Pharmacology Biochemistry & Behavior, Vol. 26, pp. 83–88, 1987. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Age-Dependent Changes of Brain GABA Levels, Turnover Rates and Shock-Induced Aggressive Behavior in Inbred Strains of Mice

JUAN CLEMENT, SIMONE SIMLER, LUCIEN CIESIELSKI,[1] PAUL MANDEL, SIMONA CABIB* AND STEFANO PUGLISI-ALLEGRA*

*Centre de Neurochimie du CNRS, 5 rue Blaise Pascal, 67084 Strasbourg-Cedex, France and *Istituto di Psicobiologia e Psicofarmacologia, C.N.R., via Reno 1, 00198, Roma, Italy*

Received 11 June 1986

CLEMENT, J., S. SIMLER, L. CIESIELSKI, P. MANDEL, S. CABIB AND S. PUGLISI-ALLEGRA. *Age-dependent changes of brain GABA levels, turnover rates and shock-induced aggressive behavior in inbred strains of mice.* PHARMACOL BIOCHEM BEHAV **26**(1) 83–88, 1987.—Shock-induced aggressive behavior (SIAB) is absent or very weak in C57BL/6 (C57) mice at the age of 12 weeks while it reaches high levels at the age of 20 weeks. This age-dependent increase of aggressive responses is absent in DBA/2 (DBA) mice. Aggressive C57 mice (20 week old) are characterized by lower GABA levels in amygdala, striatum and substantia nigra than both non-aggressive C57 (12 week old) and DBA mice (12–20 week old). Concerning turnover rate, C57 mice at the age of 20 weeks show lower turnover rate values in cerebellum and raphe and higher values in septum in comparison with 12 week old mice of the same strain. These results are discussed in terms of the role of GABA function in brain areas which are involved in the control of emotionality and aggressive behavior.

Shock-induced aggressive behavior Inbred mouse strains GABA Age

IN the last decade a body of evidence has pointed to a major role of the inhibitory transmitter γ-aminobutyric acid (GABA) in different kinds of aggressive behavior such as mouse killing by rats, isolation and shock-induced aggressive behaviors in mice and female aggression against lactating intruders [3, 8, 9, 14–16, 22, 24, 25, 27, 30, 31].

It has been recently shown that shock-induced aggressive behavior (SIAB) is absent or very weak in C57BL/6 mice at the age of 10–12 weeks while it exhibits high levels at the age of 20 weeks. This age-dependent increase of aggressive behavior is absent in DBA/2 mice which are characterized by low or no aggressive responses at the two aforementioned ages. These age- and strain-dependent differences in SIAB are not related to differences in shock sensitivity [21,25].

Moreover it has been observed that GABA agonist picrotoxin and glutamic acid decarboxylase (GAD) inhibitor, D,L-allylglycine, induced aggressive responses in non-aggressive 10 week old C57BL/6 mice and 20 week old DBA/2 mice, while GABA agonist muscimol hydrobromide and GABA-transaminase inhibitor sodium n-dipropylacetate (DPA) inhibited aggressive responses in aggressive 20 week old C57BL/6 mice [25]. These findings suggest that age-dependent changes in GABA system in C57BL/6 mice might be related to the age-dependent increase of SIAB exhibited by this strain of mice but not by DBA/2 strain. If so, aggressive C57BL/6 mice should show differences in GABA functioning in comparison with non-aggressive mice of the same strain and with mice belonging to the DBA/2 strain.

The purpose of this study was to investigate the effects of age on SIAB and GABA levels and turnover rates in different brain areas of C57BL/6 and DBA/2 mice.

METHOD

Animals

Male C57BL/6 (C57) and DBA/2 (DBA) mice (Charles River Labs., Italy) 22–25 days old and weighing 13–15 g at the beginning of the experiments were used. Upon their arrival, animals were randomly assigned to different experimental groups. Mice were housed in groups of 6 in plastic cages (27×21×13.5 cm) and maintained in a 12 hr light/12 hr dark cycle. Food and water were freely available. Mice were tested at the age of 12 and 20 weeks. For both behavioral and biochemical tests naive mice were used. The experiments were carried out during the light period (10 hr–14 hr).

