EFFECT OF ADRENOBLOCKERS ON THE ANALGESIC EFFECT OF GABA-POSITIVE DRUGS

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GABA, together with opioidergic, monoaminergic, and cholinergic neurotransmitter systems, plays an important role in the regulation of pain sensitivity [2, 4, 12]. The presence of close morphological and functional connections between processes of GABA-ergic transmission and other neurochemical systems raises the extremely urgent question of the importance of these connections for the formation of the analgesic effect of GABA-positive drugs. Meanwhile the results of investigations in this direction are few in number and contradictory in nature [3, 5, 13], due to the use of different models of nociceptive action and of the different GABA-ergic-drugs, differing significantly in their effect at the receptor level.

The aim of this investigation was to compare the role of adrenergic mechanisms in the formation of the analgesic effect of GABA-positive drugs, differing in their affinity for individual subtypes of GABA receptors.

EXPERIMENTAL METHOD

Experiments were carried out on 96 male albino rats weighing 160-210 g. The analgesic effect was assessed by the tail-flick and vocalization tests [1, 11], since the predominant integration of the nociceptive response in these tests takes place at segmental and suprasegmental levels of the brain and spinal cord, respectively [7, 11]. The following GABA-positive drugs were used: depakin (Labaz, France) 400 mg/kg, baclofen (from Polfa, Pland) 7.5 mg/kg, and THIP (generously provided by Professor P. K. Korgsgaard-Larsen, Denmark), 12.5 mg/kg, the analgesic action of which is associated with their selective effect on $GABA_A$-receptors (depakin) or $GABA_B$-receptors (baclofen) or with its actin (THIP) on both types of receptors [2, 4]. Blockers of α_1-adrenoreceptors – prazosin (from Orion, Finland) – 0.5 mg/kg and of α_2-adrenoreceptors – yohimbine (from Regis, USA) – 0.5 mg/kg [10, 15], and also FD-008 (Nippon Kayaku Co., Japan), selective blocker of dopamine-β-hydroxylase – 100 mg/kg [8] were used for neuropharmacologic analysis. All the drugs were injected intraperitoneally: depakin, prazosin, and yohimbine 30 min, baclofen and THIP 60 min, and FD-008 4 h before the experiment began. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

The GABA-positive drugs, in the doses tested, caused distinct analgesia, manifested as the significant increase in the latent period of the tail flick (+45-82%) and in the threshold of vocalization (+47-117%). It will be clear from Fig. 1 that prazosin, a selective blocker of α_1-adrenoreceptors, did not change the analgesic action of depakin, baclofen, or THIP in the tail-flick test. Depression of the emotional component of the nociceptive response, induced by depakin and THIP in the vocalization test, was weakened statistically significantly (by 40 and 80%, respectively) by prazosin, whereas the effect of baclofen was unchanged.

The manifestations of the analgesic action of baclofen did not change statistically significantly if it followed preliminary administration of FD-008 (Fig. 1). Meanwhile the analgesic effect of depakin and THIP was substantially reduced in the vocalizatin test but was unchanged in the tail-flick test.

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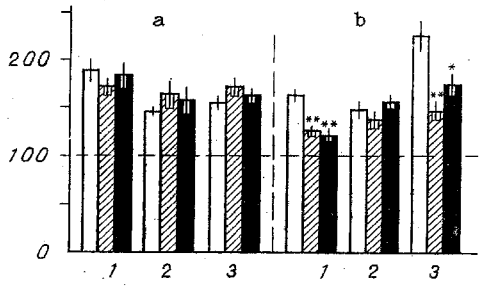

Fig. 1. Effect of prazosin and FD-008 on the analgesic effect of GABA-positive drugs in the tail-flick (a) and vocalization (b) tests. Ordinate, changes in latent period of tail flick and threshold of vocalization (in % of control level). Unshaded columns: 1) depakin (400 mg/kg), 2) baclofen (7.5 mg/kg), 3) THIP (12.5 mg/kg); obliquely shaded columns: depakin, baclofen, or THIP, respectively + prazosin (0.5 mg/kg); black columns: depakin, baclofen, or THIP, respectively + FD-008 (100 mg/kg). *P < 0.05, **P < 0.01 compared with effect of GABA-positive drug.

