SELECTIVE DEPLETION OF BRAIN REGIONAL NORADRENALINE BY SYSTEMIC 6-HYDROXYDOPAMINE IN NEWBORN RATS*

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WHEREAS the therapeutic use of amphetamine is declining, its use as a pharmacological tool in increasing. However, before the results of an increasing number of behavioural and neurochemical studies with amphetamine can be applied to any clinical situation two questions must be answered: (i) which behavioural effect of amphetamine in animals corresponds to its behavioural effects in humans and (ii) which neurochemical effect of amphetamine is involved in the mediation of these behavioural effects.

An ideal answer would be that amphetamine acted on a specific neuronal pathway involving only one neurotransmitter which resulted in a specific behavioural effect in animals that corresponded to a given disorder of the human nervous system. However, current research indicates that the situation is more complex than this. Catecholamines are involved in the mediation of the behavioural effects of amphetamines but the important problem is not so much the site of action on catecholamine neurones e.g. release, uptake or enzyme inhibition or direct action, but rather which catecholamine is involved in the behavioural effects of amphetamine. We have developed a technique which may help to resolve this problem.

Administration of 6-hydroxydopamine systemically to newborn rats causes not only a permanent destruction of the peripheral adrenergic nervous system (CLARK, LAVERTY and PHELAN, 1972) but also a prolonged depletion of noradrenaline from various regions of the central nervous system (TAYLOR, CLARK, LAVERTY and PHELAN, 1972). In subsequent experiments (LIEW and TAYLOR, 1972) we found that by restricting the period of intraperitoneal administration of 6-hydroxydopamine to one or two days during the first 12 days after birth it was possible to deplete the noradrenaline in various brain regions selectively.

6-Hydroxydopamine (100 mg kg^{-1}) was injected intraperitoneally into newborn male white rats daily on each of two consecutive days between days 1 and 20 after birth. Litter mate controls were similarly injected with the saline ascorbic acid (0·5 mg ml^{-1}) solvent. From age one month to age 3 months various physiological and behavioural measures were studied including rectal temperature, fluid intake, overnight cage activity, Y-runway exploration (STEINBERG, RUSHTON and TINSON, 1961), shock-induced aggression (ULRICH and AZRIN, 1962) and sleeping time after chloral hydrate (FASTIER, SPEDEN and WAAL, 1957). At age 3 months the rats were killed and the brains removed, dissected and analysed fluorimetrically for noradrenaline content (LAVERTY and TAYLOR, 1968).

Injection on days 1 and 2 after birth caused a depletion of noradrenaline in the cerebral cortex, hippocampus and spinal cord whereas injection on days 9 and 10 after birth caused predominantly a depletion of cerebellar noradrenaline (Fig. 1). Noradrenaline levels in the thalamus and hypothalamus and dopamine levels in the

