GENETIC FACTORS IN THE CONTROL OF BRAIN LEVELS OF BIOGENIC AMINES AND BRAIN EXCITABILITY

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SEVEN crosses among three strains of mice, ICR (low amines), C57B16J (high amines) and BALB (high amines), have been studied in regard to general behaviour and brain excitability as measured by electroshock seizure latency, and maximal electroshock seizure threshold. Seizure latency is measured as the time in seconds from the initiation of a supramaximal electroshock (via cornèal electrodes) until the beginning of the tonic extensor thrust. Seizure latency and seizure threshold are closely correlated parameters and are constant for each strain and F_1 cross studies. Levels of brain dopamine (DA), norepinephrin (NE) and serotonin (5HT) were also determined. As shown in Table 1, the amine levels for each strain give unique profiles and are remarkably constant for each strain studied. The behavioural differences are also shown. The BALB strain has a high level of dopamine and the males fight each other. This rarely occurs with the males of the other strains unless drug induced.

The seizure latencies and thresholds of the two high amine strains (C57 and BALB) are approximately double the threshold of ICR (low amine strain) mice (Table 2). All crosses of the ICR (low amine) strain with either of the high amine strains showed brain levels of DA, NE and 5HT approximately the mean of the two strains involved. Seizure latencies and thresholds of these crosses also were approximately the mean of the strains involved. Crosses of the two high amine strains resulted in high brain amines, long seizure latencies and high convulsive thresholds. The data are summarised in Table 3. Males and females gave similar data on amine levels and brain excitability tests. The genetic factors controlling levels of brain biogenic amines in the three strains of mice studied are isogenetic in the crosses studied. The seizure latency and electroshock threshold studies confirm the close correlation of brain amine levels with brain excitability and suggest a powerful inhibitory role for these neuromodulators in the control of brain excitability.

TABLE 1. BEHAVIOURAL RESPONSES AND BIOGENIC AMINES IN THREE VARIETIES OF MICE

Mouse type	DA	NE	5HT	Behaviour
ICR	0·94 ± 0·04	0·39 ± 0·01	0·61 ± 0·02	Benign, low muscle tone. DOPA-marked irritation, fighting
657B16J	1·04 ± 0·08	0·59 ± 0·02	0·71 ± 0·03	Benign, high muscle tone. DOPA-moderate irritation, no fighting
BALB	1·81 ± 0·12	0·43 ± 0·02	0·68 ± 0·02	Low muscle tone, fighting.

TABLE 2. SEIZURE LATENCY, SEIZURE THRESHOLD AND BRAIN BIOGENIC AMINES IN THREE STRAINS OF MICE

Strain	Latency (sec)	T_z Est_{50} (Volts) (CL)*	Brain conc. of amines $\mu g/g \pm$ S.E.		
			DA	NE	5HT
ICR	1·69 ± 0·02	45(44–47)	0·94 ± 0·02	0·45 ± 0·01	0·53 ± 0·01
BALB	2·49 ± 0·08	63(60–65)	1·59 ± 0·06	0·54 ± 0·01	0·68 ± 0·01
C57BL6/J	3·44 ± 0·11	74(71–77)	1·36 ± 0·03	0·65 ± 0·01	0·69 ± 0·01

* Tonic extensor electroshock $threshold_{50}$ and confidence limits.

TABLE 3. SEIZURE LATENCY AND BRAIN BIOGENIC AMINE LEVELS IN VARIOUS STRAINS AND CROSSES OF MICE

Strain or cross	No. detn.	*E*-shock latency	No. detn.	Brain amines $\mu g/g$		
				DA	NE	5HT
ICR	206	1·56 ± 0·04	59	0·98 ± 0·02	0·48 ± 0·01	0·61 ± 0·01
C57BL6J	79	3·35 ± 0·16	22	1·39 ± 0·02	0·65 ± 0·01	0·75 ± 0·01
BALB	70	2·55 ± 0·10	22	1·44 ± 0·04	0·52 ± 0·01	0·66 ± 0·01
BALB + C57BL6J	27	2·61 ± 0·11	10	1·47 ± 0·04	0·57 ± 0·01	0·74 ± 0·01
		(2·80 ± 0·13)*		(1·42 ± 0·03)	(0·59 ± 0·01)	(0·71 ± 0·01)
ICR + C57BL6J	10	2·10 ± 0·14	19	1·14 ± 0·03	0·53 ± 0·02	0·64 ± 0·02
		(2·46 ± 0·10)		(1·19 ± 0·02)	(0·57 ± 0·01)	(0·68 ± 0·01)
ICR + BALB	9	1·92 ± 0·07	2	1·29	0·47	0·66
		(2·06 ± 0·07)		(1·2 ± 0·03)	(0·50 ± 0·01)	(0·69 ± 0·01)

* Calculated isogenetic cross values = ( ).

SUMMARY

Brain concentrations of DA, NE and 5HT are highly constant for a given mouse strain. However there are large differences in amine levels in different strains and amine profiles of the three amines are unique to a given strain. All three amines are high in high amine strains and low in low amine strains. F_1 crosses of ICR, C57B16 and BALB mice gave amine levels that are the mean of the levels in the parent strains suggesting an isogenetic inheritance of brain amine level control.

Electroshock seizure latency and threshold are markedly higher in high brain amine strains suggesting a role of the biogenic amines as an inhibitory system in the control of brain excitability.

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