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Interaction Between Ascorbic Acid and Dopamine D_2 Receptor in the Nucleus Accumbens Shell in Response to Feeding

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Abstract: The aim of the present study is to evaluate the effects of intra-accumbens administration of Ascorbic Acid (AA) and co-administration of D_2 agonist, bromocriptine (Br) and the D_2 antagonist sulpiride (Su) (8, 16 μg rat^{-1}) with AA on feed intake in adult male rats. The rats (220-300 g) were divided into several groups for intra-accumbens injections: control (intact), sham AA (injected vehicle of ascorbic acid), ascorbic acid (10, 50, 250 μg rat^{-1}), sham Br (injected vehicle of bromocriptine), bromocriptine (12.5, 25, 50 μg rat^{-1}), sham Su (injected vehicle of sulpiride), sulpiride (4 and 16 μg rat^{-1}), AA (50 μg rat^{-1}) + Br (50 μg rat^{-1}) and AA (50 μg rat^{-1}) + Su (16 μg rat^{-1}). After stereotaxic operation and passing one week recovery period, drugs were injected daily (volume = 1 μL) for four days. The intra-accumbens administration of ascorbic acid (10, 50, 250 μg rat^{-1}) decreased feed intake. Intra-accumbens injection of D_2 agonist bromocriptine (25, 50 μg rat^{-1}) decreased feed intake. Co-administration of the AA (50 μg rat^{-1}) also decreased feed intake. Administration of D_2 antagonist sulpiride (8, 16 μg rat^{-1}) increased food intake and co-administration of AA (50 μg rat^{-1}) blocked this effect. These results suggest that AA can act within the Acb to decreases feed intake and it has an agonistic effect on feeding regulatory effects of D_2 receptor.

Key words: Ascorbic acid, nucleus accumbens, feed intake, bromocriptine, sulpiride

INTRODUCTION

The nucleus accumbens (Acb) is an important area of the basal forebrain involved in several behavioral processes such as appetitive and aversive related functions (Pliakas *et al*., 2001). It has been shown that multiple neurotransmitter systems within the Acb including glutamate, GABA, opioids and dopamine, may underlie different aspects encompassing feeding such as Feed Intake, seeking and rewarding (Kelley *et al*., 2005). Recent studies have shown that the release of dopamine from dopaminergic neurons is associated with ascorbic acid and the released ascorbic acid can regulate dopamine's effects. There are two novel aspects of how ascorbate enters the CNS that distinguish its uptake from that seen in other organ systems. First, although ascorbate transport across the blood-brain barrier occurs, it is very slow and second, the ability to maintain a steep ascorbate concentration gradient from blood to neuronal cells is generated by a two-step mechanism: first into the

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cerebrospinal fluid (CSF) and then into the brain cells. The major route by which ascorbate enters the CNS involves transport from plasma to the CSF across the epithelium of the choroid plexus (Angelow *et al*., 2003). More recent studies relating ascorbate modulation of glutamate dynamics with changes in rat behavior show that such modulation is complex, because it depends on the site in the brain studied, level of behavioral activity and level of extracellular ascorbate (Sandstrom and Rebec, 2007). The mechanism(s) by which ascorbate affects neuronal transmission has not been established, but could relate in part to redox changes in the N-Methyl-D-Aspartate (NMDA) receptor.

Scopolamine is a muscarinic receptor antagonist that inhibits the action of acetylcholinesterase to break down acetylcholine in the synaptic cleft. In rats fed an ascorbate-enriched diet, the acetylcholinesterase inhibition caused by scopolamine was reversed (Lee *et al*., 2001), whereas in a guinea pig vitamin C deficiency model, brain acetylcholinesterase was decreased relative to control animals. Conversely, scopolamine treatment decreased ascorbate levels in rat striatum. *In vivo* voltammetry studies of amphetamine-induced activity enhancement showed increased levels of ascorbate in the caudate nucleus. Parenteral administration of both scopolamine and MK801 (an NMDA receptor blocker) diminished the increase in ascorbate, further supporting a relationship between ascorbate release and cholinergic receptor stimulation. Ascorbate is found in high concentrations in the striatum in which it may play a role in behavioral activation (Rebec and Wang, 2001). Bilateral ascorbate oxidase infusions into dorsal hippocampus, which also has a high level of extracellular ascorbate, failed to alter behavioral activation, indicating that a loss of brain ascorbate per se does not suppress behavior. These finding about striatum showed that the extracellular level of this vitamin plays a critical role in the behavioral activation (Rebec and Wang, 2001).

