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Effects of the Potentiation of the GABAergic Neurotransmission in the Olfactory Bulbs on Mouse-Killing Behavior

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MOLINA, V , L CIESIELSKI, S GOBAILLE AND P MANDEL *Effects of the potentiation of the GABAergic neurotransmission in the olfactory bulbs on mouse-killing behavior* PHARMACOL BIOCHEM BEHAV **24**(3) 657–664, 1986 —Intra olfactory bulb administration of three classes of GABA-mimetics ($GABA_a$ agonists, inhibitors of reuptake, inhibitors of GABA degradation) clearly inhibit mouse-killing behavior, without sedation A linear correlation is observed between GABA levels increase in the olfactory bulbs and muricidal inhibition following local injection of valproic acid and gamma-vinyl GABA, two GABA-T inhibitors, the differences observed between these two compounds may be due to the differences in their mechanism of action on GABA-T activity and to the different pool of GABA on which they act No diffusion to extra bulbar sites were observed after local administration of gamma-vinyl GABA This evidence suggests an inhibitory role of GABA from olfactory bulbs in the modulation of mouse-killing behavior

GABA GABA-mimetics Gamma-vinyl GABA Mouse-killing behavior Olfactory bulbs

DURING the last years, pharmacological and biochemical data have suggested the involvement of GABAergic mechanism in different forms of experimental aggression It was demonstrated that the potentiation of GABAergic neurotransmission blocked several forms of aggressive behavior [23,24] Thus, GABA-mimetic drugs administration inhibited intraspecific aggressive behavior in mice, induced either by isolation or by electroshock [30,31] Attacks by adult virgin mice on lactating female intruders and aggressive behavior induced by chemical agents [29] are also reduced by GABA-mimetic drugs [24]

Mouse-killing behavior (MKB) by rats is widely used as a model of experimental aggression [23, 40, 42] Although there is a controversy whether to consider or not muricidal behavior as a predatory behavior, it should be pointed out that numerous investigators have shown that hunger cannot be considered as the determinant of MKB It was reported that muricidal behavior of killer (K) rats is facilitated by food deprivation [1,16] but it is not induced by hunger [10,14] Muricidal rats attack mice principally for the sake of killing in itself [17] and this behavior is described as a peculiar form of irritative aggression [2] Concerning MKB by K rats, a dose-dependent inhibition after systemic administration of different GABA-mimetic drugs has been reported These effects were without sedation [24] Synergystic effects have also been described with different types of GABA-mimetic drugs [46] Some negative results were reported by Depaulis and Vergnes [6] concerning the effects of several GABA-mimetics on MKB, unless a sedative effect was obtained The reason for these discrepancies will be described later In addition, K rats present lower levels of GABA in the olfactory bulbs [20] Moreover, MKB can be induced by olfactory bulb ablation [23] On the other hand, intraperitoneal injections of GABA-mimetic drugs on bulbectomized K rats were without effect [23] This lack of inhibitory effect seems to be specific for GABAergic neurotransmission, since MKB of K rats as well as that of bulbectomized rats are clearly blocked after systemic administration of serotonin-mimetic drugs or local injections of noradrenergic compounds in amygdala (Molina *et al* [27]) The involvement of GABAergic neurotransmission in olfactory bulbs and MKB is also supported by the fact that local injections of GABA immediately inhibited muricidal activity [21] This effect is rather specific since no inhibitory effect was observed after the injection into the olfactory bulbs of other neurotransmitters such as glycine, dopamine or serotonin [21] The only efficient drugs in MKB inhibition after injection into the olfactory bulbs were drugs performing a GABA agonistic effect and taurine [25], a putative inhibitory neurotransmitter [25] Furthermore, MKB can be induced by local administration of bicuculline and picrotoxin, GABA antagonists [21] or allylglycine, an inhibitor of glutamate decarboxylase [23]

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In order to obtain a clear-cut demonstration that GABA-mimetic drugs injected locally into olfactory bulbs block MKB, three classes of GABA-mimetic drugs were locally injected (a) $GABA_a$ agonists, (THIP, muscimol, isoguvacine), (b) GABA untake inhibitors (nipecotic acid amide, guvacine), (c) inhibitors of GABA-transaminase (valproic acid, γ-vinyl GABA) In addition, the correlation between GABA level increase after GABA-T inhibitor injection and muricidal behavior has been explored

