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Effect of Sanguinarine on the Transport of Essential Nutrients in an Everted Gut Sac Model: Role of Na^+, K^+ -ATPase

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ABSTRACT The effect of the argemone alkaloid, sanguinarine, was studied on the active transport of D-glucose and some of the L-amino acids in everted sacs of the small intestine of rats. Sanguinarine (1.0 μmole) was found to inhibit (61%) the transport of D-glucose, while an alkaloid concentration of 0.1 μmole was ineffective. Both 0.1 and 1.0 μmole of sanguinarine had no effect on the transport of the L-amino acids including aspartic acid, lysine, and tyrosine. Sanguinarine showed a dose dependent inhibition of intestinal and hepatic Na^+, K^+ -ATPase in a non-competitive manner. The inhibition of Na^+, K^+ -ATPase by sanguinarine may in turn inhibit the active transport of D-glucose which requires a sodium pump. © 1993 Wiley-Liss, Inc.

Key Words: ATPase, Sanguinarine, Nutrients, Argemone alkaloids, Glucose, Amino acids

INTRODUCTION

Argemone mexicana Linn (family Papaveraceae) is a wild plant whose seeds have superficial resemblance to the dark-coloured mustard seeds. Accidental or deliberate contamination of edible oils with argemone oil and consumption of such adulterated oils even for a short duration gives rise to a toxicity syndrome commonly referred to as epidemic dropsy [Hakim et al., 1961; Krishnamachari and Satyanarayana, 1972; Preininger, 1975; Khanna and Singh, 1983; Mohan et al., 1984; Kumar et al., 1992]. The principal constituents responsible for the toxicity of argemone oil have been identified as the benzophenanthridine alkaloids, sanguinarine and dihydrosanguinarine (Fig. 1) [Sarkar, 1948]. Among the clinical manifestations of argemone intoxication, the gastrointestinal tract disturbances are very common [Kumar et al., 1992]. Our previous studies had also identified the gastrointestinal tract as a principal target organ of sanguinarine, retaining a maximum of 27% of the orally administered alkaloids 96 hr post-administration [Tandon et al., 1992].

It is well established that glucose and amino acid transport in the small intestine is an active process in mam-

mals [Crane, 1960; Schultz et al., 1966; Kimmich, 1973]. The membrane bound enzyme, Na^+, K^+ -adenosine triphosphatase (Na^+, K^+ -ATPase), is involved in the active transport across biological membranes [Skou, 1965]. Since the gastrointestinal tract is one of the major sites of retention of sanguinarine it was of interest to study the effect of the alkaloid on the intestinal absorption of essential nutrients. In the present study, the effect of sanguinarine on the transport of D-glucose, and each of the acidic (L-aspartic acid), basic (L-lysine), and aromatic (L-tyrosine) amino acids, across the epithelium of rat small intestine and Na^+, K^+ -ATPase activity was investigated in order to understand the mechanism of its action.

MATERIALS AND METHODS

Chemicals

(C-14)L-aspartic acid (specific activity 164 mCi/mmol), (C-14)L-tyrosine (specific activity 432 mCi/mmol), (C-14)L-lysine (specific activity 288 mCi/mmol), and (C-14)D-glucose (specific activity 255 mCi/mmol) were procured from the Radio Chemicals Division, Bhabha Atomic Research Centre, Trombay, Bombay, India. L-aspartic acid and L-lysine were purchased from the CSIR Centre for Biochemicals, VP Chest Institute, Delhi, India. Tyrosine and D-glucose were obtained from BDH, Glaxo, India. 1,4-bis (5-phe-

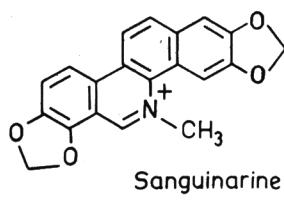
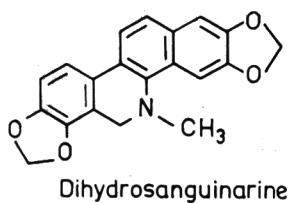


Fig. 1. Structures of sanguinarine and dihydrosanguinarine.