The control of feeding is regulated by some central areas that contain feeding behavior involvement neurotransmitters such as dopamine, glutamate, acetylcholine and all these neurotransmitters involve in the release and concentration of AA and their action is affected by AA. According to the author's knowledge, there has been no assessment of AA in Acb involvement in the feeding behavior. Also there isn't any information about the effect of ascorbic acid on dopamine feed intake. Therefore, the aim of the present study was to evaluate the effect of intra-Acb injection of AA on its own or together with either D_2 agonist or antagonist feed intake.

MATERIALS AND METHODS

Subjects in all the experiments were adult male (NMRI) rats, obtained from Pasteur Institute of Iran, Tehran (Sep, 2007 to Apr, 2008) and weighing 220-300 g upon arrival at the laboratory. Animal were maintained under a 12 h light/dark cycle (lights on at 07:00 AM). Food and water were available ad libitum. Animals were handled daily to reduce stress.

The rats were anesthetized with xylazine/ketamine mixture (4 mg kg^{-1} xylazine, 60 mg kg^{-1} ketamine, i.p.) and placed in a stereotaxic instrument (Stoeling USA) and two 15 mm length stainless steel cannula cut from 23 gauge stainless steel tubing were implanted bilaterally according to standard stereotaxic surgical procedures. Cannula was aimed at shell subregion of the Acb. For the shell placements, the coordinates were A-P: 1.7 mm anterior to bregma, LA: ±0.8 mm, DM: 5.6 mm from skull surface, the tooth bar was set at 5 mm above interaural zero. Cannula was fixed in place using self-curing dental acrylic and two anchoring stainless steel screws. Wire stylets (15 mm long, 30 gauges) were placed in the cannula to prevent blockage.

For avoiding of post surgical infection in rats, after surgery, each animal was given an intramuscular injection of penicillin (0.3 mL of a 300,000 unit mL^{-1} suspension) and placed in a recovery cage. Upon awakening, rats were returned to their home cages and given a recovery period of minimum 7 days (with daily health checks) before testing procedures commenced.

Ascorbic acid (10, 50, 250 μg rat^{-1}) was purchased from Sigma chemical co, (dissolved in 0.9% sterile saline), Bromocriptine (12.5, 25, 50 μg rat^{-1}) dissolved in Propylenglycol and Sulpiride (8, 16 μg rat^{-1}) dissolved in 0.1 N Hydrochloric acid (additional NaOH for neutralization of pH) were purchased from Tocris Cookson. Ketamine and Xylazine were purchased from Netherlands Alfasan co. All microinjections were administered bilaterally in 1 μL volumes over 60 sec through a stainless steel internal cannula (13 gauges) connected to a Hamilton microsyringe by polyethylene tubing.

The rats were housed in individual metabolic cages, with free access to water and food, in a thermostatically controlled testing room under 12 h dark/light cycle. On testing days, animals were moved from the vivarium in to the testing room. By design, we used 16 groups (n = 7) for the entire experiment. All injections were made between 08:00 and 10:00 h. Immediately after a microinjection of drugs-this action repeated for four days the animals were returned to their metabolic cages. In the metabolic cage, food was delivered in steel cup with a 6-cm hole at the top, which could be removed and weighed. Water was provided in plastic bottle closed at the top, with a spout that projected through the cage wires. A sheet of paper was placed underneath each testing cage to collect food spillage and feed intake was measured by subtracting the food cup weights at the start from the end of test.

All data are expressed as the Mean±SEM. Analysis of Variance (ANOVA) followed by Tukey post hoc test was used to test the significance of differences among the groups. $p<0.05$ was considered to be a significant difference. After the completion of testing, rats were terminated by decapitation; the brains were removed and stored in 20% formalin for 48 h. To localize the position of the probe tip, 100-150 μm transverse brain sections were prepared using a vibrotome and stained with thionine and Nissl stain. Sections were examined under a light microscope in order to determine placement of microinjector tips.