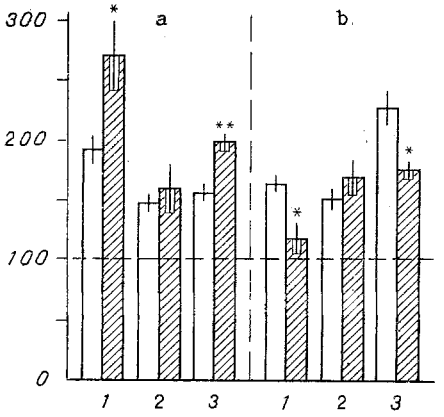

Fig. 2. Effect of yohimbine on analgesic effect of GABA-positive drugs in tail-flick (a) and vocalization (b) tests. Ordinate, changes in latent period of tail flick and vocalization threshold (in % of control level). Shaded columns: 1) depakin, 2) baclofen, 3) THIP (all + yohimbine 0.5 mg/kg). Remainder of legend as in Fig. 1.

Yohimbine, a selective antagonist of α_2-adrenoreceptors weakened the analgesic action of depakin and THIP in the vocalization test significantly (on average by 50-60%), whereas in the tail-flick test the level of analgesia induced by these drugs was significantly increased (Fig. 2). Meanwhile, just as in the experiments with prazosin, yohimbine did not change the analgesic effect of baclofen.

It can be concluded from the results of these experiments that reduction of the functional activity of α_1-adrenoreceptors is not a factor limiting the formatin of the analgesic action of the $GABA_B$ agonist baclofen. Similar results also were obtained in other investigations [5, 13], when the α-adrenoblocker phentolamine was used. However, phentolamine is not a sufficiently selective blocker of the pre- or postsynaptic component of the adrenergic system [10]. Meanwhile baclofen, as we know, can depress noradrenalin release from nerve endings, possibly on account of direct interaction with α_2-adrenoreceptors [6, 16]. Neuropharmacologic analysis yielded no evidence that the level of the analgesic action of baclofen depends on disturbance of α-adrenoreceptor function. In all probability, the reason

is that only one population (with low affinity) of $GABA_B$-receptors is located on noradrenergic terminals whereas high-affinity $GABA_B$-receptors are not connected with them [9]. We also know that systemic administration of baclofen does not cause definite changes of noradrenalin turnover [9].

Analgesia arising in response to activation of $GABA_A$-receptors is evidently realized with the participation of the α_1-adrenergic component at the suprasegmental, but not at the segmental, level. Very probably coupling between GABA-ergic and adrenergic neurotransmitter components in the regulation of pain sensitivity is not the result of direct interaction between GABA-positive agents and the adrenoreceptor [3, 14]. We know that GABA-agonists with greater affinity for $GABA_A$-receptors than for $GABA_B$-receptors (THIP, progabide) activate noradrenalin release and metabolism, thereby making the α_1-adrenoreceptors more accessible for the endogenous mediator [14, 16]. The validity of this conclusion also is confirmed by the results of our experiments with FD-008, which inhibits synthesis and release of noradrenalin [8].

Meanwhile the different effects of yohimbine on the analgesic action of depakin and THIP in the tail-flick and vocalization tests is probably evidence that interconnection between $GABA_A$- and α_2-receptor mechanisms at the segmental and suprasegmental levels is reciprocal in direction. This is probably because the formation of analgesia in response to activation of $GABA_A$-receptors is accompanied by opposite changes in functional activity of the ascending and descending noradrenergic pathways involved in the regulation of nociceptive sensitivity [12].

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