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nyl oxazolyl) benzene (POPOP) and 2,5-diphenyl oxazole (PPO) were imported from Packard Instrument Company, Zurich, Switzerland. Adenosine triphosphate (ATP; disodium salt), ammonium molybdate, and Folin-Ciocalteau reagent were the products of Sisco Research Laboratories, Bombay, India. 2-Methoxy ethanol (methyl cellosoline) was purchased from BDH, Poole, England, and sodium dithionite from E. Merck, Darmstadt, Germany.

Preparation of Sanguinarine

Argemone mexicana seeds were procured from rural areas of Lucknow and Hardoi, India. The seeds were crushed and the oil was extracted with the help of soxhlet apparatus using petroleum ether (40–60°C). The petroleum ether containing argemone oil was filtered under vacuum through a Buchner funnel containing glass wool and the solvent was distilled at 30°C under vacuum in Buchii Rotavpor-R. The oil obtained was stored in an amber glass bottle under nitrogen atmosphere. The yield of argemone oil from its seeds was 32.3% (w/v). Sanguinarine was precipitated as an orange-coloured salt by passing dry hydrochloric acid gas through argemone oil. The precipitated alkaloid was purified through resolution on an alumina column followed by crystallization from alcohol: benzene mixture as per the standard procedure of Sarkar [1948]. The yield of sanguinarine alkaloid was 0.25% from argemone oil.

Preparation of the Perfusion Medium

The perfusion medium according to Krebs and Henseleit [1932] contained 100 volumes of 0.9% sodium chloride (0.154 M); 4 volumes of 1.15% potassium chloride (0.154 M); 1 volume of 2.11% potassium dihydrogen phosphate (0.154 M); 1 volume of 3.82% magnesium sulphate (0.154 M); and 21 volumes of 1.3% sodium bicarbonate (0.154 M). The perfusion fluid was gassed with carbogen (95% oxygen: 5% carbon dioxide) for 20 min and pH adjusted to 7.2–7.3.

Transport Studies

Male Wistar albino rats (150 ± 10 g) derived from Industrial Toxicology Research Centre (ITRC) animal breeding colony, raised on commercial pellet diet (Hindustan Lever, Bombay, India) and water ad libitum, were used in this study. Everted gut sacs were prepared by the conventional technique of Wilson and Wiseman [1954]. The animals were killed by cervical dislocation and the small intestine removed. A piece of the midportion of the small intestine from each animal was excised, washed with ice cold perfusion medium, and everted. Alternate segments, each approximately 3 cm in length, were used as control or experimental material, in order to minimize the transport variability of the segments. The sacs formed were filled with 1 ml of perfusion medium and

incubated at 37°C in the same medium for 60 min. The 5 ml external medium of the experimental segments contained 0.1 μmole or 1.0 μmole of the sanguinarine in addition to 0.1 ml of radiolabelled nutrients including 22.7 μCi/6 μmole glucose/ml or 9.1 μCi/10 μmol amino acid/ml. The external medium was bubbled with a mixture of 95% O₂ and 5% CO₂ during the whole incubation period. The transport of D-glucose and L-amino acids was evaluated by measuring the radioactivity inside as well as outside the sac at the end of incubation.

Quantitation of Free and Bound Sanguinarine

The distribution of sanguinarine originally added to the external medium, into the internal medium of the sac, as well as that bound to the sac at the end of incubation was determined essentially by the method of Shenolikar et al. [1981] as modified by Kapoor et al. [1987].

For determination of intestinal bound sanguinarine, a 10% homogenate of the intestinal sac was prepared and sanguinarine or dihydrosanguinarine was extracted thrice with 3 volumes of 1% glacial acetic acid in chloroform. Suitable aliquots from this and also the ones from the external medium were reduced with 0.1 ml of 1% freshly prepared sodium dithionite solution (6 μmole) to get dihydrosanguinarine and the final volume made up to 3 ml with ethanol. The absorbance was determined at 320 nm against ethanol as blank.