RESULTS AND DISCUSSION

Results showed that, average cumulative feed intake was significantly decreased in rats that received the ascorbic acid (10, 50 and 250 μg rat^{-1}) compare to control ($F(4, 30) = 21.92$, $p<0.0001$).

Figure 1 shows that AA (10 μg kg^{-1}) significantly decreased feed intake relative to control in $p<0.001$ and relative to sham group in $p<0.01$ and also AA (50, 250 μg kg^{-1}) significantly decreased feed intake relative to control and sham groups in $p<0.001$.

Intra-accumbens bromocriptine (25, 50 μg rat^{-1}) significantly decreased feed intake compare to control and sham groups ($F(4, 30) = 114.5$, $p<0.0001$, Fig. 2). Co-administration AA (50 μg rat^{-1}) + Br (50 μg rat^{-1}) showed a trend towards an attenuation of the Br effect ($F(4, 30) = 17.53$, $p<0.0001$). Figure 4 shows that AA (50 μg rat^{-1})+Br (50 μg rat^{-1}) significantly decreased feed intake relative to control in $p<0.0001$ and relative to sham group in $p<0.01$.

Administration of sulpiride (8 and 16 μg rat^{-1}) increased feed intake ($F(4, 30) = 40.71$, $p<0.0001$). Figure 3 shows that Su (8 μg rat) significantly increased feed intake relative to control in $p<0.01$ and relative to sham group in $p<0.001$ and also Su (16 μg rat^{-1}) significantly increased feed intake relative to control, sham and Su (8 μg rat^{-1}) groups in $p<0.0001$.

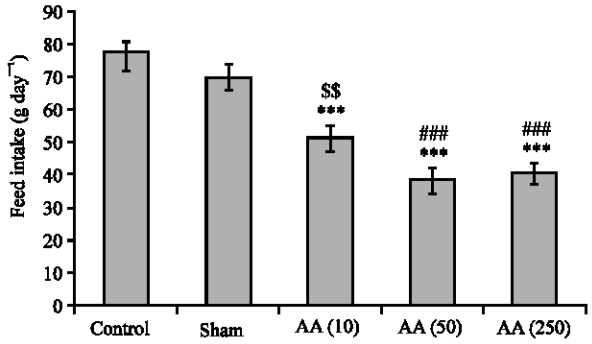

Fig. 1: Alterations in mean of feed intake (g±SEM) all of time test following administration of AA (10, 50, 250 μg rat^{-1}) doses injection bilaterally in the shell region of the Acb. The asterisks $^{***}p<0.001$ as compared to control treatment. The $^{\$\$}p<0.01$as compared to sham group and the $^{\#\#}p<0.001$ as compared to sham group (Tukey comparisons, $p<0.05$). Ascorbic Acid (AA)

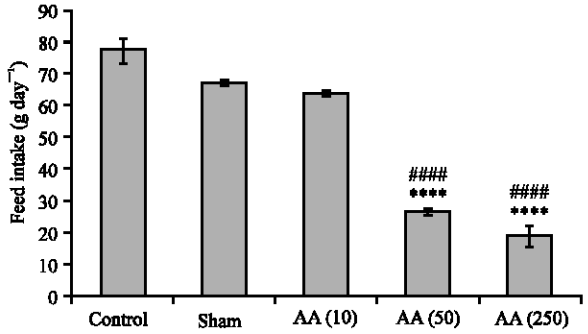

Fig. 2: Alterations in mean of feed intake (g ±SEM) all of time test following administration of Br (12.5, 25 and 50 μg rat^{-1}) doses injection bilaterally in the shell region of the Acb. The asterisks $^{****}p<0.0001$ as compared to control treatment and $^{\#\#\#\#}p<0.0001$ as compared to sham and Br (12.5 μg rat^{-1}) groups (Tukey comparisons, $p<0.05$). Bromocriptine (Br)

Co-administration AA (50 μg rat^{-1}) + Su (16 μg rat^{-1}) blocked these effect ($F(4, 30) = 73.37$, $p<0.0001$). Figure 5 shows that AA (50 μg rat^{-1}) + Su (16 μg rat^{-1}) significantly decreased feed intake relative to Su (16 μg rat^{-1}) in $p<0.001$.

