Pergamon

Pharmacology Biochemistry and Behavior, Vol. 52, No. 1, pp. 241-243, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00055-0

BRIEF COMMUNICATION

Evidence for an Action of Araboascorbic Acid on Dopaminergic Pathways of the Corpus Striatum

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Received 1 September 1992

DORRIS, R. L. *Evidence for an action of araboascorbic acid on dopaminergic pathways of the corpus striatum.* PHARMACOL BIOCHEM BEHAV 52(1) 241-243, 1995.—The relative decrease in the 2 h accumulation of administered [^{3}H]-spiperone (SPI)—2 μCi/kg, 0.0004 mg/kg, SC—in mouse corpus striatum, a brain area with a high dopaminergic input (specific plus nonspecific dopamine receptor ligand binding) and the cerebellum, a brain area with little, if any, dopaminergic input (an index of nonspecific dopamine receptor ligand binding) were used to compare the influence of araboascorbic acid (AraA) with ascorbic acid (AsA) on the dopamine receptor. The abilities of these compounds to potentiate haloperidol-induced catalepsy were also investigated. Pretreatment for 30 min with AraA (1000 or 2000 mg/kg, IP) produced the same dose-dependent decrease in SPI accumulation in corpus striatum as observed with AsA. Accumulation in cerebellum was unaffected by either agent. Furthermore, as previously shown for AsA in rats and monkeys, AsA (1000 mg/kg) potentiated the cataleptogenic effect of haloperidol (0.2 mg/kg, SC). AraA was at least as effective as AsA in potentiating catalepsy produced by the neuroleptic. Thus, it would appear that AraA influenced the dopamine receptor in a manner not unlike that already shown for AsA. Because both agents have almost identical redox potentials but divergent antiscorbutic activities, their reductive properties might be more pertinent to the observed effects than their antiscorbutic properties.

Araboascorbic acid Ascorbic acid Dopamine receptor Catalepsy

SEVERAL investigators have provided evidence for an interaction of ascorbic acid with dopamine receptors. Thus, the vitamin has been shown to interfere with [^{3}H]-spiperone (SPI) binding in corpus striatum (1) and to antagonize and potentiate the behavioral effects of amphetamine (10) and haloperidol (2,9), respectively. D-Araboascorbic acid is a synthetic analog of ascorbic acid with only one-twentieth the antiscorbutic activity (11). However, it has a redox potential very similar to that of ascorbic acid (4). The purpose of this study was to determine if the analog has an action like that of ascorbic acid on the dopamine receptor.

METHOD

Biochemical

It has previously be shown (1) that drugs with dopamine receptor antagonistic properties (e.g., haloperidol) decrease the accumulation, in vivo, of SPI in rodent corpus striatum, an area with a high dopamine receptor content, while not affecting that in the cerebellum, an area that is essentially devoid of dopamine receptors. This method was used in these studies to evaluate araboascorbic acid for an action on the dopamine receptor. Thus, mice of either sex (20-34 g)

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TEX : ICR, were injected (SC) with [^{3}H]-spiperone, 20.9 Ci/mmol, New England Nuclear, dissolved in 18% ethanol. The dose administered was approximately 0.0004 mg/kg (20 μCi/kg). L-Ascorbic acid (A.C.S., Fisher Scientific Co.) and D-araboascorbic acid (Eastman Kodak Co.) were dissolved in water for injection (IP). All drugs were injected in a volume of 0.1 ml/10 g b.wt. Some mice were injected with water (sham injected controls).

Behavior

The ability to produce catalepsy in rodents is a characteristic shared by most antipsychotic drugs. Dopamine receptor antagonism is believed to be involved in its production (3). The ability of araboascorbic acid to potentiate a minimally effective, cataleptogenic dose of haloperidol was used as a behavioral indicator of its interaction with the dopamine receptor. This action was evaluated using a technique similar to that previously used to study catalepsy in ascorbic acid treated rats (2). The method was based on that utilized by Morpurgo (5). Thus, forepaws of the mouse were placed, one at a time, on a plastic box 4 cm in height. This was repeated for each hind paw and one-half point was given for each paw that remained on the box for 10 s. The homolateral forepaw and hind paw were then placed, simultaneously, on the box and a point was given for each of the two sides that remained on the box for 10 s. Two boxes were then separated by a distance of 6 cm and the forepaws placed on one box and the hind paws on the other. Retention of this position for 10 s was assigned a value of 2 points. Thus, a maximum of 6 points was possible for each mouse at each measurement time. Ascorbic acid and araboascorbic acid were prepared for injection (1000 mg/kg, IP) as described above. Haloperidol was dissolved in a small amount of 0.01 N HCl and diluted several hundredfold for injection (0.2 mg/kg, SC) in a volume of 0.1 ml/10 g b.wt.

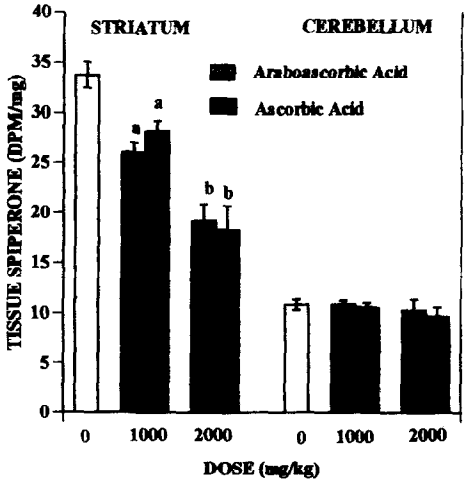

FIG. 1. Effect of ascorbic acid or araboascorbic acid on SPI accumulation in mouse brain. Ascorbic acid or araboascorbic acid were administered (IP) 30 min prior to SPI. Animals were sacrificed 2 h after SPI. Values are means ± SEM of at least six animals. Open, hatched, and shaded bars represent animals treated with water, araboascorbic acid, and ascorbic acid, respectively. [a]$p < 0.01$ compared to control but not different from each other; [b]$p < 0.01$ compared to control or 1000 mg/kg but not different from each other (Newman-Keuls test).