METHOD

Animals Two–3-month-old male Wistar rats weighing 250–300 g at the start of the experiment were used They were housed individually in plastic opaque cages (21×40×15 cm) and maintained in a 12 hr light-dark cycle (light off 7 p m)

Mouse-killing behavior After one month of social isolation, muridical responses were recorded following the introduction of an albino adult male mouse (30–35 g) into the cage of an isolated rat Those which killed mice consistently and in less than 5 min were classified as killer rats (K) The animals which did not kill the mouse were considered non-killers (NK)

Intrabulbar treatment K animals under pentobarbital anesthesia (37 5 mg/kg) were bilaterally implanted with guide cannulae (0 5 mm in diameter) into the olfactory bulbs The following coordinates were used +7 1 mm anterior from bregma, ±1 5 mm lateral to the midline and 3 5 mm below the skull The cannulae consisted of a stainless steel tube, a 0 3 mm diameter stainless steel wire served as the inner stylet The cannulae were kept in position by fixing them with dental acrylic cement to four stainless steel screws in the skull A period of 8 days was allowed for recovery from surgery At the end of this period, K rats were injected either with drugs or saline, into the olfactory bulbs under light diethyl ether anesthesia (The light diethyl ether anesthesia was by itself without any effect on MKB) The inner stylets were removed from the implanted cannulae and a 0 3 mm needle, connected with a plastic tubing to a 5 μl Hamilton syringe was inserted The tip of the needle reached a position 0 5 mm below the guide cannulae Drugs were dissolved in saline and injected bilaterally in a volume of 1 μl per side at a speed of 1 μl/min After each infusion the needle was left in place for 1 min Muricidal test was performed immediately before and 30, 60, 90, 120, 150, 240, 300, 360 min and 24 hr after the treatment At the end of the experiments, animals were sacrificed to verify the correct position of the cannulae in the posterior region of the olfactory bulbs [21]

Muricidal inhibition was measured by the following parameters (a) Percentage of K rats which no longer kill at different times after drug administration (b) Latency time necessary to reach inhibition of muricidal behavior in 40% of tested rats (hr), (c) Maximal percentage of muricidal rats which do not kill after drug administration, (d) Evaluation of the surface between a parallel to the abscissa that corresponds to the situation of controls (100% of killers) and the curve which represents the decrease in the % of animals which still kill [26), (e) Duration of inhibition of mouse-killing behavior in at least 40% of rats tested (hr)

Locomotor activity Motor activity during the saline period and under drug conditions was tested in an actograph apparatus Tests begin at 10 a m Each rat was placed in Plexiglas box (100×20 cm) with 7 pairs of infrared photo cells 2 cm above the solid floor to provide an automated measure

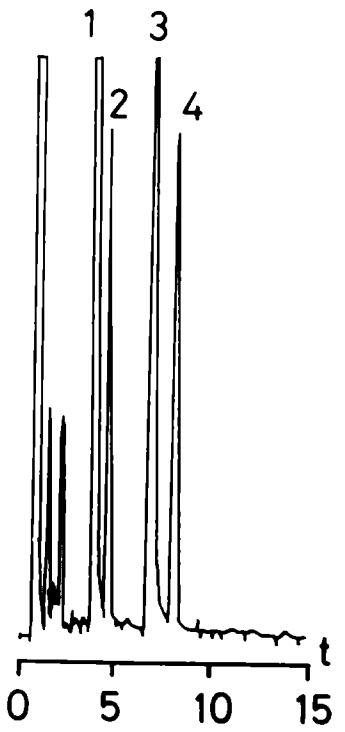

FIG 1 Typical chromatogram—Abscissa elution time in minutes (olfactory bulbs 0 5 hr after GVG administration) (1) GABA) (2) GVG (3) 5-amino valeric acid (internal standard), (4) methionine

of locomotor activity K isolated rats were administered locally into the olfactory bulbs with saline or the GABA-mimetic drugs at the same doses as those used in muricidal studies K rats were placed in the actograph 60 min following intra olfactory bulb injections Activity was evaluated by the number of photobeam interruptions/30 min, during 150 min