Intra-accumbens AA decreased feed intake which is stated for the first time. Intra-accumbens bromocriptine as a D_2 selective agonist decreased feed intake, perfusion of bromocriptine in the striatum increased feed intake (Inoue *et al*., 1997), this discrepancy may be attributed to injection site differences. The injection of bromocriptine and AA also decreased feed intake, it seems that AA attenuated the decreasing effect of bromocriptine. Intra-accumbens sulpiride as a D_2 selective antagonist increased feed intake, this result was similar to injection of sulpiride in the perifornical lateral hypothalamus (Baptista *et al*., 2002). The present data further implicate the injection of sulpiride and AA blocked the increasing effect of sulpiride. The current study suggests that D_2 receptor in accumbens has a crucial role in the feed intake and AA modulates this effect the same as a dopamine D_2 agonist.

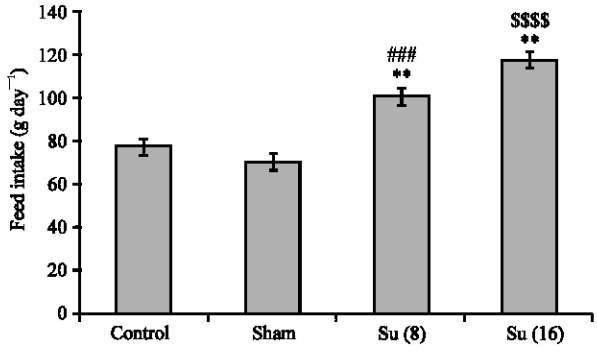

Fig. 3: Alterations in mean of feed intake (g ±SEM) all of time test following administration of Su (8 and 16 μg rat^{-1}) doses injection bilaterally in the shell region of the Acb. The asterisks $^{**}p<0.01$ as compared to control treatment and asterisks $^{****}p<0.0001$ as compared to control treatment and $^{###}p<0.001$ as compared to sham group and $^{\$\$\$\$}p<0.0001$ as compared to sham and Su (8 μg rat^{-1}) groups (Tukey comparisons, $p<0.05$). Sulpiride (Su)

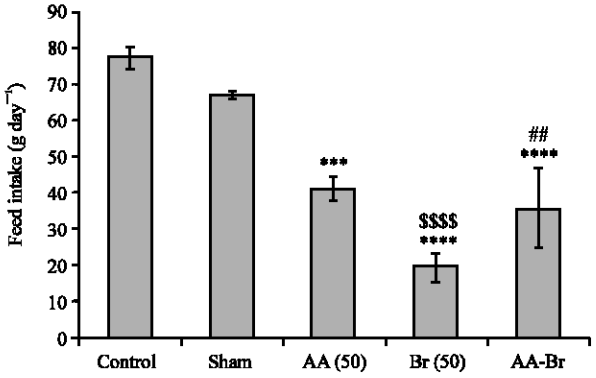

Fig. 4: Alterations in mean of feed intake (g ±SEM) all of time test following administration of the AA (50 μg rat^{-1}) in the shell region of the Acb in rats pretreated with dopamine agonist, Bromocriptine (50 μg rat^{-1}). The asterisks $^{***}p = 0.001$ as compared to control group. The asterisks $^{****}p<0.0001$ as compared to control group. The $^{##}p<0.01$ as compared to sham group. The $^{\$\$\$\$}p<0.0001$ as compared to sham group (Tukey comparisons, $p<0.05$). Ascorbic Acid (AA) and, Bromocriptine (Br)

Very little information is available about the orexigenic or anorexigenic effect of ascorbic acid. Surprisingly, there have been no studies directly evaluating the feeding effects of ascorbic acid infusion into Acb.