Preparation of Enzyme Source

Male Wistar albino rats (150 ± 10 g) were killed by cervical dislocation and the small intestine and the liver removed. The intestine was cut open longitudinally and washed with ice cold 0.15 M KCl to get rid of unabsorbed material. The liver was also washed with 0.15 M KCl to remove blood clots. Both tissues were chopped into small pieces and homogenized in 4 volumes of ice cold 0.15 M KCl. In cases of the liver Potter Elvehjem homogenizer was used while for the intestine Polytron tissue homogenizer was employed. These homogenates were used as enzyme source to determine ATPase activity.

Determination of ATPase Activity

The Na⁺, K⁺-ATPase activity was estimated by the method of Abel-Latif et al. [1970]. The reaction mixture in a final volume of 2.0 ml contained 100 mM NaCl, 20 mM KCl, and 5 mM MgCl₂ prepared in 0.2 M Tris buffer, pH 7.5 and 0.1 ml of the enzyme source (20% homogenate of liver and intestine prepared in 0.15 M KCl). The reaction was started after a 5 min temperature pre-equilibration by the addition of 4.5 mM ATP. The incubation was carried out in a shaking water bath at 37°C for 20 min. The reaction was terminated with 0.1 ml of 50% trichloroacetic acid (TCA). The inorganic phosphate (Pi) liberated from ATP was determined by the

TABLE I. Effect of Sanguinarine on the Absorption of Essential Nutrients by Everted Intestinal Sacs

Concentration of nutrient	Sanguinarine concentration	Percentage intestinal absorption of nutrient	
		Control	Experimental
D-glucose (22.7 $\mu\text{Ci}/6 \mu\text{mole}$)	1.0 μmole	2.59 \pm 0.07	0.98 \pm 0.05*
L-lysine (9.1 $\mu\text{Ci}/10 \mu\text{mole}$)	1.0 μmole	3.84 \pm 0.23	4.43 \pm 0.29
L-aspartic acid (9.1 $\mu\text{Ci}/10 \mu\text{mole}$)	1.0 μmole	6.50 \pm 0.52	6.64 \pm 0.42
L-tyrosine (9.1 $\mu\text{Ci}/10 \mu\text{mole}$)	1.0 μmole	7.08 \pm 0.24	7.40 \pm 0.28

Data represent mean \pm S.E. of six values. The incubation of intestinal sac with all the ingredients is described in Materials and Methods.

* $P < 0.05$.

TABLE II. Effect of Sanguinarine on the Na^+, K^+ -ATPase Activity

Concentration of sanguinarine	ATPase activity (nmoles/min/mg protein)	
	Liver	Intestine
0.0 (Control)	1.83 \pm 0.15	5.50 \pm 0.51
$1 \times 10^{-6} \text{ M}$	1.83 \pm 0.19	5.41 \pm 0.48
$1 \times 10^{-5} \text{ M}$	1.64 \pm 0.15 (10.4)	5.11 \pm 0.50 (7.1)
$1 \times 10^{-4} \text{ M}$	1.42 \pm 0.11 (22.4)*	4.92 \pm 0.43 (10.5)
$1 \times 10^{-3} \text{ M}$	1.08 \pm 0.09 (41.0)*	3.24 \pm 0.29 (41.1)*

Data represent mean \pm S.E. of three values. The values in parentheses indicate percent inhibition of the enzyme.

* $P < 0.05$.

method of Fiske and Subbarow [1925]. The protein concentration was estimated by method of Lowry et al. [1951] using bovine serum albumin as standard. Specific activity was expressed as nmoles of Pi produced/min/mg protein.

Effect of Sanguinarine on Kinetics of ATPase

The Michaelis-Menton constant (K_m), maximal velocity (V_{max}), and inhibitor constant (K_i) values in the presence as well as in the absence of sanguinarine were determined from the Michaelis-Menton and Lineweaver-Burk Plots for hepatic and intestinal ATPase activity.

RESULTS

Effect of Sanguinarine on the Transport of D-Glucose and L-Amino Acid Through Intestinal Membrane

Table I shows that 1.0 μmole of sanguinarine caused 61% inhibition on the absorption of glucose ($P < 0.05$) while 0.1 μmole of the alkaloid had no effect. The effect of 1.0 μmole of alkaloid on the uptake of lysine (basic), aspartic acid (acidic), and tyrosine (aromatic) is shown in Table I. The lower alkaloid concentration had no effect on the uptake while 1.0 μmole showed an insignificant increase (15%) in the absorption of lysine (Table I). There was no effect on the uptake of aspartic acid and tyrosine by 1.0 μmole of sanguinarine (Table I).

