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Effect of Glutamic Acid and Glutamine on the Pyretogenic Action of Lysergic Acid Diethylamide

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Hoff and Arnold[1] reported in 1954 that glutamic acid inhibits the psychotogenic action of lysergic acid diethylamide (LSD) in human subjects. However, in 1956 Hoch[2] indicated that glutamic acid had little effect on the psychotogenic activity of LSD. These conflicting reports may have resulted from difficulty in evaluating subjective behavioral charges. It was felt, therefore, that a quantitative measure of the effects of glutamic acid and glutamine on the pyretogenic action of LSD would be of value.

Studies by Horita and Dille[3] and Cerletti[4] have demonstrated that the pyretogenic effect of LSD in the rabbit is a sensitive and reliable measure of LSD activity. In our laboratory we were able to obtain a significant temperature rise in rabbits with dosages as low as 0.2 μg./Kg. This dosage ratio (μg./Kg. of body weight) is of the same order as that used to

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induce psychotomimetic effects in humans. However, this does not imply an identity of pyretogenic and psychotomimetic effects. The relationship between these two effects of LSD has not been established.

MATERIALS AND METHODS

Glutamic acid was administered as the sodium salt, prepared by dissolving L-glutamic acid in 0.5 *N* NaOH and neutralizing to *p*H 7 with 0.2 *N* HCl. L-Glutamine was prepared identically with L-glutamic acid. The blank contained an equivalent amount of NaCl, produced by combining NaOH with HCl in the same way as in the preparation of glutamate.

A factorial design was utilized in which 12 white male rabbits (mean weight, 1.77 Kg.; range, 1.55–2.0 Kg.) were divided into six groups of 2. On the first day of the experiment the rabbits were treated according to the schedule in table I. On the five subsequent days, each group was rotated through another treatment until all six groups had received all treatments.

Each rabbit received two injections intravenously into the marginal ear vein. The first injection constituted a pretreatment and was followed five minutes later by a second, which constituted the treatment. Groups 1, 2, and 3 were controls used in order to compare the effects of glutamic acid and glutamine alone with those obtained when these compounds were given with LSD.

Group 1 was pretreated with blank, and the treatment itself also consisted of blank. Group 2 was pretreated with L-glutamine, 25 mg./Kg., and then treated with blank. Group 3 was pretreated with L-glutamic acid, 25 mg./Kg., followed by treatment with blank.

Group 4 received pretreatment with L-glutamine, 25 mg./Kg., followed by treatment with LSD, 1 μg./Kg. Group 5 was pretreated with L-glutamic acid, 25 mg./Kg., and then

TABLE I

Treatment Schedule, Initial Temperature, and Temperature Rise for Each Observation Period

Group*	Treatment schedule		Temperature immediately prior to treatment, degrees C.		Rise from initial value, degrees C.					
					After 20 minutes		After 40 minutes		After 60 minutes	
	Pretreatment	Treatment	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
1	Blank	Blank	39.9	0.20	0.23	0.13	0.39	0.23	0.53	0.29
2	Glutamine†	Blank	40.0	0.24	0.24	0.12	0.40	0.15	0.61	0.21
3	Glutamic acid†	Blank	40.1	0.33	0.26	0.15	0.46	0.18	0.64	0.20
4	Glutamine†	LSD‡	40.0	0.15	0.35	0.18	0.60	0.13	0.82	0.14
5	Glutamic acid†	LSD‡	40.0	0.27	0.47	0.34	0.76	0.38	0.93	0.15
6	Blank	LSD‡	40.0	0.26	0.69	0.30	1.10	0.37	1.41	0.25

* Each group was rotated through all treatments on six consecutive days.

† 25 mg./Kg. dissolved in blank.

‡ 1 μg./Kg. dissolved in blank.

treated with LSD, 1 μg./Kg. Group 6 was pretreated with blank followed by treatment with LSD, 1 μg./Kg.