It has been reported that intrastriatal infusions of ascorbate oxidase (AAO), a dimeric copper-containing enzyme that metabolizes ascorbate, caused a rapid decline in both ascorbate and behavioral activation (Rebec and Wang, 2001). Bilateral AAO infusions into dorsal hippocampus, which also has a high level of extracellular ascorbate, failed to alter behavioral activation, indicating a loss of brain ascorbate per se dose not suppress behavior.

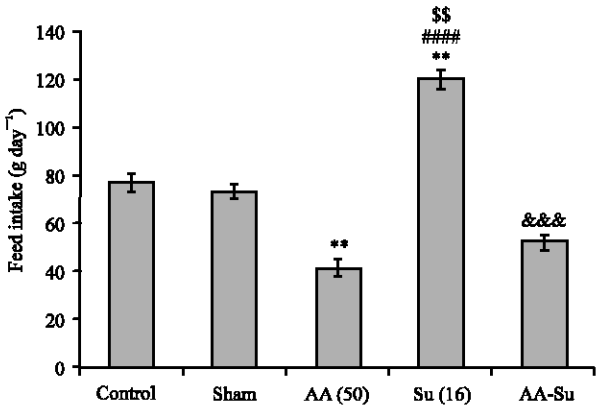

Fig. 5: Alterations in mean of feed intake (g ±SEM) all of time test following administration of the AA (50 μg rat^{-1}) in the shell region of the Acb in rats pretreated with dopamine antagonist, sulpiride (16 μg rat^{-1}). The asterisks $^{**}p<0.01$ as compared to control group. And $^{\$\$}p<0.01$ as compared to sham group and $^{\#\#\#\#}p<0.0001$as compared to AA (50 μg rat^{-1}). The $^{\&\&\&}p<0.001$as compared to 16 μg rat^{-1} (Tukey comparisons, $p<0.05$). Ascorbic Acid (AA) and Sulpiride (Su)

These results indicate ascorbate is involved in the behavioral operations of the striatum and suggest that the extracellular level of this vitamin plays a critical role in behavioral activation (Rebec and Wang, 2001).

Intra-accumbens injection of ascorbic acid can reduce feed intake-as shown in this study-like some of appetite regulator neurotransmitters. The anorexigenic effects of ascorbic acid were initially thought to be mediated indirectly through the central feeding regulatory systems such as dopamine, acetylcholine, gut peptides and hormones (Coll *et al*., 2007). However this indirect effect might not explain the full anorexigenic effects of ascorbic acid.

Ascorbic acid is necessary for optimal insulin secretion from pancreatic islets (Steffner *et al*., 2004). Several early studies identified Acb an important anatomical substrate for the dopaminergic modulation of feeding behavior (Kelley *et al*., 2005).

Both, the D_1 and D_2 antagonist markedly suppressed the total number of feeding bouts and spontaneous motor activity (Baldo *et al*., 2002). Ascorbic acid may interfere with other neurotransmitter, although the mechanism remains unclear, one possibility is a direct action of the dopamine receptor (Rebec and Pierce, 1994). In retinal slices, for example, relatively small increases in extracellular ascorbate have a positive modulating effect on voltage-gated potassium currents by D_1 dopamine receptors (Fan and Yazulla, 1999). Alternatively, as an antioxidant, ascorbate may prolong the life of dopamine in extracellular fluid (Neal *et al*., 1999). Increased dopamine may diffuse over relatively long distances (Gonon *et al*., 1980). Anatomical evidence supports this view (Nirenberg *et al*., 1996) and even suggests a mechanism for permanent level of dopamine in extracellular fluid (Descarries *et al*., 1996). Extracellular diffusion would allow for dopamine not only to interact with receptors on presynaptic terminals but also to exert distant effects on astrocytes and microvessels (Agnati *et al*., 1995). Ascorbate may facilitate this process by protecting dopamine agonist oxidative attack by constituents of extracellular fluid, supporting the suggestion that region-specific changes in extracellular ascorbate may have unique functional consequences. Both D_1 and D_2 receptors are localized on dendrites and presynaptic terminals in the shell and core regions of the Acb (Koshikawa *et al*., 1996;

Setlow, 1997), but the response of these regions to feeding are different from each other for example, infusion of glutamate receptor antagonists or gamma-aminobutyric acid (GABA) agonists into the Acb shell but not the Acb core produced intense hyperphagia (Maldonado-Irizzary *et al*., 1995) and dopamine stimulates feeding behavior within the shell but not the core regions of the Acb (Swanson *et al*., 1997). Dopamine agonists in the CNS can either increase or decrease feeding, depending on dose and individual baseline intake.

