ROLE OF THE AUTOREGULATORY COMPONENT IN RESPONSES OF BRAIN VESSELS TO AMINOPHYLLINE

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UDC 612.824.014.46:615.225.2+615.225.2.015.4:612.824

KEY WORDS: aminophylline, vessels, autoregulatory component

The action of aminophylline on the cerebral circulation has been the subject of much experimental and clinical research [1, 9], but many aspects of this problem still remain unclear. Investigators have often noted how the cerebrovascular response to aminophylline depends on the functional state of the cerebral and general hemodynamics, the systemic arterial pressure (SAP), the blood gas composition, and other factors. Many investigators [4, 5, 10] have concluded that aminophylline has a phasic action on the cerebral vessels. It has been suggested that aminophylline can modify the autoregulatory reactions of cerebral vessels, but no concrete data on this question are available.

The aim of this investigation was to determine the role of the autoregulatory component in the response of the cerebral vessels to aminophylline.

EXPERIMENTAL METHOD

Acute experiments were carried out on 23 albino rats weighing 200-260 g, anesthetized with pentobarbital sodium (40 mg/kg, intramuscularly). The volume velocity of the cerebral blood flow (CBF) was recorded by the hydrogen clearance method, using a platinum electrode located on the surface of the sagittal sinus (near the outflow of the sinuses). According to data in the literature [2] free diffusion of hydrogen through the vessel walls enables the cerebral blood flow to be measured without opening the vessels. SAP was measured with a mercury manometer in the common carotid artery, and pH and pO_2 in arterial blood samples were determined by the AZIV-2 instrument. An important condition for the study of autoregulation of CBF is maintenance of optimal pressure conditions throughout the experiment, which can be done only by artificial ventilation of the lungs. Among the various systems and methods of artificial respiration we chose the one most suitable for small laboratory animals, namely a box respirator [3]. This consists of an airtight chamber into which the animal is placed, so that its air passages communicate with the atmospheric air. Inspiration takes place when a negative pressure is created in the chamber, expiration when the pressure is normalized. In this way an increase in the intrapulmonary pressure, arising when air is injected directly into the lungs, and circulatory disturbances can be avoided. The optimal breathing schedule was established with monitoring of pH and pO_2 in the arterial blood. The use of the muscle relaxtant succinylcholine (1 mg/kg) enabled artificial ventilation of the lungs to be stabilized. The action of aminophylline on CBF and the cerebrovascular resistance (CVR) was studied during spontaneous changes in SAP (experiments of series I), during artificial stabilization of SAP [7] at near the normal level (series II), and during a stepwise change of SAP up to critical levels causing failure of autoregulation of CBF (series III). Different levels of SAP were produced by bleeding into an airtight receiver, and reinfusing the blood into the animal's arterial system. Aminophylline (2.4% solution) was injected intraperitoneally in a dose of 5-10 mg/kg.

EXPERIMENTAL RESULTS

In the experiments of series I (seven rats) the intial values of SAP, CBF, and CVR were 114.3 ± 7.7 mm Hg, 103.4 ± 11.1 ml/100 g/min, and 1.2 ± 0.1 mm Hg/ml/100 g/min respectively. Injection of aminophylline lowered SAP regularly by 12-56%. A hypotensive effect was observed 3-5 min after injection of the drug and it continued until the end of the observations (over 120 min). CBF showed phasic changes: at first (for 30-40 min) it was significantly increased by 7-52%, but later in most experiments it gradually decreased. In two cases CBF remained

Department of Pharmacology, Pyatigorsk Pharmaceutic Institute. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 12, pp. 707-709, December, 1985. Original article submitted December 21, 1984.

0007-4888/0012-1693$09.50

TABLE 1. Effect of Aminophylline (5-10 mg/kg, intraperitoneally) on SAP, CBF, and CVR (M ± m, % of initial value)