Effect of γ-Vinyl-GABA Intra Olfactory Bulbs Administration on GABA Levels From Several Brain Areas

Isolated rats were injected with 20 μg of γ-vinyl-GABA (GVG) in the olfactory bulbs (1 μl in each side at a rate of 1 μl/min) at the same coordinates used for cannulae implantations and under ether anesthesia Animals were sacrificed by rapid decapitation 0 5, 1, 2 5, 5 and 7 hr after GVG administration, in order to prevent post-mortem increase in GABA levels, exactly 2 min before sacrifice, rats were systemically injected with 100 mg/kg of 3-mercaptopropionic, an inhibitor of glutamic acid decarboxylase [44] Brain areas were quickly removed and dissected on a glass frozen plate and stored in liquid nitrogen

Sacrifices were done between 2 and 4 p m to avoid the effects of a possible circadian rhythm Control rats were administered with saline The sampled brain areas were lyophylized, weighed and analyzed for their GABA and GVG content by means of gas-chromatography with silica capillary column separation and electron capture detection The derivation procedure is mainly that described by Schmid and Karobath [36] with some modifications Samples were homogenized in 0 1 M formic acid containing 100 nmol of 5-aminovaleric acid as internal standard, the homogenization were performed in 0 6 ml saarsted centrifuge tubes with laboratory made pestles which had been cast in identical cen-

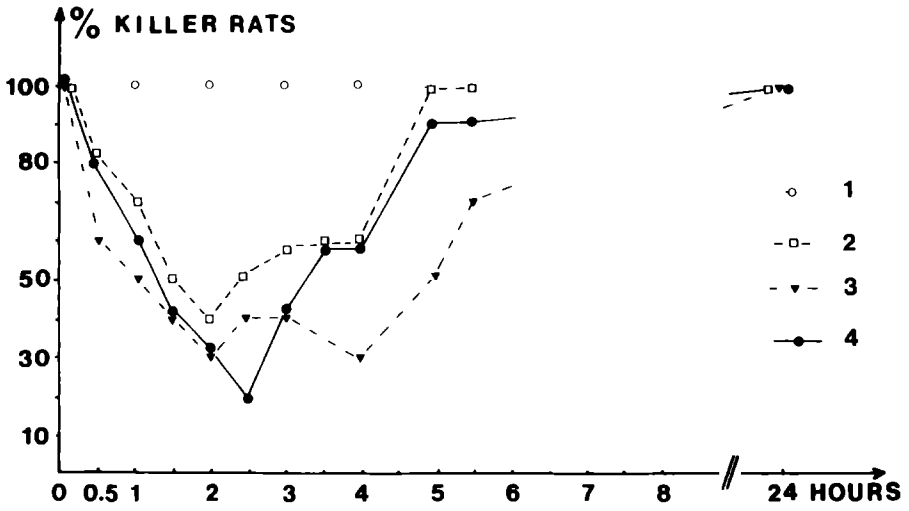

FIG 2 Effects of intra olfactory bulbs administration of $GABA_a$ agonists on mouse-killing behavior induced by isolation Abscissa time (hr) after intra olfactory bulbs administration of 0 15 μmol Ordinate incidence of muricide % (N=10) (1) saline, (2) muscimol, (3) THIP, (4) isoguvacine

TABLE 1

EFFECTS OF GABA-MIMETIC COMPOUNDS INTO THE OLFACTORY BULBS ON MOUSE-KILLING BEHAVIOR

Compounds	Dose (μmol/rat)	Latency time (hr) (b)	Maximal % of inhibition of MKB (c)	Efficiency (5h30) Conv units (d)	Duration of inhibition (hr) (e)
Muscimol	0 15	1 25	60	30	2 75
THIP	0 15	0 5	70	52	4 75
Isoguvacine	0 15	1 0	80	38	3 0
Nipecotic acid amide	0 15	1 5	40	30	2 5
Guvacine	0 15	0 5	60	34	2 0
DPA	0 15	0 25	95	50	3 5
GVG	0 15	0 75	80	56	6 5