Inoue *et al*. (1997) showed that bromocriptine perfusion via a microdialysis probe into the ventrolateral striatum of rats fasted for 22 h, increased food intake in a dose-dependent manner.

Fluctuations in striatal ascorbate also are likely to modulate dopamine function, but the direction of effect depends critically on ascorbate concentration. Injections of high systemic (Rebec *et al*., 1985) or intrastriatal (White *et al*., 1990) dose have a dopamine antagonist effect on behavior (Rebec and Wang, 2001).

Perfusion of (-) sulpiride, a selective D_2 receptor antagonist, in the striatum decreased food intake, pretreatment with (-) sulpiride perfusion for 1 h prior to bromocriptine perfusion inhibited the increase of food intake induced by bromocriptine (Inoue *et al*., 1997). Notwithstanding, acute sulpiride administration in the perifornical lateral hypothalamus significantly increased food intake and water intake (Baptista *et al*., 2002). In the present study has been shown that perfusion bromocriptine and sulpiride in the Acb shell decrease and increase feed intake, respectively.

There is evidence indicating, that the Acb is also involved in the neural circuits mediating feeding behavior via neurotransmitters such as opioids (Bakhshi and Kelley, 1993) and dopamine (Gilbert and Cooper, 1995). Pretreatment with either opioid or dopaminergic D_1 receptor antagonist in the nucleus accumbens shell reduced μ opioid agonist-induced feeding (Znamensky *et al*., 2001). Pretreatment with either the D_1 antagonist or the D_2 antagonist in the Acb produced mild and inconsistene effects upon deltrophin-induced feeding in the Acb across the time course (Pliakas *et al*., 2001). These investigations showed that dopamine receptors are involved in opioid-induced feeding within the shell region of the Acb (Rebec *et al*., 1985).

Acb μ agonist-induced feeding was significantly reduced by Acb pretreatment with the D_1 antagonist (Ragnauth *et al*., 2000). The behavioral activation induced by amphetamine and other dopamine agonists is accompanied by a parallel increase in striatal ascorbate (Mueller, 1989). Bassareo and Chiara (1999) showed that extracellular dopamine level in the Acb Sh of rats raise during first-time consumption of a highly palatable snack food. Different neuronal pathway is involved in regulation of drug-induced ascorbic acid in different part of the brain (Dai *et al*., 2006). Ascorbate may play a direct role in Acb information processing by modulating glutamate function such as its function in striatum. In awake rats for example ascorbate iontophoresis enhances the magnitude of glutamate-induced neuronal excitations (Kiyatkin and Rebec, 1998). Both AMPA and NMDA in the nucleus accumbens shell significantly and dose-dependently increased feed intake over 4 h (Echo *et al*., 2001). Infusion of glutamate receptor antagonists into the Acb shell of rats, elicited intense hyperphagia in ad libitum rats (Basso and Kelley, 1999; Kelley and Swanson, 1997; Maldonado-Irizzary *et al*., 1995; Stratford and Kelley, 1997). Local injections of glutamate receptor antagonists or GABA receptor agonists into the AcbSh elicit an increased feeding response without interfering with other behaviors in satiated rats (Yang *et al*., 2005). Inhibition of Acbsh leads to increased feeding (Yang *et al*., 2005). In this investigation intra-accumbens injection of AA decreased feed intake, showing that AA is involved in central regulation of feed intake.

CONCLUSION

Intra-accumbens injection of AA and co-administration with dopamine D_2 receptor agonist and antagonist inhibited feed intake, the exact mechanism of AA-decreasing feed intake within Acbsh has been reminded unclear and we showed that it may interfere in the effect of feeding regulatory of D_2 dopaminergic system.

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