Aggressive Behavior

Shock-induced aggressive behavior was measured in an

[1]Requests for reprints should be addressed to Lucien Ciesielski.

apparatus in which the bites between two mice are recorded through a counter [23].

SIAB in mice has been shown to be largely an aggressive offensive behavior [4]. Previous studies [4, 20, 21, 23] have shown that in different experimental conditions the number of bites and fighting time are highly correlated. Moreover when no social conflicts occur following electric shocks (e.g., when young animals or some strains of mice are considered or when mice are under the effect of drugs) mice show either freezing postures and/or escape attempts from the experimental cage and very rarely upright postures [20, 21, 23, 25]. Furthermore, some pharmacological studies have shown that biting allows a reliable measure of dose-related changes in aggressive behavior produced by drug treatment [20, 22, 24, 25]. Thus it seems to us that biting is a reliable and useful measure of aggressive behavior induced by electric shock in the mouse.

The apparatus consists of an experimental chamber (9×9×14 cm). Two holes (1 cm diameter at 1 cm above the grid floor) allow the tails to extend out of the chamber on two opposite walls. A threaded bush previously glued on each tail by means of Bostik is fixed by a nut in the center of a ball bearing, so that the mouse can move freely with no danger to the tail. The two ball bearings work as slip rings for a contact detector.

A low current (2 μA) passing through both mice during biting is amplified by the contact detector so that all bites, but no other body contact, can be recorded by a digital counter. Aggressive behavior was induced by shocking simultaneously both mice. The electric shock (0.25 mA) was applied by means of two electrodes to the part of the tail available between the hole and the ball bearing.

In our experiments each experimental group consisted of ten pairs of mice which were used one time only. Each experimental session lasted for four min in which shocks of 0.5 sec duration were delivered each 3 sec. Prior to each encounter, the mice were placed in opposite halves of the experimental cage, separated by a sliding door. After a 60 sec adaptation period the sliding door was raised, and shocks were delivered. The experimental cage was cleaned between testing sessions in order to remove odors. Mice of each pair came from different breeding groups.

Determination of GABA Levels

Mice were sacrificed by focused microwave irradiation (2 kW, 2.45 gigahertz, 3 sec; Litton 70–50 as modified by Medical Engineering Consultants, Lexington, MA). The fast inactivation of brain enzymes induced by this method allows dissection and sampling without postmortem GABA increase [1,10]. Brains were removed from the skulls. The different brain regions were dissected according to the mouse atlas of Lehmann [13] and lyophilized (the raphe slice was a 1-mm-thick slice containing the raphe and surrounding areas).

GABA level determinations were performed according to one of the following methods: (a) Electron capture gas-liquid chromatography of the fluorinated derivative obtained through acylation of GABA with trifluoro-acetic anhydride and 1,1,1,3,3,3-hexafluoroisopropanol (Aldrich Europe, Beerse) according to the method of Schmid and Karobath [28]. 5-Aminovaleric acid (Fluka, Buchs) was used as an internal standard. (b) Thin-layer chromatography of the stable fluorescent lactame obtained through the condensation of GABA with 5-dimethylamino-1-naphthalenesulfonyl chloride (Fluka, Buchs) and direct scanning on a spectrofluorometer (Aminco Bowman, Silver Spring) according to the method of Seiler and Wiechmann [29].

TABLE 1

EFFECT OF AGE ON SHOCK-INDUCED AGGRESSIVE BEHAVIOR IN C57 AND DBA MICE

Age (weeks).	C57	DBA
12	5.0 ± 4.5	2.3 ± 1.9
20	43.6 ± 14.1*†	6.5 ± 3.8

Aggression was expressed by the number of bites exchanged between two mice (mean ± S.E.).

*Significantly different from 12 week old mice of the same strain.

†Significantly different from 20 week old mice of the other strain. $p<0.01$.

Estimation of GABA Turnover Rates

GABA turnover rates were estimated according to the method of Bernasconi *et al.* [2] using D,L-gabaculine (5-amino-1,3-cyclohexadiene carboxylic acid, hydrochloride) 100 mg/kg IP (0.57 mmol/kg). D,L-Gabaculine is a K-cat inhibitor of GABA-T. According to this method, the turnover rate (nanomol GABA formed/min/mg dry weight) was computed by least-squares regression analysis, as the slope of the line GABA level=f (time) in the interval 15–60 min during which the initial GABA level increase is linear after intraperitoneal injection of gabaculine.