Parameters (b) (c) (d) (e) are described in the Method section

trifuge tubes from electron microscopy embedding resin After centrifugation of the homogenates (12,000 g during 20 min), supernatants were absorbed on amberlite AG CG 120, 100–200 mesh H^+ form columns (internal diameter 0 6 cm, resin bed 1 cm), after extensive washing with distilled water, GABA and GVG were eluted with 2 ml of 3 M ammonia The derivation of the lyophylized eluates were performed with 50 μl of 1-1-1-3-3-3 hexafluoro isopropanol (Aldrich, Beerse) and 100 μl of trifluoro-acetic anhydride (Aldrich, Beerse) for 1 hr at room temperature Excess reagents were evaporated under a gentle stream of dry nitrogen and 600 μl of 2-2-4-trimethyl pentane were added Electron capture gas chromatography was performed on a Hewlett-Packard 5840-A apparatus Chromatographic conditions 12 meter fused silica capillary column coated with methyl silicone (inside diameter 0 2 mm, carbowax deactivated), 0 4 μl splitless injection, flow A 20 ml/min, flow B 60 ml/min, injection temperature 160°C, oven temperature 65°C, (isothermal) detector temperature 280°C, time per analysis 15 min In this chromatic system methionine can be quantified Figure 1 shows a typical chromatogram

Drugs Agonist of $GABA_a$ receptor muscimol (Sigma Chemical Co) [3], 4,5,6,7tetrahydroxazolo (5,4-c)-pyridine-3-ol (THIP) (kindly supplied by Dr Krogsgaard-Larsen, Denmark) [8,19], isoguvacine (kindly supplied by Dr Krogsgaard-Larsen, Denmark) [8,19] Inhibitors of GABA uptake nipecotic acid amide (NCS3) [46] and guvacine [12] Inhibitors of GABA degradation valproate (DPA), (Labbaz, Paris) [9] and γ-vinyl GABA (GVG), (Merrel Research Institute, Strasbourg, France) [13]

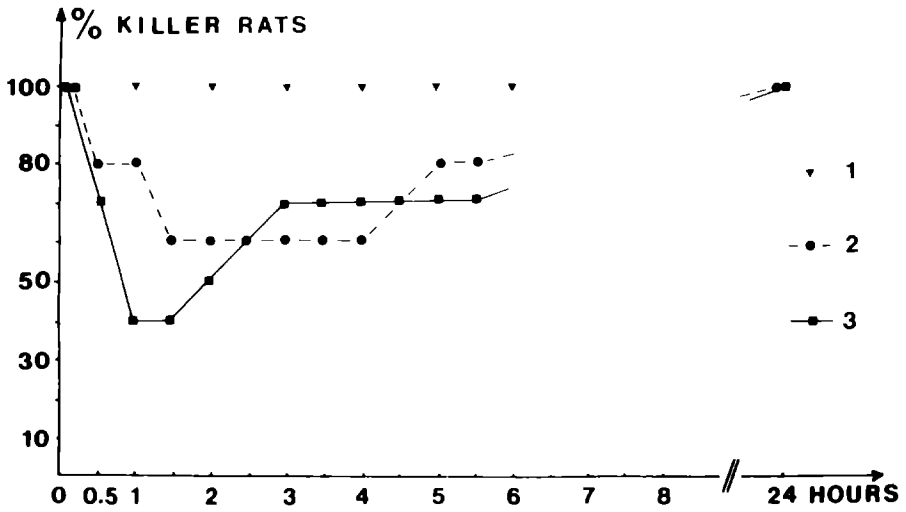

FIG 3 Effects of intra olfactory bulbs administration of GABA reuptake inhibitors on mouse-killing behavior induced by isolation Abscissa time (hr) after intra olfactory bulbs administration of 0 15 μmol Ordinate incidence of muricide % (N=10) (1) saline, (2) nipecotic acid amide, (3) guvacine

