INVOLVEMENT OF CENTRAL CHOLINERGIC SYSTEM IN DECREASE OF SERUM FATTY ACIDS AFTER INTRACEREBROVENTRICULAR ADMINISTRATION OF CHLORPROMAZINE

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We reported that an injection of chlorpromazine (CPZ) into the lateral ventricle caused a transient decrease in serum FFA. The involvement of the central dopaminergic mechanism in this decrease was considered (1). The dopaminergic-cholinergic antagonistic relationship in the nigro-striatal system, indicated by metabolic (2-6), behavioral (6, 7) and microiontophoretical (8) evidence, is now well known. Therefore, in order to know the involvement of the central cholinergic system in the control of peripheral lipid mobilization after intracerebroventricular (i.c.v.) injection of CPZ, we examined the effect of cholinergic agents on the change in the serum FFA level after the i.c.v. injection of CPZ in rats.

Male Wistar-lmamichi rats weighing 180–280 g were kept in an air-conditioned room (23±2°C, 55±5% humidity) lighted 14 hr a day (06:00 to 20:00) and maintained on a rat standard diet and water ad libitum. For injections into the cerebral ventricles, a stainless steel cannula was implanted into the right lateral ventricle under sodium pentobarbital anesthesia (nembutal, 40 mg/kg i.p.). After a 7-day post-operative recovery period, drugs were injected through this cannula without any anesthesia. For injections into the cerebral ventricles, a stainless steel cannula was implanted into the right lateral ventricle under sodium pentobarbital anesthesia (nembutal, 40 mg/kg i.p.). After a 7-day post-operative recovery period, drugs were injected through this cannula without any anesthesia. All i.c.v. injections of drugs were made in the same volume (20 µl/kg) over a period of 20 sec. All the drugs (CPZ hydrochloride: Shionogi Pharmaceutical Co. Ltd., acetylcholine (ACh) chloride: Daiichiseiyaku Co. Ltd., carbamylcholine (CAR) chloride: Sigma Chemical Co. Ltd., atropine sulfate: Iwakiseiyaku Co. Ltd., neostigmine methyl sulfate: Shionogi Pharmaceutical Co. Ltd.) were dissolved in saline, and the solution was adjusted to a pH of 6.8. All doses of drugs used are given in the results as the amount of free base. Blood samples for determination of FFA were obtained from the jugular vein of rats with a disposable syringe. Serum FFA was determined colorimetrically according to the method of Novak (9).

As is described in the previous report (1), the i.c.v. injection of CPZ produced a marked transient decrease in serum FFA with the two doses (200, 500 µg/kg) examined, whereas the same volume of vehicle (20 µl/kg) had no effect. Serum FFA levels reached a minimum 30 min after injection of CPZ and then returned to the initial level during the second hour. With a lower dose of 100 µg/kg CPZ, only a slight decrease was observed, but this was not statistically significant. Microinjection of either ACh alone at a dose of 20 µg/kg or carbachol at the same dose did not affect the serum concentration of FFA. The simultaneous administration of ACh and CPZ at 100 µg/kg into the right lateral ventricle accelerated the fall in the serum FFA level, whereas the simultaneous admin-
istration of ACh with two higher doses of CPZ (200 or 500 µg/kg) did not show any modification. On the other hand, the fall in the serum FFA level after CPZ at 100 or 200 µg/kg i.c.v. was significantly accelerated with the simultaneous injection of 20 µg/kg carbachol. However, at a dose of 500 µg/kg i.c.v. CPZ, the significant modification following the simultaneous injection of carbachol was not observed. The potentiation by carbachol of CPZ was more pronounced and long-lasting than that of ACh (Fig. 1).

Further, in an attempt to examine the effect of an anticholinergic agent and anticholinesterase, 50 µg/kg atropine or 5 µg/kg neostigmine was injected intracerebroventricularly 10 min prior to the injection of CPZ, ACh and carbachol. As shown in Fig. 2, the potentiation by simultaneous injection of ACh with 100 µg/kg CPZ was significantly blocked by the prior i.c.v. injection of atropine, indicating that muscarinic synaptic receptors are involved in this effect. However, the potentiation by carbachol was hardly inhibited by preinjection of atropine, suggesting that the mechanisms of the potentiation by carbachol may be different from that by ACh. After the i.c.v. injection of 5 µg/kg neostigmine, the tendency of the opposite response in the potentiation of CPZ action by these two cholinergic agents (ACh, carbachol) was observed, even though it was not significant. These results after preinjection of atropine or neostigmine suggest that carbachol produced the potentiation of CPZ action as well as ACh; but the details of the mechanisms of the action by this drug is probably different from ACh, i.e., the possible

Fig. 1. Effect of simultaneous injection of ACh (20 µg/kg i.c.v.) or carbachol (20 µg/kg i.c.v.) alone with CPZ (100, 200, 500 µg/kg) on the decrease in serum FFA. Numbers in parentheses represent the numbers of animals employed. The vertical lines indicate the S.E. of the mean. P values were calculated by the Student’s t-test. *P<0.05, **P<0.01 as compared to CPZ alone.
involvement of the muscarinic cholinergic receptors in the potentiation by ACh of CPZ action was revealed, but presumably not in the potentiation by carbachol.

On the other hand, it has been already demonstrated that there is an antagonistic relationship between the dopaminergic and cholinergic system in the striatum (2–8), although it remains still controversial whether nigro-striatal dopamine neurons exert an excitatory (10, 11) or inhibitory (2, 12) effect on cholinergic interneurons in the striatum. Furthermore, several reports have shown that dopamine or dopamine-mimetic drugs inhibits the cholinergic cells in the caudate nucleus, reducing ACh turnover or release, and resulting in an increase in ACh content in this area. The opposite effect is produced by

![Graph](image)

Fig. 2. Effect of preinjection of atropine (50 μg/kg i.c.v.) or neostigmine (5 μg/kg i.c.v.) on the acceleration of the decrease in serum FFA after the simultaneous injection of ACh (20 μg/kg i.c.v.) or carbachol (20 μg/kg i.c.v.) with CPZ (100 μg/kg i.c.v.). Atropine or neostigmine was injected 10 min. prior to the injection of CPZ, ACh and carbachol. Values show the mean standard error at 30 min after administration of CPZ, ACh and carbachol. Figures at the foot of each of the columns represent the numbers of animals employed. *P<0.05, **P<0.01.
dopamine antagonists or dopamine-depleting agents (2, 4, 13, 14).

In this experiment herein, the effect of CPZ on the decrease in serum FFA was potentiated by the cholinergic agents such as ACh and carbachol. On the contrary, this effect was blocked by dopamine and apomorphine as described in our previous report (1). Now, a possible cholinergic involvement in the control of peripheral lipid mobilization induced by CPZ is also suggested. It is therefore possible to say that the central dopaminergic-cholinergic system is involved in the peripheral lipid mobilization induced by CPZ.

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References