Initial value	Time after injection of aminophylline, min					
	15	30	45	60	90	120
With unstabilized SAP						
SAP = 114,3±7,7 mm Hg	−32,9±5,1	−30,7±4,1	−32±3,4	−33±4,2	−31,9±4,6	−33,7±5,7
P	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001
CBF = 103,4±11,1 ml/100 g/min	+23±5,0	+15±5,3	+13±10	+10±12,9	−3±9,7	−17±10,7
P	<0,05	<0,05	>0,05	>0,05	>0,05	>0,05
CVR = 1,2±0,1 mm Hg/ml/100 g/min	−45±4,1	−40±3,7	−38±4,8	−37±5,1	−27±5,6	−16±6,6
P	<0,001	<0,001	<0,001	<0,001	<0,001	<0,05
With stabilized SAP						
SAP = 117,5±2,8 mm Hg	−3±1,5	−2,2±1,2	−1,3±0,9	−2,7±1,5	−4,2±2,4	−2±1,1
P	>0,05	>0,05	>0,05	>0,05	>0,05	>0,05
CBF = 125±15,3 ml/100 g/min	+30,8±9,0	+18,8±10,5	+18±9,3	+0,8±11,4	−5,8±13,3	−26,2±10,9
P	<0,05	>0,05	>0,05	>0,05	>0,05	<0,05
CVR = 1,1±0,2 mm Hg/ml/100 g/min	−24,3±5,7	−15,5±7,0	−15,2±5,6	+2±11,0	+9,7±13,9	+45,3±23,0
P	<0,01	0,05	<0,05	>0,05	>0,05	>0,05

Legend. Here and in Table 2: +) increase, −) decrease.

TABLE 2. Changes in CBF, CVR, and K_r with Fall in SAP in Control Experiments and after Administration of Aminophylline (M ± m)

Experimental conditions	SAP, mm Hg	Number of tests	CBF, % of initial value	*P*	CVR, % of initial value	*P*	K_r
Control	100	14	−3,5±3,0	>0,05	−27,9±2,0	<0,001	0,95±0,11
	80	20	−4,7±2,2	>0,05	−38,9±1,8	<0,001	0,87±0,06
	60	18	−6,0±5,9	>0,05	−46,7±3,5	<0,001	0,88±0,2
	50	15	−20,3±4,4	<0,01	−50,6±3,7	<0,001	0,67±0,09
	40	14	−43,9±3,6	<0,001	−47,8±4,0	<0,001	0,38±0,05
	30	14	−61,4±3,7	<0,001	−35,3−6,4	<0,001	0,18±0,05
Injection of aminophylline	80	6	+9,3±8,6	>0,05	−24,3±4,5	<0,01	1,25±0,31
	60	7	−1,1±6,8	>0,05	−31,9±3,7	<0,001	1,16±0,23
	50	6	−3,3±1,9	>0,05	−42,0±5,6	<0,001	0,89±0,06
	40	6	−28±5,6	<0,01	−32,7±3,9	<0,001	0,58±0,18
	30	6	−51±4,1	<0,001	−22±7,1	<0,001	0,21±0,02

above the initial level until the end of the observations, and accordingly, its mean value 120 min after injection of aminophylline was lower, though not significantly, than initially. CVR in all experiments was considerably reduced after injection of aminophylline, especially after 15 min (on average by 45%), but later it gradually recovered (Table 1; Fig. 1a). Thus the increase in CBF (despite the decrease in SAP) under the influence of aminophylline was due to a marked decrease in cerebrovascular tone. With restoration of the latter, with continuing general hypotension, CBF decreased.

In the experiments of series II (six rats) the initial values of SAP, CBF, and CVR were 117.5 ± 2.8 mm Hg, 125 ± 15.3 ml/100 g/min, and 1.1 ± 0.2 mm Hg/ml/100 g/min respectively. Aminophylline caused regular biphasic changes in CBF and CVR. A particularly marked increase in CBF (by 13-57%) and decrease in CVR (by 13-40%) were observed 15-20 min after administration of the drug. Later CBF gradually decreased but CVR increased, and after 50-60 min both these parameters had reached their original values; after 2 h, however, a decrease in CBF and an increase in CVR were observed (Fig. 1b).

Thus when SAP was stabilized the second, vasoconstrictor phase of the action of aminophylline on the cerebral vessels was manifested more clearly, whereas in a situation of general hypotension the first, vasodilator phase, predominated. Consequently, the dilator response of the cerebral vessels to aminophylline is potentiated by the parallel fall of SAP, which is evidently due to an autoregulatory cerebrovascular effect.