Rectal temperatures were taken by means of a Tele-Thermometer immediately prior to treatment and at 20 minute intervals thereafter for a total period of one hour. For 10 days prior to the administration of the experimental compounds, the animals were placed on rabbit boards and temperatures were taken to accustom them to the handling procedures involved in the study. At the end of this 10 day period, handling produced no more than 0.2 C. rise in one hour in any of the rabbits used.

RESULTS

Table I is a summary of results of the administration of each treatment to the 12 rabbits. An analysis of variance was performed for the following effects and found not significant: (1) Differences between day of treatment, (2) initial temperature for each treatment, (3) differences between order of treatment. Thus, no significant tolerance was found under the conditions of this study. Also, minor variations in the ambient temperature (about 22 C.) did not systematically affect the response.

No significant difference was found between the effects of control treatments of glutamine, glutamic acid, and blank during the 60 minute observation period (t test). The pyretogenic effect in rabbits treated with LSD was significantly greater than that in rabbits receiving control treatments ($P < 0.001$).

Pretreatment with glutamine significantly inhibited the pyretogenic effect of LSD at 20, 40, and 60 minute intervals ($P < 0.01$, $P < 0.01$, and $P < 0.001$ respectively). Glutamic acid, on the other hand, produced significant inhibition only at the 60 minute interval ($P < 0.01$). However, when the glutamine effect was compared with the glutamic acid effect, no significant difference occurred at any interval.

COMMENT

Under the conditions of this study, the pyretogenic effect of LSD has been shown to be inhibited by both glutamine and glutamic acid. The mechanism of interaction of these compounds with LSD is not clear. However, glutamic acid and glutamine do not have a general hypothermic effect, as evidenced by their lack of inhibition of the slight temperature rise produced by the blank (table I). Therefore, the inhibition observed in this experiment appears to be the result of a specific interaction of these compounds with LSD.

Neuhold, Taeschler, and Cerletti[5] demonstrated that the pyretogenic action of LSD occurs in decorticate, but not decerebrate, preparations. They suggest that the site of action of LSD is central and occurs in the diencephalon.

Since glutamic acid and glutamine did not inhibit the temperature rise produced by the blank, but did inhibit the pyretogenic effect of LSD, it would appear that its inhibitory effect occurs at the site of pyretogenic action of LSD. Since it appears that the inhibition occurs centrally, the more rapid inhibition produced by glutamine may be related to the findings of Schwerin, Bessman, and Waelsch[6] that glutamine more rapidly penetrates the intact brain than does glutamic acid. The different time curves of inhibition for glutamic acid

and glutamine may therefore reflect the lesser permeability of the brain barrier to glutamic acid.

SUMMARY

The effects of L-glutamic acid and L-glutamine on the pyretogenic action of lysergic acid diethylamide in rabbits were studied. Both glutamic acid and glutamine were found to inhibit this pyretogenic effect significantly. The inhibitory action of glutamine occurred at a faster rate than that of glutamic acid. This may be related to the relative impermeability of the brain to glutamic acid.

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RESUMEN

Se estudiaron los efectos del ácido L-glutámico y de la L-glutamina sobre la acción pirogénica de la dietilamida del ácido lisérgico, en conejos. Se halló que tanto el ácido glutámico como la glutamina inhibían en forma significativa este efecto pirogénico. La acción inhibitoria de la glutamina se produjo con mayor rapidez que con el ácido glutámico. Este fenómeno puede depender de la relativa impermeabilidad del cerebro al ácido glutámico.

RESUME

Les effets chez le lapin de l'acide L-glutamique et de la L-glutamine sur l'action pyrétogène du diéthylamide de l'acide lysergique font l'objet de cette étude. L'auteur a constaté que tant l'acide glutamique que la glutamine inhibaient sensiblement cette action pyrétogène. L'effet inhibiteur de la glutamine s'est manifesté plus rapidement que celui de l'acide glutamique. Il est possible que cette différence soit due à l'imperméabilité relative du cerveau à l'acide glutamique.

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