BIOGENIC AMINES AND THEIR METABOLISM IN THE STUDY OF AGGRESSIVE BEHAVIOUR IN RATS

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VARIOUS models of animal aggression may involve different central mechanisms and separate neurotransmitters. Shock-induced aggression, spontaneous aggression, and predatory aggression are facilitated or inhibited differentially by altering central brain amine systems. Shock-induced aggression is an experimental model which pairs two rats in a small enclosure and subjects them to footshock (in these studies: 50 footshocks of 2 mA intensity and 0·4 sec duration given every 7·5 sec). In this paradigm the numbers of attacks made are tabulated (EICHELMAN, 1971). Predrug baseline levels of aggression are established and compared with levels following drug treatment. Spontaneous aggression is defined as a category of aggression where rats when placed together in a small enclosed space will attack each other without further stimuli being necessary to elicit aggressive behaviour. Predatory aggression was studied by placing mice in cages with rats whose mouse-killing behaviour was previously determined and observing whether this behaviour changed over a 24 hr period (i.e. whether non-killers commenced killing, or whether killers no longer were muricidal).

Alteration of serotonin metabolism with the tryptophan hydroxylase inhibitor para-chlorophenylalanine induced muricide in 9 of 34 rats when used in doses ranging from 100 mg/kg to 600 mg/kg. There were no conversions in the vehicle-treated group. Even though there were increases in footshock sensitivity in the pCPA-treated rats, their shock-induced fighting level changed insignificantly from 19 to 26·8% (EICHELMAN and THOA, 1973). In these studies no marked changes in spontaneous aggression occurred.

Stimulation of dopamine receptors with the drug apomorphine (1 mg/kg, i.v.) elicited spontaneous fighting in rats, which was markedly exaggerated in rats which had previously had brain norepinephrine and dopamine lowered by intracisternal injections of 200 μg of 6-hydroxydopamine (THOA *et al.*, 1972a). However, in spite of facilitated spontaneous aggression, levels of shock-induced fighting remained insignificantly altered (pre-drug baseline: 11 per cent; post-drug mean: 8·4 per cent) (THOA *et al.*, 1972b).

In contrast, alteration predominantly of norepinephrine metabolism appears to greatly affect shock-induced fighting without altering the other models of aggression. Depletion of brain norepinephrine and dopamine and damage to central catecholamine nerve terminals with intracisternal 6-hydroxydopamine (200 μg) elevates shock-induced fighting from a baseline level of 9·3 per cent to 37·9 per cent (EICHELMAN *et al.*, 1972a). This same effect can be achieved by treating rats with intraventricular injections of 6-hydroxydopa (90 μg) which depletes only brain norepinephrine. This also raises fighting levels, from 6·4 up to 23·3 per cent (THOA *et al.*, 1972c). The effect of these two drugs appears to relate to more than amine depletion, possibly

involving the development of supersensitivity to endogenously released neurotransmitter, since the increase occurs over several days and is not observed when other central amine lowering drugs are used (alpha-methylparatyrosine or FLA 63) (THOA *et al.*, 1972b). This would imply that activation of central noradrenergic systems facilitates shock-induced fighting.

Further evidence that shock-induced fighting is facilitated by activation of a central noradrenergic system is furnished by ancillary studies. Treatment of rats with rubidium chloride (1·5 mequiv, bid, i.p.) for 15 days raises shock-induced fighting from 17·4 to 40·4 per cent while norepinephrine turnover is increased by 300 per cent (EICHELMAN, 1972b). Conversely lithium chloride decreases functional norepinephrine by increasing re-uptake and deamination (SCHANBERG, *et al.*, 1967) and decreases shock-induced aggression (EICHELMAN *et al.*, 1973). Chronic immobilization stress to rats for over one month (2 hr/day) markedly increases shock-induced fighting. These stressed rats have elevated levels of hypothalamic tyrosine hydroxylase suggesting increased central adrenergic metabolism (LAMPRECHT *et al.*, 1972). REM deprivation for five days raises shock-induced fighting from a baseline of 41·8 to 67·4 per cent. This stress is also associated with increased catecholamine and serotonin turnover rates (STERN *et al.*, 1971). Administration of monoamine oxidase inhibitors in an attempt to facilitate central amine activity also facilitates shock-induced fighting. Pargyline (20 mg/kg/4 da), nialamide (100 mg/kg/4 da) and iproniazid (150 mg/kg/4 da) all raise shock-induced fighting significantly from baseline levels of 17–24 per cent to postdrug levels of 40–50 per cent. Lastly, imipramine, a tricyclic antidepressant, when given over repeated doses increases norepinephrine turnover (SCHILDKRAUT *et al.*, 1970). Given similarly (10 mg/kg/bid/5 da) imipramine increases shock-induced fighting from baseline levels of 18·8 to postdrug levels of 33·9 per cent.

In contrast, rats more aggressive in terms of shock-induced fighting do not show alterations in predatory behavior. Rats treated with 6-hydroxydopamine, rubidium, or immobilization stress do not become muricidal.

Thus, it appears that different models of aggression are more closely related to specific putative neurotransmitters. Alteration of serotonin metabolism can induce muricidal behavior, stimulation of dopaminergic terminals can induce spontaneous aggression, and alteration of adrenergic, probably noradrenergic, systems facilitates irritable or shock-induced aggression.

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