Effect of Substance P on the Content of Catecholamines and on the Enzymes of Their Synthesis in the Brain of Chronically Alcoholized Rats

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UDC 612.821.3.014.46:547.262]-006:
612.822.1:577.175.522

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 118, № 7, pp. 46-48, July, 1994
Original article submitted November 13, 1993

The effect of a single administration of the endogenous peptide substance P on the content of dopamine (DA), and norepinephrine (NE), and on the activity of tyrosine hydroxylase (TH) and dopamine β-hydroxylase (D-β-H) is studied in the hypothalamus and midbrain of rats after a 6-month alcoholization.

Key Words: *substance P; dopamine β-hydroxylase; tyrosine hydroxylase; catecholamines; alcohol*

Specific disturbances of the catecholamine system play a crucial role in the pathogenesis of alcohol addiction [1-4,7]. An altered content of biogenic amines, in particular, catecholamines (CA), in various structures of the brain, primarily in the hypothalamus and midbrain of alcoholized animals, together with a high concentration of the well-known endogenous peptide substance P (SP) in these structures, prompted us to study the effect of SP on CA and the enzymes of their synthesis in the brain of chronically alcoholized rats.

MATERIALS AND METHODS

Unbred male white rats weighing 400 g were used in the experiments. All animals were alcoholized during 6 months by substituting 15% ethanol for water in their ration. The rats were then tested for alcohol intake during 10 days under conditions of free choice of alcohol and water (two-dish test). Two groups of animals were used: rats with a developed alcohol craving (more than 50% of the total liquid consumed being alcohol - "heavy drinkers") and "light drinkers", drinking less than 50% alcohol.

SP was injected singly intraperitoneally in a dose of 125 mg/kg body weight. The amount of alcohol intake was recorded during 8 days post-injection. Four groups of animals were studied: controls with and without injection of SP, and chronically alcoholized rats (heavy and light drinkers) with and without injection of SP. The content of CA in the hypothalamus and midbrain was determined by high-performance liquid chromatography with electrochemical detection [8]. TH activity in various structures of the brain was measured as described elsewhere [5]; D-β-H activity was assessed by a modified method [9,10].

RESULTS

Comparison of alcohol intake (% of total liquid consumed per day) in animals with a developed alcohol craving injected with either physiological

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0007-4888/94/0007-0728$12.50

saline or SP revealed marked differences (Fig. 1). We see that alcohol intake declined during 7 days after injection of SP, which is in conformity with published data on a possible therapeutic effect of SP on pathological alcohol motivation [6].

The results presented in Figs. 2-5 suggest that 6-month chronic alcoholization changes the level of CA and the activity of the enzymes of their synthesis in the brain structures in quiestion. The most pronounced changes were revealed in the content of DA in the hypothalamus. It should be noted that the changes in the content of DA in the hypothalamus differed in rats with different alcohol intakes. For example, in rats with a developed alcohol craving the content of DA was considerably increased and attained 160% of the control value (Fig. 2, *a*), while in light drinkers it significantly dropped and comprised 71% of the control value (Fig. 2, *b*). The activity of CA-synthesizing enzymes in animals with high alcohol consumption correlates with the content of DA in the hypothalamus: increased activity of TH (Fig. 3, *a*) together with considerably decreased activity of D-β-H (Fig. 3), possibly resulting in an elevated content of DA (Fig. 2, *b*). A single intraperitoneal administration of SP to animals with low alcohol intake virtually did not change the content of DA in the hypothalamus, but markedly reduced it in

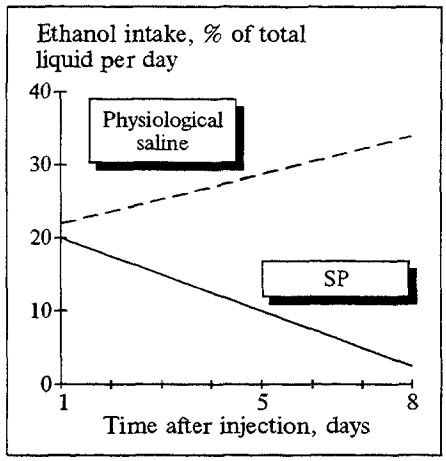

Fig. 1. Ethanol intake (% of total liquid) of chronically alcoholized rats after intraperitoneal injection of SP or physiological saline. Abscissa: time after injection, days; ordinate: ethanol intake (% of total liquid per day).