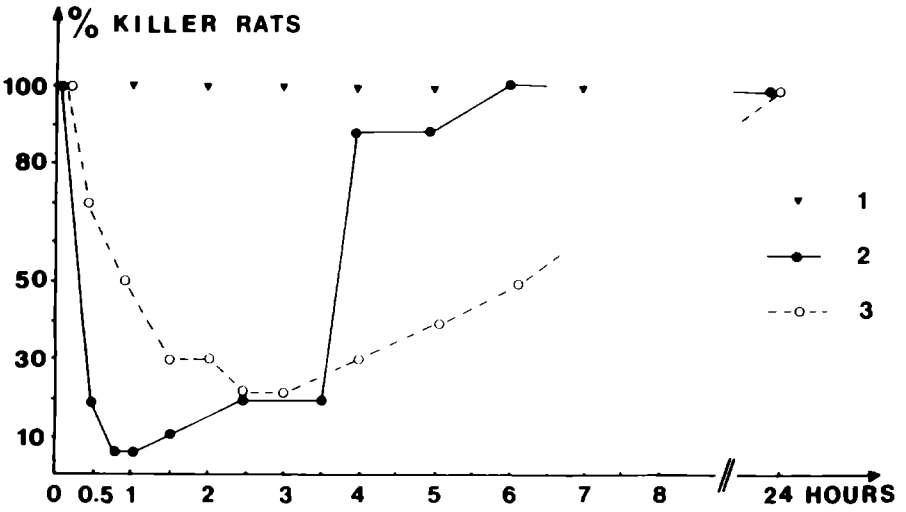

FIG 4 Effects of intra olfactory bulbs administration of GABA-T inhibitors on mouse-killing behavior induced by isolation Abscissa time (hr) after intra olfactory bulbs administration of 0 15 μmol Ordinate incidence of muricide % (N=10) (1) saline, (2) DPA, (3) GVG

Statistical Analysis of Data

Muricidal responses after drug administration were evaluated by Fisher-exact probability test (at the time of maximal effect) [18, 27, 35] Statistical significance for GABA levels means was evaluated by analysis of variance or Student's *t*-test Correlation between biochemical and behavioral data was looked for by least-square regression analysis, regression coefficients were compared through variance analysis [7] Motor activity values were analysed by two-way ANOVA

RESULTS

Effect of GABA Agonists on Mouse-Killing Behavior

The administration into the olfactory bulbs of muscimol, THIP or isoguvacine blocked muricidal activity These compounds interacted directly with GABA recognition sites as they displace radio-labelled ligands such as ^{3}H-GABA [3], blocked muricidal activity of K rats (Fig 2) According to our parameters of muricidal inhibition, the latency time and the duration of inhibition, THIP seems to be the most effective of the 3 agonists tested (Table 1)

Effect of GABA Uptake Inhibitors on Mouse-Killing Behavior

A decrease of muricidal behavior was observed after guvacine and nipecotic acid amide administration into the olfactory bulbs (Fig 3, Table 1) Both drugs block GABA uptake mechanism [12,46] The latency time seems shorter for guvacine