Statistics

The results were statistically analyzed by two-factor analysis of variance (ANOVA), the factors being strain (2 levels=C57, DBA) and age (2 levels=12 and 20 weeks). Further analyses for individual between-group comparisons were carried out with post hoc tests (Duncan multiple range test).

A two-factor ANOVA was carried out for each brain area. GABA turnover rates were compared through variance analysis [7]. Single statistical analyses were carried out for each brain area.

RESULTS

Aggressive Behavior

Concerning the number of bites (biting), ANOVA showed a significant strain main effect, $F(1,36)=65.97$, $p<0.001$, a significant age main effect, $F(1,36)=76.29$, $p<0.001$, and a strain × age interaction, $F(1,36)=49.28$, $p<0.001$.

At the age of 12 weeks both C57 and DBA mice present low or no aggressive responses without differences between strains. Concerning the C57 strain, individual between-group comparisons show that mice aged 20 weeks exhibit higher aggressive responses than mice aged 12 weeks ($p<0.01$). The aggressive scores of DBA mice aged 20 weeks are not different from those of mice of the same strain at the age of 12 weeks. Moreover the aggressive responses of C57 mice aged 20 weeks are significantly higher ($p<0.01$) than those of DBA mice of the same age (Table 1). It is worth noting that mice exhibiting low levels of biting did not show other aggressive

TABLE 2

GABA LEVELS IN BRAIN AREAS OF 12 AND 20 WEEK OLD C57 AND DBA MICE

		C57		DBA	
Brain Area	ANOVA	12 week old	20 week old	12 week old	20 week old
Pons	a,b	8.2 ± 0.5 (6)	5.7 ± 0.3 (9)	6.5 ± 0.7 (5)	4.6 ± 0.5 (11)
Cerebellum	a,c	5.0 ± 0.5 (7)	5.8 ± 0.5 (11)	7.1 ± 0.7 (6)	6.5 ± 0.7 (11)
Ant. Coll.	b	14.4 ± 1.0 (6)	12.2 ± 0.5 (8)	13.8 ± 1.4 (5)	12.0 ± 0.5 (8)
Post. Coll.	b,c	12.5 ± 1.1 (6)	12.3 ± 1.1 (10)	15.0 ± 0.7 (7)†	10.1 ± 1.0 (10)
Amygdala	c	15.2 ± 1.5 (6)*	12.0 ± 2.1 (10)	13.6 ± 3.7 (5)	14.8 ± 3.2 (11)
Thalamus	b,c	12.2 ± 1.1 (7)	11.8 ± 1.3 (11)	13.5 ± 2.7 (6)†	9.4 ± 0.8 (10)
Olf. Bulb	a	29.0 ± 2.6 (7)	28.1 ± 4.1 (10)	24.3 ± 2.7 (6)	24.2 ± 3.5 (9)
Olf. Tub.	a,b	16.3 ± 2.5 (7)	13.3 ± 2.4 (11)	22.9 ± 3.4 (5)	20.1 ± 1.3 (10)
Striatum	a,b,c	13.8 ± 0.9 (6)†	9.5 ± 1.6 (10)	12.3 ± 1.3 (6)	13.8 ± 0.9 (10)
Raphe	a,b	12.3 ± 1.6 (6)	10.2 ± 1.0 (11)	9.7 ± 1.0 (6)	8.1 ± 1.3 (10)
Fr. Cortex	b,c	8.6 ± 0.7 (7)	8.2 ± 0.6 (11)	8.1 ± 0.3 (7)†	10.2 ± 2.1 (10)
Hypothal.	a,b	16.0 ± 2.3 (7)	13.8 ± 1.2 (9)	19.8 ± 2.5 (6)	15.1 ± 2.3 (11)
Septum	a,b	14.1 ± 1.3 (6)	12.0 ± 1.1 (11)	16.8 ± 2.7 (5)	12.4 ± 1.6 (8)
Hippoc.	a,b,c	10.2 ± 1.3 (7)	9.9 ± 1.2 (11)	8.2 ± 0.8 (7)†	10.1 ± 0.7 (10)
S. Nigra	c	22.1 ± 1.5 (6)†	18.4 ± 2.1 (11)	19.1 ± 2.6 (10)	19.9 ± 3.9 (9)