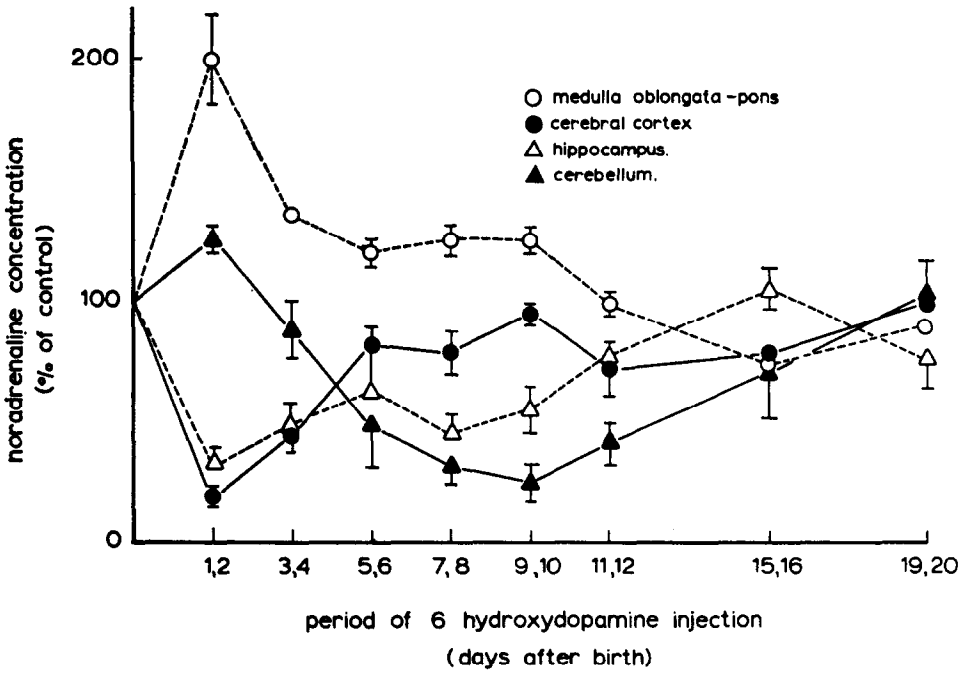

FIG. 1.—The effect of 6-hydroxydopamine (100 mg kg^{-1} intraperitoneally on 2 consecutive days) on the noradrenaline concentration of brain regions of rats aged 3 months. Each point represents the mean ± S.E.M. from 6 to 8 animals. The control group consisted of 20 animals.

striate regions were not affected; noradrenaline levels in the pons-medulla were increased, particularly following treatment on days 1 and 2.

Behavioural tests on these animals showed that animals treated on days 1 and 2 were lighter in weight, but had similar temperature regulation, food and fluid consumption to controls or animals treated on 9 and 10 days. There was no sign of the fluid appetite changes reported in rats given repeated intraventricular injections of 6-hydroxydopamine (SORENSON, ELLISON and MASUOKA, 1972).

Only rats treated on days 1 and 2 showed a prolonged sleeping time after chloral hydrate or increased shock-induced aggression (Table 1). This suggests that these effects may be due to loss of cortical or hippocampal noradrenaline. That shock-induced aggression is affected by brain noradrenaline levels has already been suggested (THOA, EICHELMAN, RICHARDSON and JACOBOWITZ, 1972). Activity as measured by entries (Table 1) or by rearing in a Y-runway or by overnight cage activity (unpublished observations) was not markedly changed by these treatments with 6-hydroxydopamine.

Rats treated on 1 and 2 days had an increased response to a low dose of amphetamine (Table). At higher doses of amphetamine no difference in Y-runway activity between treatments was observed; all groups showed stereotyped behaviour.

At this stage it is not possible to state whether this is an action of amphetamine causing stimulation of supersensitive activating adrenoceptors in cortical neurones or due to the removal of a cortical noradrenergic inhibitory system. Effects on sleeping time may be explained by the removal of an adrenergic activating system whereas

TABLE 1.

	Control	6-Hydroxydopamine Days 1 & 2	6-Hydroxydopamine Day 9 & 10
No. of rats	8	9	9
Body weight (g)	189·5 ± 6·6	122·6 ± 12·3*	160·5 ± 4·3
Rectal temperature (°C)			
at room temperature (20°)	36·8 ± 0·1	36·8 ± 0·1	36·3 ± 0·1
after 1 hr at 4°C	36·9 ± 0·1	36·1 ± 0·1	35·2 ± 0·2
after 3 hr at 4°C	36·6 ± 0·1	36·2 ± 0·2	35·8 ± 0·2
Fluid intake (ml day^{-1} rat^{-1})			
Water	36·8 ± 4·4	37·3 ± 2·1	33·5 ± 1·4
Sucrose (2%)	57·4 ± 4·5	59·1 ± 3·7	67·1 ± 3·0
Quinine (0·02%)	25·4 ± 2·3	24·2 ± 0·8	25·4 ± 3·3
Duration of hypnosis after chloral hydrate (min)	42·8 ± 2·8	65·7 ± 3·3*	40·6 ± 4·3
Shock-induced aggression (responses in 20 trials)	2·6 ± 1·7	7·5 ± 1·7*	1·4 ± 0·6
Activity in Y-runway (entries in 3 min)			
Baseline	5·2 ± 0·4	5·9 ± 0·5	4·0 ± 0·4
After amphetamine (0·5 mg kg^{-1} i.p.)	4·8 ± 1·0	10·4 ± 1·5*‡	4·4 ± 0·7
Noradrenaline content (ng g^{-1})			
Cortex	146 ± 10	34 ± 4*	120 ± 10
Hippocampus	339 ± 30	50 ± 10*	177 ± 20
Spinal Cord	233 ± 20	112 ± 20*	293 ± 40
Cerebellum	120 ± 10	173 ± 20	34 ± 10*
Hypothalamus	869 ± 60	802 ± 90	986 ± 70

Results are expressed as means ± S.E.M.
* Significantly different ($P < 0·05$) from controls
‡ Significantly different ($P < 0·05$) from baseline.

increased shock-induced aggression could be due to removal of an inhibitory system. These preliminary experiments show the application of these techniques of selective regional depletion of brain noradrenaline to the problems of site and mode of action of psychotropic drugs such as amphetamine.

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