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BRIEF COMMUNICATION

Survival Effect of Coenzyme Q_{10} and Naloxone on Experimental Stroke Gerbils

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OGAWA, N , S TSUKAMOTO, Y HIROSE AND H KURODA *Survival effect of coenzyme Q_{10} and naloxone on experimental stroke gerbils* PHARMACOL BIOCHEM BEHAV **24**(2) 315–317, 1986 —Coenzyme Q_{10} (CoQ_{10}) and the opiate antagonist naloxone were compared as to their effect on the survival of mongolian gerbils with unilateral carotid ligation-induced stroke Without medication all of the stroke gerbils died within 28 hours, but with a subcutaneous implantation of a 10 mg pellet of naloxone, 20% of the gerbils lived for 4 weeks When a 250 mg pellet of CoQ_{10} was implanted subcutaneously, a definite effect on survival was observed, with 45% of the stroke gerbils living for 4 weeks Considering that the action mechanisms of CoQ_{10} and naloxone are different, the combined use of these drugs in the treatment of stroke needs to be investigated

Stroke gerbils Survival effect Coenzyme Q_{10} Opiate antagonist Naloxone Levallorphan Hanging stroke test

ALTHOUGH there has been much clinical and experimental research on the pharmacological treatments of acute stroke, the results have not been particularly encouraging Recently, however, the opiate antagonist naloxone has received attention as a possible therapy for cerebrovascular disorders Baskin and Hosobuchi reported the relief of neurologic symptoms in cerebral ischemia patients after naloxone treatment [2] and found naloxone to be temporarily effective against ischemic neurologic deficit (stroke) in gerbils [7] We found that not only naloxone but also levallorphan was effective in a similar experimental model [15] Nevertheless, there are numerous reports which deny the effectiveness of opiate antagonists in the treatment of stroke [4, 6, 8], and the therapeutic value of opiate antagonists against stroke remains to be determined

In the present study, the effect of naloxone on the survival of gerbils with experimentally induced stroke was examined along with the effect of coenzyme Q_{10}, a component of the mitochondrial electron transport system involved in oxidative phosphorylation [13] and reputed to have a beneficial effect on cerebral infarction [3]

METHOD

Cerebral infarction was induced in 250 mongolian gerbils weighing 70 g by ligating the right common carotid artery in 2 places 5 mm apart under ketamine anesthesia The presence or absence of stroke (neurologic deficit) was determined 4 hours after the ligation Animals in which it was difficult to judge the presence of stroke were hung by the left hind leg with tweezers (hanging stroke test) Those which could not lift themselves up were considered to have a stroke

Four hours after the ligation, a 10 mg pellet of naloxone or levallorphan, or a 250 mg pellet of coenzyme Q_{10} (Neuquinon, Eisai Co Ltd , Japan, CoQ_{10}) was subcutaneously implanted in the right abdomen of gerbils which developed stroke symptoms There were 20 animals in each treatment group The control animals underwent the implantation operation without receiving a drug pellet The life span of the gerbils was recorded The right side was chosen for the implantation since with left hemiplegia there was the possibility of disturbed uptake of the drug on that side due to circulatory dysfunction

To confirm that CoQ_{10} was absorbed and the blood level rose, another group of gerbils implanted with 250 mg of CoQ_{10} were decapitated at various times and serum CoQ_{10} level was determined by high performance liquid chromatography [1]

RESULTS

Out of the 250 gerbils, 104 (41 6%) developed stroke symptoms This percentage is close to that reported previously [11,12]

Twenty gerbils which developed stroke symptoms died 16 8±6 7 (mean±SD) hours after carotid ligation The longest survivor out of 20 gerbils died 28 hours after ligation of the right carotid artery, and more than 90% of the gerbils died within 24 hours On the other hand, all of the gerbils which were not afflicted with stroke (146 out of 250 gerbils)

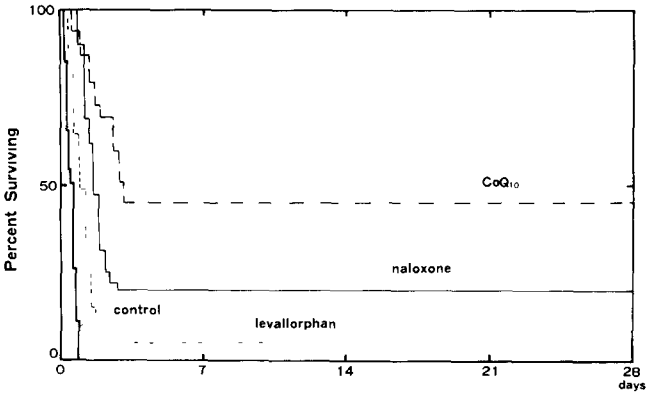

FIG 1 The effect of opiate antagonists and CoQ_{10} on the survival of gerbils that developed stroke after unilateral carotic ligation Twenty gerbils were examined in each treatment group