Effect of Sanguinarine on the Na^+, K^+ -ATPase Activity and Its Kinetics

The activity of the Na^+, K^+ -ATPase in intestine and liver at varying concentrations of sanguinarine is shown in Table II. Sanguinarine showed a concentration dependent inhibition of intestinal and hepatic Na^+, K^+ -ATPase activity. A respective inhibition of 10.5 and 22.0% of intestinal and hepatic enzyme activities occurred at $1 \times 10^{-4} \text{ M}$ concentration of alkaloid while $1 \times 10^{-3} \text{ M}$ concentration of sanguinarine caused an inhibition of 41% in the enzyme activity from both the sources.

Michaelis-Menton and Lineweaver Burk Plots of both intestinal (Fig. 2) and hepatic (Fig. 3) enzymes in the absence as well as in the presence of sanguinarine ($1 \times 10^{-3} \text{ M}$) show that while the K_m value of the enzyme remains unchanged, the V_{max} value is decreased in the presence of the alkaloid. The K_m value of the enzyme from hepatic and intestinal sources in the absence as well as in the presence of alkaloid was 11.1 mM. The V_{max} value of Na^+, K^+ -ATPase in liver was found to be 33.3 and 25.0 in the absence and in presence of sanguinarine, respectively. The V_{max} value of the intestinal enzyme was 100 in the absence and 50 in the presence of alkaloid. The K_i value for sanguinarine was $3.03 \times 10^{-3} \text{ M}$ for the hepatic and $1 \times 10^{-3} \text{ M}$ for the intestinal enzyme.

Influence of Nutrients on the Uptake of Sanguinarine

Sanguinarine absorbed through the intestine, together with the amount left over and that got bound to the intestinal wall in the presence of micronutrients at the end of incubation, is given in Table III: In the absence of any nutrients, 40% of sanguinarine was absorbed through the intestinal epithelium, 37% remained unabsorbed after the incubation period of 1hr, while 21% was bound to the intestinal sac. In the presence of glucose, 26% of the sanguinarine added externally was found in the internal medium at the end of incubation, 21% was found to be bound to the sac, while 52% was left in the external medium (Table III). The binding of sanguina-

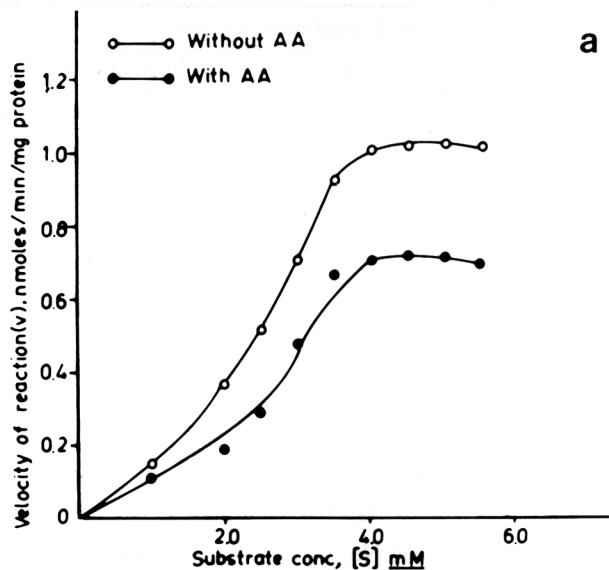


Fig. 2. Kinetics of hepatic Na^+, K^+ -ATPase inhibition by sanguinarine in rats. **a:** Michaelis-Menton plot; **b:** Lineweaver-Burk plot.

rine to the intestinal wall again was to the same order (23%) in the presence of lysine. Similarly, neither the absorption (41%) nor the left over alkaloid quantity (35%) were influenced by lysine more than the ones seen in the absence of any nutrient. In the case of aspartic acid, a slightly less quantity (17%) of the added sanguinarine was found bound to the sacs, whereas the alkaloid passage through the intestinal wall appeared to be facilitated, as is evident by a proportionately higher absorption (47%) of the sanguinarine. The account of sanguinarine left unabsorbed after 1 hr was 35%. In the presence of tyrosine, 18% of the sanguinarine remained bound to the sacs, 46% was transported inside, while 34% of the added alkaloid was left in the external medium (Table III).