GABA steady-state levels are expressed as nmol/mg dry weight ± S.E.
Number of animals is expressed in parentheses.
For each brain area: a=strain main effect, b=age main effect, c=strain × age interaction.
*$p<0.05$, †$p<0.01$; in comparison with 20 week old mice of the same strain.

responses or defensive postures but only escape attempts from the testing cage.

GABA Levels

The results are shown in Table 2. Two-factor ANOVA showed a significant strain main effect for pons, $F(1,27)=51.5$, $p<0.001$, cerebellum, $F(1,31)=42.8$, $p<0.001$, olfactory bulb, $F(1,28)=12.2$, $p<0.01$, olfactory tubercle, $F(1,29)=60.7$, $p<0.001$, striatum, $F(1,28)=8.9$, $p<0.01$, raphe, $F(1,29)=27.3$, $p<0.001$, hypothalamus, $F(1,29)=11.3$, $p<0.01$, septum, $F(1,26)=5.8$, $p<0.05$, and hippocampus, $F(1,31)=5.7$, $p<0.05$; a significant age main effect in pons, $F(1,27)=132.5$, $p<0.001$, anterior colliculus, $F(1,23)=34.9$, $p<0.001$, posterior colliculus, $F(1,29)=52.8$, $p<0.001$, thalamus, $F(1,30)=17.8$, $p<0.001$, olfactory tubercle, $F(1,29)=11.9$, $p<0.01$, striatum, $F(1,28)=9.7$, $p<0.01$, raphe, $F(1,29)=17.0$, $p<0.001$, frontal cortex, $F(1,31)=4.4$, $p<0.05$, hypothalamus, $F(1,29)=20.6$, $p<0.001$, septum, $F(1,26)=26.8$, $p<0.001$, and hippocampus, $F(1,31)=5.7$, $p<0.05$. A significant strain × age interaction was evident in cerebellum, $F(1,31)=10.1$, $p<0.01$, posterior colliculus, $F(1,29)=44.7$, $p<0.001$, amygdala, $F(1,28)=5.4$, $p<0.05$, thalamus, $F(1,30)=12.2$, $p<0.01$, striatum, $F(1,28)=36.3$, $p<0.001$, frontal cortex, $F(1,31)=9.4$, $p<0.01$, hippocampus, $F(1,31)=11.2$, $p<0.01$, and substantia nigra, $F(1,32)=5.8$, $p<0.05$.

Individual between-group comparisons showed that 20 week old C57 mice exhibited lower GABA levels in amygdala, striatum and substantia nigra in comparison with mice of the same strain aged 12 weeks. DBA mice at the age of 20 weeks showed lower GABA levels in posterior colliculus and thalamus and higher levels of the neurotransmitter in frontal cortex and hippocampus when compared with DBA mice at the age of 12 weeks.

GABA Turnover Rates

Results are shown in Table 3. C57 mice at the age of 20 weeks showed lower turnover rate values than mice of the same strain aged 12 weeks in cerebellum and raphe while higher values were evident in septum of older mice. DBA mice aged 20 weeks showed lower turnover rate values in comparison with 12 week old mice of the same strain in anterior colliculus, amygdala, thalamus, frontal cortex, hippocampus and septum.