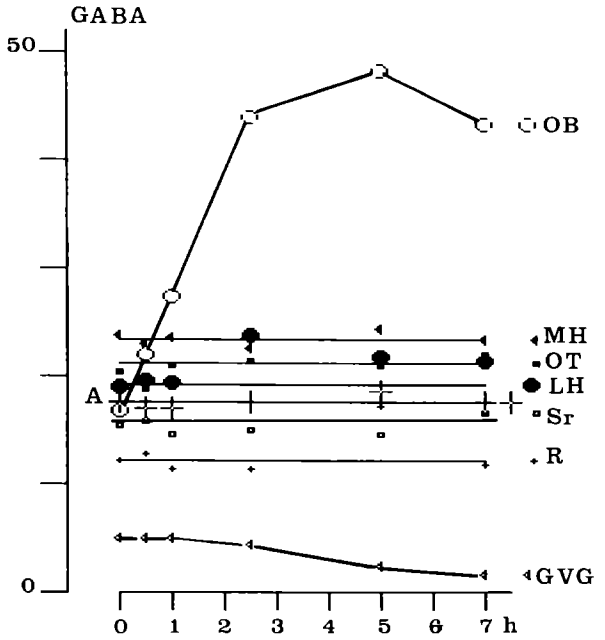

FIG 5 Evolution of GABA contents after intra olfactory bulbs administration of 0 15 μmol GVG GABA nanomole/mg dry weight Brain areas OB, olfactory bulbs, MH, median hypothalamus, OT, olfactory tubercles, LH, lateral hypothalamus, A, amygdala, Sr, Striatum, R, raphe slice Time expressed in hours GVG evolution of GVG contents of the olfactory bulbs—nanomole/mg dry weight, same scale as for GABA (Olfactory bulbs, ANOVA $F(4,5)=22\ 4$)

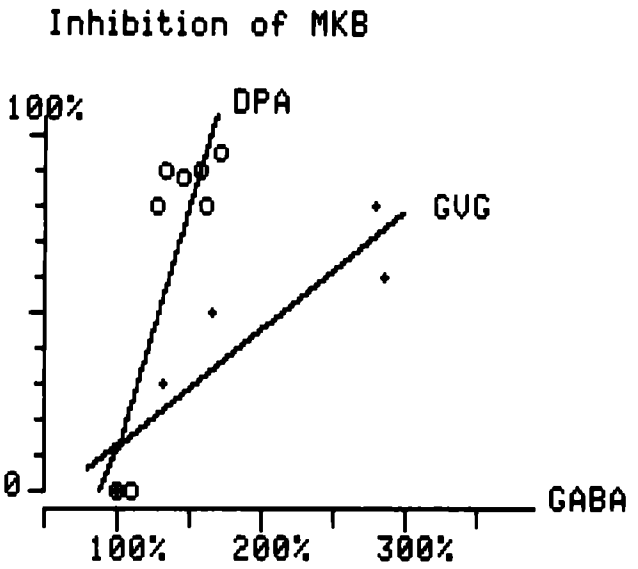

FIG 6 Inhibition of MKB by intra olfactory bulb administration of GABA-T inhibitors as a function of GABA level in the olfactory bulbs Abcissa GABA level as % of control (values for DPA from 21) Ordinate % inhibition of MKB Both GABA-T inhibitors were injected at the same molar dosage 0 15 μmol +=GVG, ○=DPA Results of the linear regression analysis DPA, $r=0\ 83$, $p<0\ 01$ regression coefficient $1\ 27\pm0\ 32$, GVG, $r=0\ 90$, $p<0\ 02$, regression coefficient $0\ 32\pm0\ 09$

Effect of GABA-T Inhibitors on Mouse-Killing Behavior

The injection into the olfactory bulbs of GVG, an irreversible inhibitor of GABA-T, induced a long-lasting inhibition of muricidal activity (Fig 4) The maximal effect was obtained 2 5 hr after drug administration (inhibition of MKB in 80% of animals, Table 1) Valproate, a competitive inhibitor of GABA-T [5], administered locally into the olfactory bulbs reduces muricidal activity with a maximal inhibitor effect 1 hr after drug administration (Fig 4, Table 1)

Effect of GABA-Mimetic Drugs on Locomotor Activity

With the doses used for MKB studies, no sedative effect was observed following intra-olfactory bulb administration of the most effective agents When compared to the locomotor activity of controls, the mean values as % of controls are the following THIP 113%, guvacine 111%, GVG 119%

Effect of Intra-Olfactory Bulbs Administration of GVG on the GABA Content in Several Brain Areas

GVG administration into the olfactory bulbs at the same coordinates as those used for behavioral studies induced a significant increase of the GABA content only in this brain area (Fig 5) A plateau in GABA level was observed 2 5 hr after drug injection, which corresponds to the time of maximal muricidal inhibition (Fig 4) As shown in Fig 6 there is a significant correlation ($p<0\ 01$) between GABA level increase in olfactory bulbs and muricidal inhibition There is no increase in GABA levels in the other brain regions investigated after GVG injection (olfactory tubercle, raphe slice, amygdala, median and lateral hypothalamus and corpus striatum) Figure 5 shows a detectable GVG content, only in the olfactory bulbs On the contrary, GVG could not be detected in any other brain areas