DISCUSSION

The intestine serves as a selective barrier to foreign molecules. Chemicals entering the gastrointestinal tract

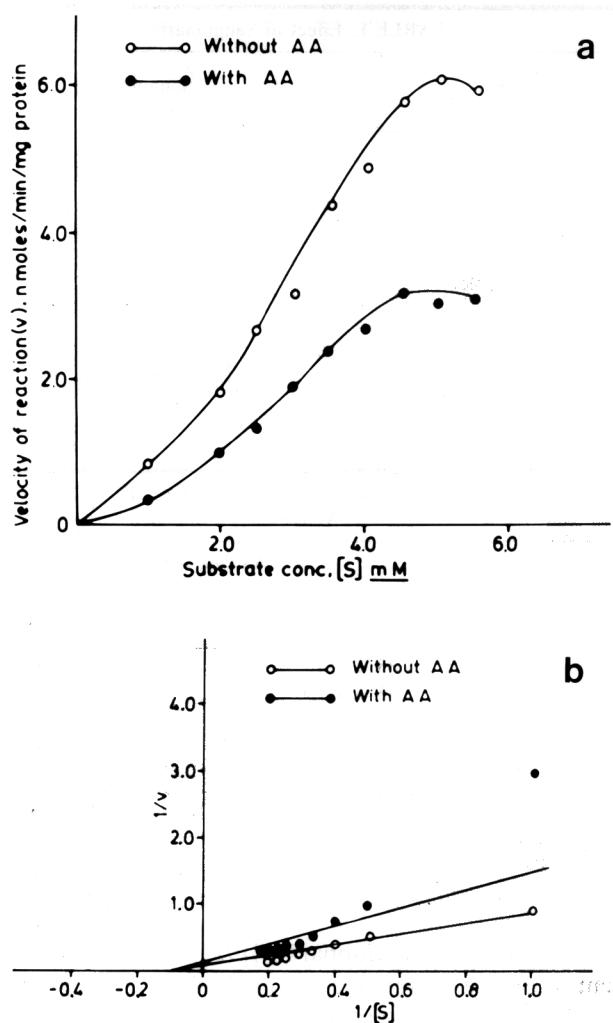


Fig. 3. Kinetics of intestinal Na^+, K^+ -ATPase inhibition by sanguinarine in rats. **a:** Michaelis-Menton plot; **b:** Lineweaver-Burk plot.

can cause injury to the tract and alter the normal functions [Schiller et al., 1984]. The solubility, size, and reactivity of the xenobiotics, together with specific organism factors such as age, genetic defects, and disease state, may influence their interaction with the gastrointestinal mucosa [Schiller, 1979].

Studies have been carried out on the specificity and kinetics of absorption in the tied-off loops of small intestine. The most accepted mechanism by which sugars and amino acids are actively transported through the intestinal epithelium suggests that a carrier located at the apical mucosal cell membrane (brush border), transports the compound from the lumen to the cell interior [Crane, 1960]. This carrier is able to bind simultaneously with sugar (or amino acid) and sodium ions. In this way, the driving force for this process is the difference in sodium electrochemical potential across the brush border membrane. Since the intracellular sodium electrochemical potential is lower than the extracellular, the coupled trans-

TABLE III. Effect of Nutrients on the Absorption and Intestinal Binding of Sanguinarine

	Absorbed	Percentage of sanguinarine	
		Left over	Bound
Nil	40	37	21
Glucose	26	52	21
Lysine	41	35	23
Aspartic acid	47	35	17
Tyrosine	46	34	18

Data represent mean of three values from a typical experiment. The incubation of intestinal sac with all the ingredients are described in Materials and Methods.