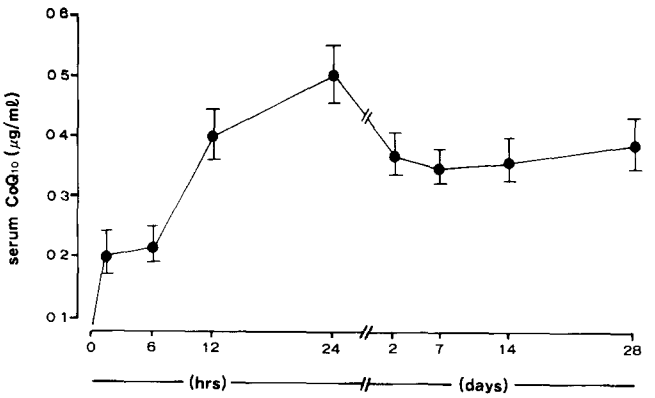

FIG 2 The change in serum CoQ_{10} level after the subcutaneous implantation of a 250 mg pellet of CoQ_{10} into the abdomen of normal gerbils Values are expressed as the mean±SEM of 5–6 gerbils

lived over 4 weeks This results indicates that the method of evaluating stroke used in this study was accurate

As shown in Fig 1, 4 (20 0%) of the 20 gerbils implanted subcutaneously with a 10 mg pellet of naloxone lived for 4 weeks One of the 4 gerbils which survived 4 weeks had a very slight left hemiparesis, but the other 3 showed no symptoms of paralysis Thus, naloxone was shown to have a survival effect. Levallorphan (10 mg pellet) extended the life span as did naloxone, but none of the animals which received levallorphan lived more than 2 weeks

The life-extending effect of a 250 mg subcutaneous pellet of CoQ_{10} was obvious, with 9 (45 0%) of the 20 animals living 4 weeks (Fig 1) Though 5 of the 9 animals which lived 4 weeks had right ptosis or partial left hemiparesis, it was characteristic of the gerbils impalnted with CoQ_{10} to maintain normal posture and look healthy until just before their death

Because of CoQ_{10}'s insolubility in water, we checked to be sure that CoQ_{10} was being taken up and that its concentration in the blood increased An hour after the implantation, the blood concentration of CoQ_{10} was 0 2 μg/ml, and for 28 days after the implantation the concentration of CoQ_{10} in the blood remained high (Fig 2)

DISCUSSION

It is well-known that some Mongolian gerbils have a congenital defect in the circle of Willis and that ligation of the common carotid artery on one side easily induces stroke in these animals [11,12] Present result is consistent with that reported by Hosobuchi *et al* that stroke gerbils all died within 48 hours [7] The hanging stroke test used by the present authors to evaluate the gerbils' condition clearly distinguished between those with stroke and those without, as evidenced by the sharp difference in the life span between the two groups

Hosobuchi *et al* reported that, with an implantation of a 10 mg pellet of the opiate antagonist naloxone, 44% of the animals survived for more than 2 weeks without any neurologic deficit [7] There was only one animal out of the 20 implanted with levallorphan that lived 7 days The lesser survival effect of levallorphan than that of naloxone may be related to pharmacological features of agonist-antagonist to opiate receptors of levallorphan [16] Hosobuchi *et al* have already reported that the administration of opiate agonists brings out neurologic symptoms or makes them worse [7]

CoQ_{10} has been reported to improve metabolism in brain damage induced by anoxia [11] For example, CoQ_{10} has been shown to control the free radical peroxidation of membrane lipids, a factor contributing to ischemic brain damage [13] This effect prevents the destruction of the blood-brain barrier in rats with cerebral ischemia [3], and delays the decline in electroencephalographic activity in rabbits with experimental asphyxic anoxia [10]

As far as the effect on survival, the results show that CoQ_{10} (250 mg) is superior to naloxone (10 mg) The facts that survival rate is very high and the majority of animals have some neurologic deficit indicate that CoQ_{10} is effective in increasing the life span of more seriously affected animals in which neurologic symptoms remain

Although CoQ_{10} is lipophilic, a high blood level was sustained in gerbils implanted subcutaneously with a pellet CoQ_{10}, as shown in Fig 2 The level achieved with the implanted pellet was much greater than that obtained with a single oral dose [5,14], and the length of action was beyond comparison Thus, the subcutaneous implantation of a pellet appears to be an excellent method for the sustained administration of a drug to small animals like gerbils

Since the mechanisms of action of CoQ_{10} and naloxone are different, the combined use of these drugs in the treatment of stroke needs to be investigated

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