DISCUSSION

Some working hypotheses emerge from the present findings concerning the role of GABA system in the control of SIAB. We observed that aggressive C57 mice (20 week old) are characterized by lower GABA levels in amygdala, striatum and substantia nigra than both non-aggressive C57 (12 week old) and DBA mice (12–20 week old). In the last decade, a number of studies have pointed out an inverse relationship between GABA levels in the brain and aggressive responses in different kinds of aggressive behavior. A decrease of GABA levels in the olfactory bulb was observed in muricidal rats [3, 14–16]. Compensation for this decrease in GABA content of the olfactory bulb produced by systemic injections of GABA-transaminase inhibitors sodium n-dipropylacetate (DPA) and aminooxyacetic acid (AOAA) suppressed killing behavior [3,14]. A similar inhibition of muricidal behavior was observed after local injection in the olfactory bulb of DPA, 2,4-diaminobutyric acid, an agent that blocks GABA reuptake, and of the GABA agonist muscimol [15,16]. On the other hand, injection of picrotoxin (a GABA antagonist) or allylglycine (an inhibitor of glutamate decarboxylase (GAD)) induced killing behavior [15]. Moreover, the decrease of GABA in the olfactory bulb and

TABLE 3

GABA TURNOVER RATES IN BRAIN AREAS OF 12 AND 20 WEEK OLD C57 AND DBA MICE

	C57		DBA	
Brain Area	12 week old	20 week old	12 week old	20 week old
Pons	0.12 ± 0.02	0.10 ± 0.01	0.08 ± 0.01	0.12 ± 0.02
Cerebellum	0.20 ± 0.01†	0.14 ± 0.01	0.08 ± 0.01	0.12 ± 0.02
Ant. Coll.	0.12 ± 0.02	0.12 ± 0.01	0.14 ± 0.02†	0.06 ± 0.01
Post. Coll.	0.15 ± 0.03	0.09 ± 0.01	0.11 ± 0.03	0.06 ± 0.02
Amygdala	0.34 ± 0.04	0.26 ± 0.03	0.35 ± 0.04*	0.22 ± 0.04
Thalamus	0.12 ± 0.02	0.15 ± 0.02	0.33 ± 0.08*	0.14 ± 0.02
Olf. Bulb	0.45 ± 0.08	0.34 ± 0.04	0.45 ± 0.04	0.38 ± 0.05
Olf. Tub.	0.21 ± 0.04	0.22 ± 0.03	0.22 ± 0.03	0.17 ± 0.03
Striatum	0.11 ± 0.03	0.12 ± 0.02	0.18 ± 0.03	0.12 ± 0.03
Raphe	0.16 ± 0.03*	0.09 ± 0.02	0.14 ± 0.03	0.11 ± 0.02
Fr. Cortex	0.31 ± 0.03	0.27 ± 0.02	0.03 ± 0.01‡	0.19 ± 0.02
Hypothal.	0.35 ± 0.05	0.38 ± 0.04	0.43 ± 0.05	0.35 ± 0.06
Septum	0.27 ± 0.03‡	0.47 ± 0.02	0.48 ± 0.04†	0.30 ± 0.03
Hippoc.	0.31 ± 0.03	0.30 ± 0.03	0.32 ± 0.04*	0.20 ± 0.03
S. Nigra	0.10 ± 0.02	0.10 ± 0.02	0.11 ± 0.02	0.08 ± 0.04

GABA turnover rates (nmol GABA formed/mg dry weight) ± S.E. were determined from GABA measurement at 15 min (n=7–9) and 60 min (n=7–9) after injection of gabaculine (100 mg/kg, IP).

For each brain area: *$p<0.05$, †$p<0.01$, ‡$p<0.0005$; in comparison with 20 week old mice of the same strain.

in the striatum in isolated high aggressive mice in comparison with isolated low aggressive mice was reported when either outbred or inbred mice were considered [8,30]. Sodium n-dipropylacetate, muscimol and nipecotic acid amide (an inhibitor of GABA reuptake) have been shown to decrease agonistic behavior in isolated mice [22]. Da Vanzo and Sydow [6] reported that AOAA and gamma-acetylenic GABA produce a suppression of isolation-induced agonistic behavior in mice and a concomitant increase of brain GABA levels. Recently, Simler and coworkers [31] have shown that systemic injection of DPA antagonized agonistic behavior of isolated mice in a time-dependent fashion in parallel to an increase of GABA levels in olfactory bulb and striatum.

Potegal *et al.* [18] reported an inversed number of high affinity binding sites in the brain "midregion" (including striatum) of aggressive hamsters in comparison with non-aggressive animals. These results are consistent with a decrease of brain GABA functioning in aggressive subjects.

