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EFFECTS OF *N*-BENZYL-L-VALINE ON CONTRACTIONS OF GUINEA-PIG MYOMETRIUM *in vitro*

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A claim that *N*-benzylvaline is an exceedingly potent stimulant of guinea-pig myometrium has not been confirmed, but less potent stimulant or inhibitory effects were seen in a few experiments.

Introduction Koroza, Kudrin, Kost & Sagitullin (1969) stated that certain *N*-substituted amino acids markedly enhanced the contractions of the guinea-pig uterus, when applied in exceedingly low concentrations for periods of 10–15 minutes. The most potent one was stated to be *N*-benzylvaline (Na salt), which was claimed to intensify contractions at concentrations of the order of 10^{-19} M, or to cause spasm at 10^{-13} M. Since a number of common amino acids at much higher concentrations have recently been shown to stimulate the uterus (Bedwani, Ishizawa, Pickles & Suwankrughasn, 1977), and as there are a few simple *N*-substituted amino acids of pharmacological or physiological interest, it seemed worthwhile to see if the claim by Koroza *et al.* (1969) could be substantiated.

Methods *N*-benzyl-L-valine (NBV) with the addition of the equivalent amount of $NaHCO_3$ was dissolved in Krebs-Henseleit solution to give 10 mM stock solutions, which were kept at 4°C until they were diluted for use. Guinea-pig uteri were suspended in Krebs-Henseleit solution as in the experiments of Bedwani *et al.* (1977), except that animals in oestrus were not avoided; 2 of the 17 animals used appeared to be in this phase. For short-term applications, NBV was applied by injection into the organ bath. When longer-term application was needed, as in the experiment shown in Figure 1a, the NBV was added in the desired final concentration to the reservoir of Krebs-Henseleit solution in a duplicate supply system, so that steady slow flows of medium either with or without NBV could be alternated at will while all other

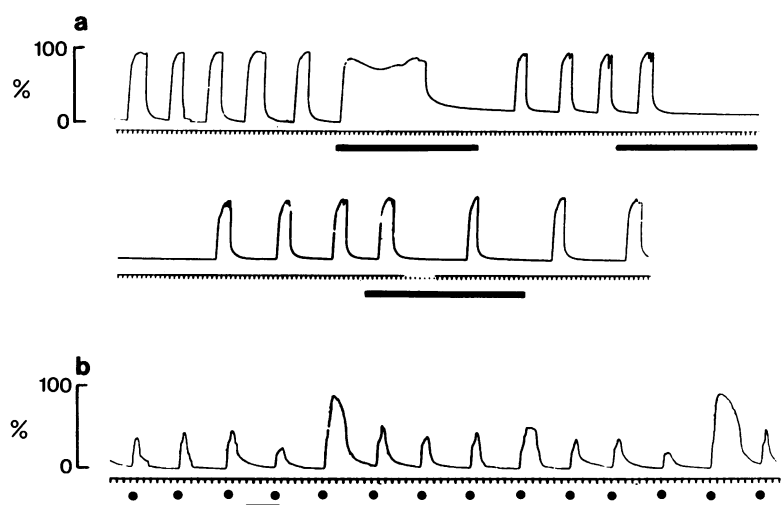

Figure 1 (a) Effects of *N*-benzyl-L-valine (NBV) on spontaneous contractions of a guinea-pig uterus. The medium flowed continuously through the 4 ml organ bath at a rate of 2.8 ml/min; during the periods shown by bars it contained 0.6 μM NBV. The record is continuous. (b) Delayed potentiation of responses to acetylcholine (ACh, 1 μM, 1-min applications at dots) by 4 mM NBV. The potentiation is approximately equivalent to a doubling of the dose of ACh. It was seen in each of 5 similar trials in this experiment, and in a similar one with 4 mM L-valine but in this case without the delay. Time-marker 1 min in both traces. Ordinate scales: % maximum contraction height.

conditions were kept constant. By either means, the bath concentration of NBV was usually within the range 0.5 μM to 1.0 mM.

Results In only 2 of the 17 experiments was a strong effect of the type described by Koroza *et al.* (1969) seen, and this only with higher concentrations (0.6 and 60 μM). One of these is shown in Figure 1a. On repeated application the NBV no longer stimulated, but inhibited the spontaneous contractions. Prolonged inhibition without preceding stimulation was seen in another two experiments. In seven further experiments, NBV was applied for 4–10 min before acetylcholine, prostaglandin E_2 or vasopressin, which were added in its presence, and the responses were compared with those in the absence of NBV. Again, most results were negative but a repeatable delayed potentiation was seen in one experiment, in which an exceptionally high concentration (4 mM) of NBV was used. Part of this experiment is shown in Figure 1b. Inconstant trace responses of various kinds were seen in a few other experiments.

Discussion These results do not support the claim of Koroza *et al.* (1969) for *N*-benzylvaline. However, they do show that this compound, or at least the L enantiomer which we used, has some activity on a minority of uteri. In such instances the effect may be either stimulation or inhibition of the contractions, or one of these effects may lead to the other. The concentration of NBV sometimes producing stimulation is less than that of the common amino acids showing a similar effect (Bedwani *et al.*, 1977), but the potentiation of other spasmogens given by low concentrations of those acids was not given by NBV.

There may be several possible reasons for the difference between the present results and those of Koroza *et al.* (1969) but their account gives no detail of experimental method and speculation would be futile. In the present series, similar preparations from different animals have given widely differing results. Stimulant and inhibitory responses were found with approximately equal frequencies but the two types showed no constant relationship, suggesting two unrelated mechanisms. Their relative slowness (especially for inhibition) may indicate that the actions are indirect; and here it may be noted that Koroza *et al.* (1969) theoretically derived their compounds from two others then in use as monoamine oxidase-inhibitors, which they also said were stimulants of the guinea-pig myometrium. Possibly NBV modulates the spontaneous contractile activity of some uteri by one or more actions on endogenous catecholamine or 5-hydroxytryptamine metabolism.

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