port process tends to accumulate the sugar in the interior of the cell [Skou, 1965]. The sodium concentration gradient is built by a Na^+, K^+ -ATPase (Na pump) present in the basolateral membrane of the mucosal cell. Once the sugar is accumulated into the cell interior, it is transported passively across the baso-lateral membrane to the serosal side. The Na^+, K^+ -ATPase uses energy from hydrolysis of intracellular ATP to transport Na^+ ions outward and K^+ ions inward [Skou, 1965]. Because more Na^+ ions are pumped out than K^+ are pumped in, the activity of the enzyme generates an outward movement of positive charge [Glynn, 1985]. One of the functions of Na^+, K^+ -ATPase is thus to maintain an osmotic stability in animal cells.

The lowered glucose uptake in the everted intestinal sac model by the sanguinarine, in the present study, appears to be concentration dependent. Although there was no effect at the lower concentration of sanguinarine, the higher concentration (1.0 μmole) did lead to a significantly diminished transport of glucose across the intestinal wall. Inhibition of Na^+, K^+ -ATPase by sanguinarine further supports the reduction of glucose transport against intestinal membrane. Inhibition of active transport of glucose by everted sacs of rat by DDT was reported by Iturri and Wolff [1982] wherein inhibition of the sodium pump was postulated as a possible mechanism. No substantial effect on the uptake of amino acids, lysine, tyrosine, and aspartic acid was brought about at the two concentrations of sanguinarine, thus indicating that the transport of these three L-amino acids remains unaffected at the tested sanguinarine levels.

The study of the inhibition of Na^+, K^+ -ATPase by sanguinarine and the enzyme kinetics throws further light on the mode of enzyme inhibition. The inhibition of Na^+, K^+ -ATPase may hamper the uptake of vital nutrient, viz glucose. Such an inactivation of an essential enzyme may lead to biochemical lesions. Studies on the kinetics of hepatic and intestinal Na^+, K^+ -ATPase in the presence of sanguinarine reveal that it causes a decrease in the maximal velocity (V_{\max}) of the enzyme but the Michaelis-Menton constant (K_m) remains unaltered. This indicates that sanguinarine acts by bringing a non-

competitive type of inhibition of Na^+, K^+ -ATPase activity. In vitro inhibition of Na^+, K^+ -ATPase (41%) by 1×10^{-3} M sanguinarine could be considered a physiologically attainable concentration as 50 ml intake of 50% argemone contaminated oil per day for 1 week can lead to an accumulation of 1.4 mM sanguinarine. Even accounting for bioclearance, which is 25 to 30% in 96 hr [Tandon et al., 1992], the concentration of sanguinarine still remains around 1 mM.

Cohen et al. [1978] showed that there is a high degree of structural specificity for sanguinarine on inhibition of guinea pig brain Na^+, K^+ -ATPase. This conclusion was derived from the fact that small deviations in the ring substituent pattern of sanguinarine had resulted in large differences in inhibition. The presence of the less bulky, less hydrophobic methylenedioxy groups enhanced inhibition. This may mean that the benzacridine, a green metabolite of sanguinarine [Tandon et al., 1992], which is devoid of the two methylene dioxy groups originally present in both sanguinarine and dihydrosanguinarine, is likely to be less inhibitory towards Na^+, K^+ -ATPase. However, this assumption needs substantiation.

The iminium compounds have been shown to possess varying inhibitory degrees towards Na^+, K^+ -ATPase, which range from no inhibition to 97% inhibition. Sanguinarine is both water-soluble and lipid-soluble. Thus, in the present case, the iminium function is likely to be an important, but not an absolute factor in sanguinarine inhibition of Na^+, K^+ -ATPase. Physicochemical properties, for example, solubility and partition-coefficient, may also play an important role in the inhibition of Na^+, K^+ -ATPase activity by sanguinarine. The Na^+, K^+ -ATPase activity can be protected against sanguinarine inhibition by some sulphur nucleophiles, presumably by attacking the iminium carbon [Cohen et al., 1978]. It can, therefore, be concluded that sanguinarine interferes in the glucose uptake through blocking of the sodium pump, via Na^+, K^+ -ATPase, thus inhibiting the active transport of glucose across the intestinal barrier.

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