Concerning SIAB in mice, it was previously shown [25] that GABA antagonist picrotoxin and GAD inhibitor D-L-allylglycine induced aggressive responses in non-aggressive C57 mice (aged 10 weeks) and DBA mice, while DPA and muscimol inhibited aggressive behavior in aggressive C57 mice (aged 20 weeks).

In light of the findings discussed above and in particular of those concerning SIAB in C57 and DBA mice, our present results indicate that the decrease of GABA levels in 20 week old C57 mice in comparison with 12 week old mice of the same strain might be related to the expression of aggressive responses. In particular, a decrease of the neurotransmitter levels were observed in amygdala, striatum, and substantia nigra of C57 but not of DBA mice. Although striatum is a brain area which is considered to play a role in the expression of SIAB [12], it must be taken into account that C57 mice after 8 weeks of social isolation (20 week old at the moment of testing) present a clear-cut decrease of SIAB [20] and a decrease of GABA levels in the striatum [30] in comparison with grouped mice of the same age. On the basis of these previous results it seems difficult to relate a decrease of GABA levels in this area to an increase in SIAB. Amygdala is well known to play a major role in SIAB, in particular it exerts a facilitatory influence on this behavior [17]. Thus a decrease of bioavailability of an inhibitory neurotransmitter such as GABA may accentuate this influence in C57 mice at the age of 20 weeks. Also the decrease of GABA levels in substantia nigra might be related to the increase of aggressive responses in 20 week old C57 mice. GABAergic transmission in the nigra has been related to the control of neural activity of nigro-striatal dopaminergic neurons in that GABA inhibits activity of dopaminergic neurons [5]. Apomorphine was shown to increase dramatically SIAB in 12 week old C57 and DBA mice, an effect antagonized by pretreatment with DPA [24]. Thus it may be that the decrease of GABA in the nigra is related to an increase of dopamine activity in nigro-striatal neurons which could be involved in the increase of SIAB in 20 week old C57 mice.

Concerning turnover rates, C57 mice at the age of 20 weeks show lower turnover values in cerebellum and raphe and higher values in septum in comparison with 12 week old mice. It is questionable whether these changes in turnover rate are related to the increase of SIAB exhibited by 20 week old mice. Turnover rate decrease in raphe of 20 week old mice may indicate either lower energy metabolism or lower activity of GABA. Such changes in this area which play a major role in reactivity and behavioral arousability [32] might be related to altered emotional responsivity to noxious

stimuli (shock). Concerning cerebellum a possible decrease of GABA functioning indicated by turnover rate decrease is hard to relate to SIAB. Cerebellum has been reported to be involved in predatory behavior of cat [26] but little or nothing is known about its role in intraspecific aggressive behavior induced by noxious stimuli in the mouse. Lastly, the increase of turnover rate in septum observed in 20 week old C57 mice which accompanies a decrease in steady-state levels may reflect an increase of GABAergic activity in this brain area. It is worth noting that potentiation of GABA functioning in the septum by local injections of muscimol has been reported to increase behavioral reactivity and interspecific aggression in the rat [19], a result that suggests a possible role of septum in the expression of SIAB in C57 mice.

Differences in GABA functioning of about 25–100% between aggressive and non-aggressive mice observed in our study are related to 8–9-fold differences in aggressive behavior. A similar relationship between GABA and behavioral changes have been found in previous studies in which 20–40% of GABA changes in striatum and olfactory bulb were related to 7–10-fold changes in other kinds of aggression such as isolation-induced aggressive behavior and mouse-killing by rats [14–16, 30, 31]. Such quantitative relationship between GABA functioning changes and behavioral output seems to indicate that the changes observed at neurochemical level switch on some neural mechanism, possibly involving other neurotransmitter systems, which is able to elicit behavioral changes many fold larger than the neurochemical ones.

In conclusion, our results show that at the age of 12 weeks C57 and DBA mice present low or no aggressive responses. C57 mice at the age of 20 weeks show high levels of aggressive responses while in DBA mice at the same age aggressive responses are not different from those exhibited by 12 week old mice of the same strain. Concerning GABA levels the results strongly suggest that the decrease of the neurotransmitter in amygdala and substantia nigra in C57 mice aged 20 weeks in comparison with 12 week old C57 mice are related to high levels of SIAB exhibited by 20 week old mice. In addition to this a relationship between aggressive responses and changes in turnover rates in septum (increase) and raphe (decrease) was pointed out by the present results.