DISCUSSION

In this work different types of GABA-mimetic drugs which enhance GABAergic transmission via three main mechanisms of action were used (a) $GABA_A$ agonists, (b) inhibitors of GABA reuptake process, (c) inhibitors of GABA degradation (by blocking GABA-T activity) As shown in this paper, the injection of all these compounds into the olfactory bulbs clearly blocked muricidal activity A similar MKB inhibition was described following systemic administration of GABA-mimetic drugs [24] Moreover, muricidal behavior induced by olfactory bulb ablation is not inhibited by IP or per os GABA-mimetic administration, suggesting strongly the importance of an increase of GABA neurotransmission in the olfactory bulb either by local injection or by systemic administration In addition, local injections into the olfactory bulbs of allylglycine, an inhibitor of glutamate decarboxylase, bicuculline, a GABA antagonist on receptor site or picrotoxin, which blocks chloride channels, induces muricidal aggression in non-killer rats [23] Biochemical evidence has shown a reduction of GABA levels in the olfactory bulbs of rats with muricidal activity [20] The inhibition of MKB by compensation of this GABA deficiency suggests an inhibitory role of GABA from olfactory bulbs on MKB modulation Although all the GABA-like compounds tested reduced muricidal display, differences in antimuricidal efficiency were observed even between drugs acting through the same mechanism As an example, a higher antimuricidal effect is observed after THIP administration as

compared to muscimol or isoguvacine, all GABA agonists, this may be explained by a more specific action on GABA receptors since it was suggested that THIP is more selective as GABAergic agonist when compared to muscimol [8] Concerning GABA-uptake inhibitors, both drugs used at the same doses provoked a similar antimuricidal effect, however, the inhibition of MKB is apparently less efficient than that obtained with GABA agonist At the same μmolar dosage the intraolfactory bulbs injection of GABA-T inhibitors reduced muricidal activity with a similar efficiency and maximal percentage of inhibition

One might expect that, after intra-bulbar administration of drugs, GABA agonists would have shorter latencies than inhibitors of degradation or of reuptake In contrast, the results obtained show that this is not the case A speculative hypothesis is that GABA agonists bind to all receptors of all GABAergic neurons, including interneurons which may inhibit other GABAergic neurons Moreover, it is likely that, because of the dilution of agonists among all binding sites, the effective binding of agonists to the neurons involved in the inhibition of aggressive behavior is relatively lower Furthermore, it seems likely that where excitatory discharges occur, inhibitory discharges are triggered, GABA-T inhibitors or inhibitors of reuptake, since they potentiate the effects of GABA discharges locally on the sites involved in the behavior investigated, may be more efficient than GABA agonists It is noteworthy that GABA agonists appear to be less effective than valproic acid in the treatment of convulsive disorders or epilepsy [22] Here again one may suggest that in the epileptic focus there is a spontaneous discharge of GABA in order to inhibit the discharges of the epileptic focus [43], inhibition of GABA degradation or of reuptake would also be more efficient than GABA agonists acting on all GABA receptor sites in the brain, including those on GABAergic interneurons

