

## COMBINED ACTION OF CAFFEINE AND SYDNOCARB

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KEY WORDS: caffeine; sydnocarb; combined action.

One method of potentiating the main action and weakening the side effect of drugs is by combining them in optimal doses. This situation was the motivation behind an investigation of the stimulating effect of caffeine on nervous activity when used in combination with sydnocarb. The stimulating effect of caffeine on nervous activity in therapeutic doses is often inadequately expressed, and an increase in its dose as a rule is accompanied by side effects (tachycardia, dyspnea). Sydnocarb likewise is not free from side effects. The toxicity of neither drug is considerable, and it might therefore be expected that a combination of caffeine and sydnocarb would be perfectly rational, in particular because they differ in their mechanism of action. The present investigation was undertaken to test this hypothesis.

## EXPERIMENTAL METHOD

The following criteria were used in a study of the combined action of caffeine and sydnocarb: the conditioned avoidance reflex, impulse summation in the CNS, forced swimming, antagonism with hexobarbital, effect on the ECG and blood pressure, and acute toxicity. The conditioned avoidance reflex was studied in rats by Cook's method, i.e., the time taken to form a conditioned reflex (jumping on a vertical rod during painful electrical stimulation of the limbs in a chamber with "electrode floor," the conditioned stimulus was light) and the latent period of this reflex were recorded. Impulse summation was tested in intact rabbits by determining the number of subthreshold electrical stimuli of different amplitude applied to the skin of the hind limb (foot) in response to which flexion of that limb took place. Experiments with forced swimming were carried out on albino mice in a bath of water (temperature 26°C, extra load 10% of body weight), and the time spent by the animals on the surface of the water was recorded. Antagonism with hexobarbital in a standard dose of 60 mg/kg was studied in mice by recording the duration of sleep (side position). The effect on the ECG (in standard lead II) and arterial pressure (in the common carotid artery) was investigated in rabbits under general anesthesia by the usual method. Toxicity was determined in albino mice by Kärber's method.

## EXPERIMENTAL RESULTS

Caffeine and sydnocarb separately in these experiments had a stimulating effect on all parameters of nervous activity investigated. In a combination as the results showed, they exhibited an additive action (Table 1).

The results in Table 1 show that with a combination of caffeine and sydnocarb an additive effect was observed, for the 100% effect was achieved with respect to all criteria by a combination of caffeine and sydnocarb in doses corresponding to 50% of the average doses. Although as regards toxicity caffeine and sydnocarb also exhibit an additive action, this is a matter of virtually no importance, because the toxicity of these drugs is relatively low and the doses in which they were effective, according to the chosen criteria, were very far from toxic. According to our observations caffeine and sydnocarb separately, in doses of 10 mg/kg, caused an almost imperceptible rise of arterial pressure and tachycardia. During the combined action of sydnocarb and caffeine in doses of 5 mg/kg no rise of blood pressure or tachycardia was observed. With a combination of caffeine and sydnocarb, although the neurotropic effects are preserved, their action on the circulation, which is usually undesirable (i.e., a side effect), can be avoided. This is evidence that a combination of caffeine

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TABLE 1. Activity of Caffeine and Sydnocarb Separately and in Combination

Parameter studied	Caffeine	Sydnocarb	Caffeine + Sydnocarb
	dose, mg/kg		
Conditioned avoidance reflex time of formation (reduction by not less than two-thirds) latent period (shortening by not less than one half)	10	10	5+5
Summation of impulses (facilitation by at least twofold)	10	0,5	5+0,25
Time of swimming (at least twofold increase)	20	10	10+5
Antagonism with hexobarbital (60 mg/kg; shortening of sleep by 50% at $P < 0.001$ )	20	10	10+5
Blood pressure, ECG	10	10	5+5
Toxicity $D_{50}$	250	500	125+250

and sydnocarb can be used with advantage in medical practice. Yet another advantage of the combined use of caffeine and sydnocarb is that they have different mechanisms of action. The former, for instance, according to data in the literature [1-3], increases the cAMP concentration in nerve tissue, by reducing phosphodiesterase activity and causing its degradation, whereas the latter increases adenylate cyclase activity and stimulates its formation.

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#### MECHANISM OF THE INHIBITORY EFFECT OF ATYPICAL ANTIDEPRESSANTS AND PSYCHOSTIMULANTS ON SYNAPTOSOMAL MONOAMINE UPTAKE

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Antidepressants and psychostimulants can actively inhibit monoamine reuptake into nerve endings in the CNS [3-6, 11], but the character of interaction of different groups of drugs with the hypothetical carriers of neurotransmitters in the presynaptic membrane has not yet been explained. The problem of the presence of three different carriers in the mammalian brain for noradrenalin, dopamine, and serotonin, or a single universal carrier has not yet been settled.

The object of this investigation was to analyze the type of inhibition by atypical antidepressants and psychostimulants of the uptake of noradrenalin, dopamine, and serotonin by the coarse synaptosomal fraction of rat cerebral cortex.

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