Given the wide distribution of GABA in the central nervous system it is conceivable that this neurotransmitter is involved in many behaviors if not in all [11], including aggression. A large body of evidence has shown a GABA involvement in different kinds of aggressive behavior controlled by different neural substrate (brain areas) [9, 14–16, 30, 31]. The present results add further evidence to the growing literature on GABA and aggression indicating that GABA functioning in specific brain areas, different from those crucial in the expression of other kinds of aggression [32], play a major role in the control of SIAB in the mouse.

ACKNOWLEDGEMENTS

The authors wish to thank Miss A. C. Schaettel and Mr. J. G. Lorentz for their excellent technical assistance. This work was supported by Italian and French National Research Council Research Grants. We are indebted to Dr. Maitre (Ciba-Geigy, Basel) for the gift of gabaculine.

REFERENCES

1. Balcom, G. J., R. H. Lenox and J. L. Meyerhoff. Regional γ-aminobutyric acid levels in rat brain determined after microwave fixation. *J Neurochem* **24:** 609–613, 1975.
2. Bernasconi, R., L. Maitre, P. Martin and F. Raschdorf. The use of GABA-transaminase for the determination of GABA turnover in mouse brain regions: An evaluation of aminooxiacetic acid and gabaculine. *J Neurochem* **38:** 57–66, 1982.
3. Bolin, P. and J. P. DaVanzo. The influence of isolation and aminooxyacetic acid (AOAA) on GABA in muricidal rats. *Psychopharmacology (Berlin)* **76:** 367–370, 1982.
4. Brain, P. F., S. Al-Maliki and D. Benton. Attempts to determine the status of electroshock-induced attack in male laboratory mice. *Behav Process* **6:** 171–189, 1981.
5. Cattabeni, F., A. Bugatti, A. Groppetti, A. Maggi, M. Parenti and G. Racagni. GABA and dopamine: their mutual regulation in the nigro-striatal system. In: *GABA-Neurotransmitters*, edited by P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod. Copenhagen: Munksgaard, 1979, pp. 107–117.
6. DaVanzo, J. P. and M. Sydow. Inhibition of isolation-induced aggressive behavior with GABA transaminase inhibitors. *Psychopharmacology (Berlin)* **62:** 23–27, 1979.
7. Diem, K. *Documenta Geigy-Tables Scientifiques*. Basle: J. R. Geigy, S. A., 1963, pp. 176–180.
8. Early, C. J. and B. E. Leonard. The effect of testosterone and cyproterone acetate on the concentration of γ-aminobutyric acid in brain areas of aggressive and non-aggressive mice. *Pharmacol Biochem Behav* **6:** 409–413, 1977.
9. Haug, M., S. Simler, L. Kim and P. Mandel. Studies on the involvement of GABA in the aggression directed by groups of intact or gonadectomized male and female mice towards lactating intruders. *Pharmacol Biochem Behav* **12:** 189–193, 1980.
10. Knieriem, K. M., M. A. Medina and W. B. Stavinoha. The levels of GABA in mouse brain following tissue inactivation by microwave irradiation. *J Neurochem* **28:** 885–886, 1977.
11. Koella, W. P. GABA systems and behavior. In: *Amino Acid Neurotransmitters*, edited by F. V. DeFeudis and P. Mandel. New York: Raven Press, 1981, pp. 11–21.
12. Kolb, B. Studies on the caudate-putamen and the dorsomedial thalamic nucleus of the rat: implications for mammalian frontal-lobe functions. *Physiol Behav* **18:** 237–244, 1977.
13. Lehmann, A. *Atlas Stereotaxique du Cerveau de la Souris*. Paris: CNRS, 1974.
14. Mandel, P., G. Mack, E. Kempf, A. Ebel and S. Simler. Molecular aspects of a model of aggressive behavior. In: *Interactions Between Putative Neurotransmitters in the Brain*, edited by S. Garattini, J. F. Pujol and R. Samanin. New York: Raven Press, 1978, pp. 285–303.
15. Mandel, P., G. Mack and E. Kempf. Molecular basis of some models of aggressive behavior. In: *Psychopharmacology of Aggression*, edited by M. Sandler. New York: Raven Press, 1979, pp. 95–110.
16. Mandel, P., L. Ciesielski, M. Maitre, S. Simler, G. Mack and E. Kempf. Involvement of central GABAergic systems in convulsion and aggressive behavior. In: *GABA Biochemistry and CNS Function*, edited by P. Mandel and F. V. DeFeudis. New York: Plenum Publishing Corp., 1979, pp. 475–492.
17. Miczek, K. A., T. Brykczynski and S. Grossman. Differential effects of lesions in the amygdala, periamygdaloid cortex, and stria terminalis on aggressive behaviors in rats. *J Comp Physiol Psychol* **87:** 760–771, 1974.
18. Potegal, M., A. S. Perumal, A. I. Barkai, G. E. Cannova and A. D. Blau. GABA binding in the brains of aggressive and non-aggressive female hamsters. *Brain Res* **247:** 315–324, 1982.
19. Potegal, M., B. Yoburn and M. Glusman. Disinhibition of muricide and irritability by intraseptal muscimol. *Pharmacol Biochem Behav* **19:** 663–669, 1983.