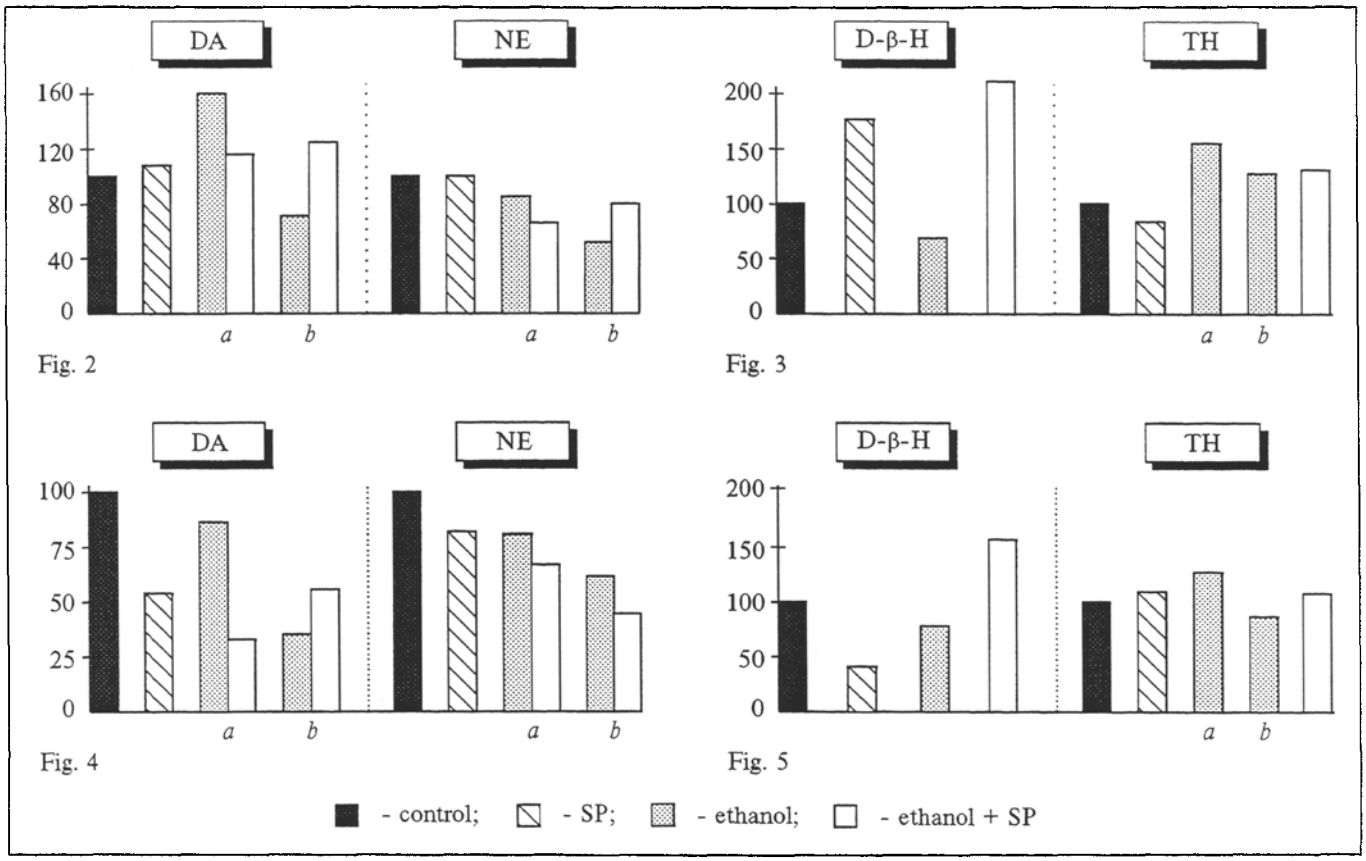

Fig. 2. Content of DA and NE (%) in the hypothalamus of chronically alcoholized rats after a single injection of SP. Here and in Figs 3–5: *a*) heavy drinkers; *b*) light drinkers.

Fig. 3. Activity of D–β–H and TH (%) in the hypothalamus of chronically alcoholized rats after a single injection of SP.

Fig. 4. Content of DA and NE (%) in the midbrain of chronically alcoholized rats after a single injection of SP.

Fig. 5. Activity of D–β–H and TH (%) in the midbrain of chronically alcoholized rats after a single injection of SP.

the midbrain in comparison with the control (Figs. 2, *b* and 4, *b*).

Administration of SP to chronically alcoholized rats with high alcohol intake normalized the content of DA in the hypothalamus and reduced it in the midbrain (Figs. 2, *a* and 4, *a*). The activity of D-β-H in the midbrain of heavy drinkers was considerably reduced (Fig. 5), whereas the activity of TH was increased (Fig. 5, *a*). Injection of SP to these animals somewhat increased the activity of TH and greatly increased the activity of D-β-H (Fig. 5), which corresponded to a lowered content of DA in the midbrain in comparison with the control (Fig. 4, *a*).

The reduced level of CA in the midbrain of animals with a developed alcohol craving against the background of SP injection may be considered as a positive therapeutic effect resulting from normalized functioning of the enzyme system involved in the synthesis of CA.

Our results confirm published data on the modulating and regulating effect of endogenous peptides (in our case, SP) on the metabolism of CA in the brain, which manifests itself in a changed content of DA and NE, and on the activity of the enzymes of CA synthesis in the hypothalamus and midbrain. The SP-induced changes in CA metabolism induced in the hypothalamus and midbrain were revealed 8 days after single administration of the preparation, which suggests its long-term effect and the ability to induce long-term changes in the content of NE and DA.

The peculiarities of CA metabolism in different brain structures manifest themselves in opposite changes in the content of DA and NE in the hypothalamus and midbrain, as well as in a different intensity of changes in enzymatic activity in response to SP.

Analysis of the findings allows us to conclude that injection of SP reduces voluntary alcohol consumption in rats with a developed pathological alcohol motivation. The reduced level of addiction may be partially caused by normalized functioning of the catecholamine (in particular, dopaminergic) system due to the effect of SP via a number of mutually regulated factors on the activity of enzymes of CA synthesis. Further studies of these factors will broaden our understanding of the mechanisms of the disturbances which determine alcohol addiction and its possible regulation.

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