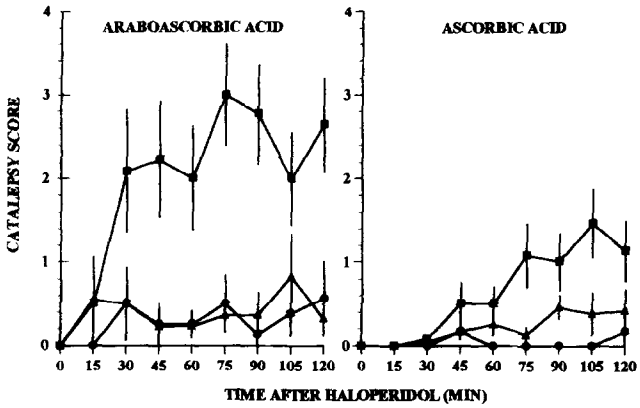

FIG. 2. Potentiation of cataleptogenic effects of haloperidol by ascorbic acid or araboascorbic acid. Mice were injected with ascorbic acid, araboascorbic acid (1000 mg/kg, IP), or and equivalent volume of water. Fifteen minutes later, some mice were injected with haloperidol (0.2 mg/kg, SC) and some with water. Except for cases in which ascorbic acid injections were followed by water ($n = 3$) or araboascorbic acid ($n = 8$), values are means ± SEM of at least 11 mice. Shaded circles represent mice injected with either araboascorbic acid or ascorbic acid followed by water; shaded triangles represent mice injected with araboascorbic acid or ascorbic acid followed by water and shaded squares represent mice injected with araboascorbic or ascorbic acid followed by haloperidol. Areas under the curves were calculated (trapezoidal method) for each animal and means evaluated by the one-tailed Student's t-test. Ascorbic acid plus haloperidol vs. haloperidol alone—$p < 0.024$; araboascorbic acid plus haloperidol vs. haloperidol alone—$p < 0.002$.

RESULTS

As previously reported (1), ascorbic acid produced a dose-dependent decrease in SPI binding in corpus striatum while not significantly altering that in the cerebellum (Fig. 1). The results with araboascorbic acid were not different from those of ascorbic acid. As previously reported in rats and a nonhuman primate (2), ascorbic acid, at 1000 mg/kg, potentiated the cataleptogenic effect of a minimally effective dose of haloperidol (Fig. 2). The same was true for araboascorbic acid. In fact, the analog may have been even more effective in this regard.

DISCUSSION

As pointed out in the introduction, there is evidence for an interaction of ascorbic acid with the dopamine receptor. Thus, the vitamin interfered with receptor ligand binding in vitro and in vivo (1) and antagonized the behavioral effects of drugs that are believed to act via a dopaminergic mechanism (10). Furthermore, ascorbic acid potentiated the cataleptic effects of the antipsychotic, haloperidol (2,9), an agent believed to cause catalepsy by acting as a dopamine receptor antagonist in the basal ganglia (3). It is generally accepted that the mechanism whereby antipsychotic drugs improve behavior in schizophrenics is by antagonizing the action of dopamine in the limbic portions of the brain. Large doses of ascorbic acid reportedly benefit behavior in schizophrenics (8), and this is consistent with data from animal experiments suggesting that the vitamin interacts with the dopamine receptor. The present report shows that the synthetic analog of ascorbic acid, D-araboascorbic acid, also interacted with the dopamine receptor in that it antagonized SPI binding and in a dose-dependent

manner that was not different from that of ascorbic acid. Additionally, it was at least as effective as ascorbic acid in potentiating the cataleptogenic effect of haloperidol. Thus, it would appear that araboascorbic acid has an action on the dopamine receptor not unlike that of ascorbic acid.

As already pointed out, other reports showed that ascorbic acid antagonized the action of an indirectly acting dopamine receptor agonist (10) and provided additional evidence suggesting an antagonistic action of the vitamin at the dopamine receptor. If, indeed, ascorbic acid and its analog do act as antagonists to the dopamine receptor it might be asked why neither agent produced catalepsy when given alone but only potentiated that produced by a known dopamine receptor antagonist. In this regard it is recognized that potentiation of the cataleptogenic effects of one agent by another drug is not evidence in itself that the potentiation is via an dopamine antagonism. Nevertheless, the dopamine receptor ligand binding data obtained with the two agents are consistent with such an action and whatever the mechanism of the binding changes, it would seem to relate to the reductive more so than to the antiscorbutic properties of the compounds. As pointed out in the introduction, araboascorbic acid has only one-twentieth the antiscorbutic action of ascorbic acid (11); whereas, the two compounds have similar redox potentials (4).

Large doses of ascorbic acid, reportedly, relieve some of the symptoms of schizophrenia (8). If that is true, the results from the present study would suggest that araboascorbic acid might also be effective. However, they would also suggest that both agents might potentiate the troublesome extrapyramidal side effects associated with antipsychotic drugs and that the use of either of these agents as adjuncts in the treatment of psychosis would be counterproductive.

ACKNOWLEDGEMENTS

This research was supported by Baylor College of Dentistry and Baylor University research funds. The author is grateful to McNeil Laboratories for the gift of haloperidol (HALDOL) used in these experiments.

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