To test this hypothesis the experiments of series III were carried out (on 10 rats). Autoregulatory reactions of the cerebral vessels to a fall of SAP were judged by changes in CBF and CVR and in the coefficient of regulation (K_r), calculated by the equation in [6]. In each experiment two or three tests of autoregulation of CBF were carried out before injection of aminophylline (control) and after its injection. The initial levels of SAP, CBF, and CVR in the control experiments were 140 ± 3.5 mm Hg, 147 ± 10.9 ml/100 g/ min, and 1.07 ± 0.1 mm Hg/ml/100 g/min respectively. A fall of SAP to 120 mm Hg was accompanied by some

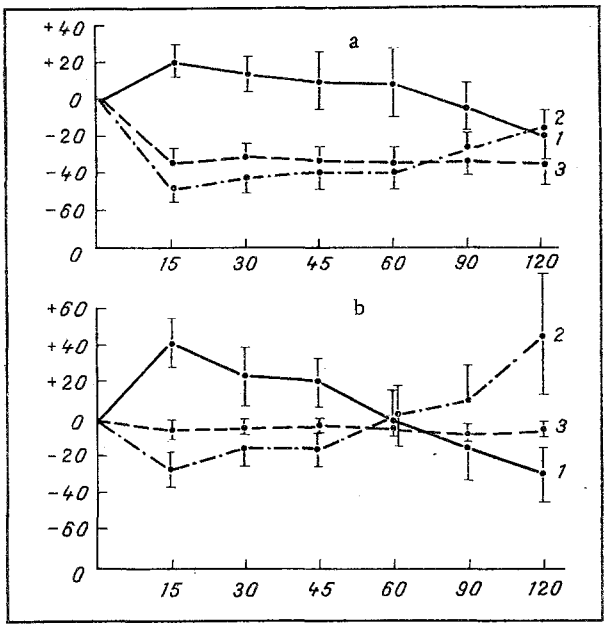

Fig. 1. Effect of aminophylline (5-10 mg/kg, intraperitoneally) on CBF (1) and CVR (2) with arterial pressure unstabilized (a) and stabilized (b). Abscissa, time of investigation (in min); ordinate, changes in parameter (in % of initial value).

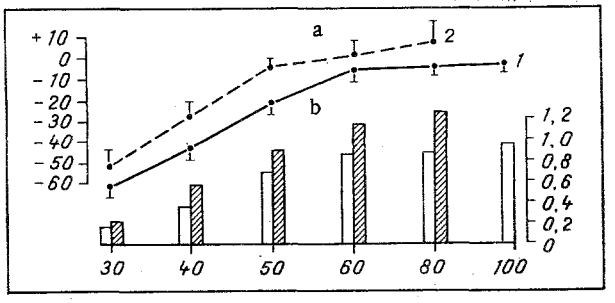

Fig. 2. Time course of changes in CBF (a) and K_r (b) during fall of SAP in control experiments (1, unshaded columns) and after injection of aminophylline (2, shaded columns). Abscissa, SAP (in mm Hg); ordinate: on left — changes in blood flow (in % of initial value), on right — K_r.

increase in CBF and a considerable decrease in CVR, evidence of hyperregulatory reaction of the cerebral vessels ($K_r > 1$). With a further decrease in SAP to 60 mm Hg CBF remained at virtually a stable level due to the progressive decrease in CVR and the comparatively high value of K_r (about 0.9). The critical level of SAP was 50 mm Hg, at which CBF was reduced by 20% but K_r was reduced to 0.67. A further decrease in SAP to 40 mm Hg was accompanied by a sharp reduction in blood flow (by 43.9%) and in K_r to 0.38. Consequently, the lower limit of autoregulation of CBF in the control can be considered to be an SAP level of 50 mm Hg (Table 2, Fig. 2).

The levels of SAP, CBF, and CVR 30-40 min after injection of aminophylline in dose of 5-7 mg/kg were 90 ± 3.6 mm Hg, 136.9 ± 13.5 ml/100 g tissue/min, and 0.72 ± 0.08 mm Hg/ml/100 g/min respectively. Against this background a fall in SAP to 80 mm Hg was accompanied by a hyperregulatory reaction of the cerebral vessels ($K_r > 1$), with the result that CBF in

most experiments was increased together with a considerable decrease in CVR. With a further decrease in SAP to 60-50 mm Hg CBF remained comparatively stable, whereas K_r was high. The lower limit of autoregulation of CBF against the background of aminophylline may be considered to be an SAP level of 40 mm Hg, for if it was reduced to 30 mm Hg this was accompanied by a marked decrease in CBF and K_r, i.e., by failure of autoregulation. Consequently, aminophylline shifts the lower limit of autoregulation toward lower SAP levels and thus maintains the blood supply to the brain under conditions of general hypotension.

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