As shown in this report, there is a significantly linear correlation between mouse-killing inhibition and GABA level increase in the olfactory bulbs ($r=0\ 90$, $p<0\ 02$) after local GVG administration The antimuricidal effect of GVG is selective on GABA levels from olfactory bulbs since we did not observe any modification on GABA content in other brain areas investigated Since at the same dosage DPA and GVG induced similar muricidal reduction (50 and 56 conventional units), it was then possible and interesting to look for a linear correlation between muricidal inhibition and GABA levels increases in olfactory bulbs following local injection of DPA Taking into account the present results on MKB and those previously obtained in GABA levels in the olfactory bulbs [21], a significant linear correlation is in fact also observed ($r=0\ 83$, $p<0\ 01$) It is important to point out that the regression coefficient for DPA is significantly higher than that obtained with GVG This means that an increase of GABA levels in the olfactory bulbs induced by DPA is more efficient to inhibit muricidal activity than a similar increase due to GVG According to a large body of evidence, the explanation of this observation may be that DPA increases GABA content in the synaptic pool, while GVG increases GABA levels in the cytosolic pool [11, 32, 47, 48] DPA is a reversible, competitive inhibitor of GABA-T [5], in principle it may also act as an inhibitor of semialdehyde succinic dehydrogenase [44] Nevertheless, the increase on GABA levels is likely induced by its GABA-T inhibitor properties since local injection of succinic semialdehyde does not produce an increase of GABA in the olfactory bulbs [37] On the other hand, GVG is a suicide GABA-T inhibitor, it irreversibly inactivates GABA-T [33,34] The higher increase of GABA content (+180% of controls) is reached 2 5 hr after GVG administration, while GABA increase previously observed for DPA (+70% of controls) is reached at a shorter period of time According to these observations, maximal muricidal inhibition is obtained 1 hr after DPA administration while a maximal antimuricidal effect is obtained 2 5 hr after GVG injection Thus it is highly probable that the kinetic differences observed between GVG and DPA effects also arise from the difference in the mechanism of action of these two drugs on the synaptic and cytosolic pool So, the latter effects of GVG as compared to DPA may be due to an action first on the cytosolic pool followed by an increase on the GABA content of the synaptosomal pool [47,48]

Since GVG levels were only detected in the olfactory bulbs, we may conclude that there is no diffusion of this drug from the injection site in the olfactory bulbs to other brain areas Similarly, intra-olfactory bulbs injection of ^{3}H-succinic semialdehyde at the same coordinates as those presently used showed a lack of diffusion into other brain areas, in fact 95% of succinic semialdehyde was recovered in the olfactory bulbs [37] Thus, the same coordinates being used for local administration of the other GABA-mimetics as well as of GABA, the antimuricidal effects obtained are specific for GABA from olfactory bulbs A possible local anesthesic effect following injection into the olfactory bulbs of GABA-mimetic drugs seems unlikely, since Mack [21] did not observe any MKB inhibition after local administration of a local anesthesic drug Anosmia induced by nasal mucose lesion or by surgical removal does not induce muricidal activity [38,39] The olfactory bulb system is not exclusively involved in sensory olfaction but also modulates the limbic balance through connections with preoptic nuclei, lateral hypothalamus and the corticomedial amygdala [28,41]

An increase of GABAergic neurotransmission in the olfactory bulbs is also obtained by IP injections of GABA-mimetic drugs like DPA and GVG which increase GABA in several brain areas The reality of this assumption is confirmed by the fact that after IP administration of these substances a long lasting increase in GABA is also obtained in the olfactory bulbs [26] In summary, inhibition of MKB by GABA-mimetic drugs after IP administration was reported by Mandel *et al* [24] and Bolin and Da Vanzo [4] Depaulis and Vergnes [6] do not observe MKB inhibition after IP injection of several GABA-mimetic drugs unless a sedative effect was observed These discrepancies may arise from differences in experimental conditions, first of all, isolation conditions were different In our case, as well as in previous experiments, in which DPA clearly inhibits MKB [23,24], rats were maintained to opaque cages which did not allow visual contact with other rats Moreover, the dimension of the housing cages were large enough to provide room for ample displacement When systemic administration of GABA-mimetic failed to inhibit MKB [6] cages were transparent (wire cages) and of very restricted dimension, these housing conditions may add some stressful factors to the social isolation Finally, we may imagine that the aggressive impulsion in some selected strains and in some conditions may be so that the dosage of GABA-mimetics necessary is also sedative Nevertheless, let us remember that according to Karli [15], a sedative effect by itself unless very strong does not interfere with MKB

In summary, the data observed in this investigation support an inhibitory role of GABA from olfactory bulbs In

addition, a GABA deficiency in the olfactory bulbs of isolated K rats has been described [20,21], the compensation of this deficiency, either by GABA itself or by different GABA-mimetic drugs, block MKB Thus, we may conclude that a deficiency of GABAergic neurotransmission in the olfactory bulbs plays a crucial role in MKB

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