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BRIEF COMMUNICATION

Verapamil-Induced Behavioral, Autonomic and Motor Effects in Cats

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BELESLIN, D B R SAMARDŽIC, D JOVANOVIC-MICIC AND B TERZIC *Verapamil-induced behavioral, autonomic and motor effects in cats* PHARMACOL BIOCHEM BEHAV **24**(2) 329–331, 1986 —The effects of verapamil, a calcium antagonist, injected into the cerebral ventricles on behavior, autonomic and motor activity of unanesthetized cats have been investigated Verapamil evoked emotional behavior (miaowing and alertness), autonomic responses (mydriasis, tachypnoea, dyspnoea, defecation, micturition, licking and panting) and motor phenomena (ataxia, muscular weakness and adynamia) These effects lasted from a few minutes to several hours The most consistent phenomena were miaowing, alertness, mydriasis and respiratory irregularities The possible mechanism of action of verapamil on behavior, autonomic and motor activity may be an action on voltage-operated calcium channels in the brain

Verapamil Intracerebroventricular injections Behavior Autonomic changes Motor changes Calcium antagonist

THERE is abundant evidence that calcium modulates a vast number of bodily processes However, the functional role of calcium is better understood in peripheral organ systems and tissue than in the central nervous system Nevertheless, a number of investigations in recent years have demonstrated that calcium is involved in thermoregulation [12], blood pressure regulation [2], paradoxical sleep [15] and feeding behavior [8,13] In addition, neuroleptic drugs of the diphenylbutylpiperidine type, but not other phenothiazines and butyrophenones, act on voltage dependent calcium channels [9]

Therefore, it was of interest to investigate the behavioral, autonomic and motor effects of verapamil, a relatively selective calcium channel antagonist, after it was injected into the cerebral ventricles of the unanesthetized cat

METHOD

In these experiments, 22 cats of either sex, weighing between 2–4 kg, were anesthetized with 35–40 mg/kg intraperitoneal sodium pentobarbital Following aseptic precautions, a hole was drilled 7–8 mm from the zero line and 4–5 mm from midline A Collison cannula was screwed into the calvarium, the tip of the cannula resting in the left lateral ventricle [4] The lower end of the cannula shaft was made of polyethylene tubing, with a side opening 1 0 mm from its closed tip and positioned with the lumen facing the foramen of Monro Post-mortem dye studies indicated that the injected material passed from the lateral into the third and fourth ventricles Postoperatively, penicillin was administered intramuscularly, and an interval of five days was allowed to elapse before an experiment began

On the test day, cats were acclimated to the test environment, a wire-mesh cage measuring 110×130×150 cm, for at least 1 0 hour before intracerebroventricular drug injections Behavioral, autonomic and motor changes were monitored continuously for a period of 4 0 hr and intermittently for 24 hr

Verapamil chloride was dissolved in sterile, pyrogen-free 0 9% sodium chloride The solution was then injected into the cerebral ventricles by hand from a 1 0 ml syringe, in a volume of 0 1–0 2 ml, over a period of 15–20 sec and washed in with 0 1 ml of saline All reasonable aseptic precautions were taken Each cat was used only once in these experiments Doses of verapamil refer to verapamil chloride

RESULTS

When verapamil chloride (0 5–5 0 mg) was injected into the cerebral ventricles of unanesthetized cats, behavioral, autonomic and motor changes were observed after a short latent period of a few minutes (Table 1) The threshold doses of intracerebroventricular verapamil chloride were 0 5–1 0 mg After the injection of low doses of verapamil chloride (1 0–2 5 mg), the cats became lively and alert, and miaowed, and the respiratory rate increased over 100/min Defecation, micturition and mydriasis also occurred, sometimes short periods of panting, ataxia and muscular weakness were observed With larger doses of intracerebroventricular verapamil chloride (2 5–5 0 mg), ataxia, muscular

weakness and adynamia occurred These changes were associated with mydriasis and respiratory irregularities The effects lasted from a few minutes to several hours As a rule, the animals fully recovered within four hours

In control experiments, when 0 3 ml of 0 9% sodium chloride was injected into the cerebral ventricles in the unanesthetized cat, the only response was occasional miaowing

DISCUSSION

As shown in these experiments, verapamil injected into the cerebral ventricles of unanesthetized cats evokes behavioral, autonomic and motor phenomena It has already been reported that when the cerebral ventricles of the unanesthetized cat are perfused with a calcium-free solution, intense hyperthermia, respiratory irregularities, panting and alertness develop [3] In this connection, it is interesting to note that intracerebroventricular verapamil produces long-lasting hyperthermia preceded by short-lasting hypothermic effect in unanesthetized cats [14]. By comparing the doses of intracerebroventricular verapamil, it is seen that verapamil, micro-injected into the cerebral ventricles in doses at least ten times larger than that which evokes changes in the body temperature, induces behavioral, autonomic and motor changes in cats Voltage-dependent calcium channels in the cardiovascular system as well as in the central nervous system are blocked by calcium antagonists [6, 9, 16] Accordingly, the most reasonable explanation underlying the mechanism of intracerebroventricular effects of verapamil is its action on voltage-dependent calcium channels in the brain On the other hand, when calcium in excess is micro-injected into the hypothalamus or injected into the cerebral ventricles of the unanesthetized cat, sedation, a sleep-like state, depression or abolition of carbachol-induced aggressive behavior occurs [1, 3, 5, 13]

Another interesting finding is that when verapamil is injected into the cerebral ventricles of unanesthetized cats, alertness is the only emotional behavioral symptoms produced Recently, it was postulated that neuroleptic drugs of the diphenylbutylpiperidine type reverse negative schizophrenic symptoms such as emotional withdrawal and lack of affect [7, 10, 11], probably by impairing verapamil-sensitive calcium influx [9] Accordingly, behavioral alterations, such as alertness, evoked by intracerebroventricular verapamil could be related to an action on voltage-sensitive calcium channels in the brain Conceivably, the respiratory irregularities may also contribute to the alertness Finally, the low incidence of side effects of verapamil in the central nervous system could be related to high partitioning of the drug into the cardiovascular system or the relative specificity of this calcium antagonist to calcium channels in the central nervous system

TABLE 1

GROSS BEHAVIORAL EFFECTS FOLLOWING INTRACEREBROVENTRICULAR INJECTION OF VERAPAMIL IN UNANESTHETIZED CATS

Effects	Verapamil 0 5–5 mg	0 3 ml of 0 9% NaCl
Emotional		
restlessness	–	–
alertness	+	–
miaowing	+	±
rage	–	–
attack	–	–
fighting with paws	–	–
biting	–	–
flight	–	–
Autonomic		
mydriasis	+	–
tachypnoea	+	–
dyspnoea	+	–
panting	±	–
licking	±	–
vomiting	–	–
salivation	–	–
defecation	±	–
micturition	±	–
Motor		
scratching	–	–
ataxia	+	–
muscular weakness	+	–
adynamia	+	–
tremor	–	–
myoclonic jerks	–	–
convulsions	–	–

+ symptom present, ± symptom inconsistent, – symptom absent

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