20. Puglisi-Allegra, S. Deux exemples de comportement d'agression chez la souris: étude comportementale, neurochimique et pharmocologique. Thèse de Doctorat d'Etat, Strasbourg, 1984.
21. Puglisi-Allegra, S. and S. Cabib. The effect of age on two kinds of aggressive behavior in inbred strains of mice. *Dev Psychobiol* **18:** 477–482, 1985.
22. Puglisi-Allegra, S. and P. Mandel. Effects of sodium n-dipropylacetate, muscimol hydrobromide and (R,S) nipecotic acid amide on isolation-induced aggressive behavior in mice. *Psychopharmacology (Berlin)* **70:** 287–290, 1980.
23. Puglisi-Allegra, S. and P. Renzi. A technique for the measurement of aggressive behavior in mice. *Behav Res Meth Instr* **9:** 503–504, 1977.
24. Puglisi-Allegra, S., G. Mack, A. Oliverio and P. Mandel. Effects of apomorphine and sodium di-n-propylacetate on the aggressive behavior in three strains of mice. *Prog Neuropsychopharmacol* **3:** 491–502, 1979.
25. Puglisi-Allegra, S., S. Simler, E. Kempf and P. Mandel. Involvement of the GABAergic system on shock-induced aggressive behavior in two strains of mice. *Pharmacol Biochem Behav* **14:** Suppl 1, 13–18, 1981.
26. Reis, D. J., N. Doba and M. A. Nathan. Predatory attack, grooming, and consummatory behaviors evoked by electrical stimulation of cat cerebellar nuclei. *Science* **182:** 845–847, 1973.
27. Rodgers, R. J. and A. Depaulis. GABAergic influences on defensive fighting in rats. *Pharmacol Biochem Behav* **17:** 451–456, 1982.
28. Schmid, R. and M. Karobath. Specific and sensitive method for determination of GABA using gas chromatography with electron capture or mass fragmentographic detection. *J Chromatogr* **131:** 101–109, 1977.
29. Seiler, V. N. and M. Wiechmann. Die Bestimmung der γ-Aminobuttersaure in 10 Mol-Bereich als 1-Dimethylamino-naphtalin-S-Sulfonyl-Derivat. *Hoppe Seylers Z Physiol Chem* **349:** 588–594, 1968.
30. Simler, S., S. Puglisi-Allegra and P. Mandel. γ-Aminobutyric acid in brain areas of isolated aggressive and non-aggressive inbred strains of mice. *Pharmacol Biochem Behav* **16:** 57–61, 1982.
31. Simler, S., S. Puglisi-Allegra and P. Mandel. Effects of n-di-propylacetate on aggressive behavior and brain GABA level in isolated mice. *Pharmacol Biochem Behav* **18:** 717–720, 1983.
32. Valzelli, L. *Psychobiology of Aggression and Violence*. New York: Raven Press, 1981.