopamine appeared to be most sensitive to the effects of tetrabenazine since its levels in the striatum and hypothalamus were reduced by 70–75%. Tetrabenazine depleted cortical levels of noradrenaline and reduced the concentration of 5-HT in the rat cortex, striatum and hypothalamus to a similar extent. On the other hand noradrenaline level (similar to beclamide effect in the present study) in the hypothalmus was most resistant to tetrabenazine. Such regional differential effects have also been reported for reserpine (Anden 1967).

Several drugs in acute doses increase dopamine turnover, including cocaine, nomifensine, amphetamine, neuroleptics and bioamine depletors (Di Guilio et al 1978; Hong et al 1987a). These drugs raise synaptic dopamine concentration by various mechanisms: disruption of storage granules

Table 4. Comparison of the effects of acute administration of oxypertine, tetrabenazine, reserpine, chlorpromazine, trifluperazine (Hong et al 1987a) and beclamide (present study) on the steady state levels of dopamine and its major metabolites DOPAC and HVA in the rat striatum.

Acute	Dosage	Dopamine	DOPAC	HVA
Control		492·7±26·1	41·9±2·7	36·2±3·8
Oxypertine	10 mg kg^{-1}, i.p.	305·7±20·4	121·3±9·4*	99·8±6·6*
Tetrabenazine	50 mg kg^{-1}, i.p.	27·2±4·2*	130·0±8·2*	138·0±8·7*
Reserpine	2·5 mg kg^{-1}, i.p.	131·9±7·12*	65·3±7·7*	45·0±6·4*
Chlorpromazine	5·0 mg kg^{-1}, i.p.	487·5±42·8	121·9±4·8*	98·9±5·5*
Trifluoperazine	0·5 mg kg^{-1}, i.p.	631·0±62·7	140·3±10·7*	91·4±4·9*
Control	0·75% CMC	565·0±35·0	103·0±9·0	23·0±1·8
Beclamide	400 mg kg^{-1}, p.o.	176·0±40·0***	399·4±43·0***	67·5±11·0***

Concentrations expressed as mean pmol (mg prot.)$^{-1}$ (±s.e.m.) obtained from 4–6 animals. Group differences between control and beclamide pretreated animals were assessed using Student's *t*-test. Hong et al (1989) used Dunnett's test and their data are converted to pmol (mg prot.)$^{-1}$ (125 mg protein in rat striata was found to be equivalent to 1 g wet tissue). * $P<0·05$, *** $P<0·01$.

(Iversen 1967), release of neurotransmitter from nerve terminals (McKenzie & Szerb 1968) or by inhibition of reuptake (Coyle & Snyder 1969). From Table 4 it appears that the acute effects of beclamide on monoamine levels and turnover closely follow the profile of bioamine depletors (Hong et al 1987a). Thus like reserpine, tetrabenazine and oxypertine, beclamide acutely reduced the striatal synaptic dopamine level and increased the concentration of its metabolites considerably. The neuroleptics, chlorpromazine and trifluperazine, were also reported to increase striatal dopamine turnover, however they failed to decrease dopamine levels after 1 h pretreatment (Hong et al 1987a).

Several studies have suggested that apart from their monoamine presynaptic releasing effect, both oxypertine and tetrabenazine may also block D_2-receptors (Costall & Naylor 1973; Costall et al 1983; Reches et al 1983). More recently, Hong et al (1987a, b) have reported that, in-vitro, reserpine has no affinity for D_2-receptors, whereas oxypertine in nM concentrations displaced the specific binding of [^{3}H]spiperone from D_2 sites and tetrabenazine was only active at mM levels. Arising from the present study, it appears that beclamide behaves more like reserpine in that it has no affinity for dopaminergic D_2-receptors and fails to displace [^{3}H]spiperone from striatal D_2-receptors.

Beclamide also lacks affinity for β, α_2, 5-HT_1 and 5-HT_2 binding sites. The monoamine-depleting drugs are clinically used in the treatment of tardive dyskinesia and other hyperkinetic syndromes associated with cerebral dopaminergic overactivity (Kazamatsuri et al 1973; Asher & Aminoff 1981; Reches et al 1983). The therapeutic effect of these compounds is generally attributed to their ability to deplete dopamine and other monoamines. Since long term treatment with tetrabenazine and oxypertine may lead to supersensitivity of D_2-receptor function (Hong et al 1987b), therefore exaggerating the clinical syndrome, and reserpine induces irreversible damage to presynaptic storage granules, beclamide might conceivably have a potential use in conditions like tardive dyskinesia and other hyperkinetic syndromes.

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