Possible mechanism of action of β-phenethylamine in migraine

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Many dietary precipitants of migraine are known. They include some cheeses, citrus fruits, some alcoholic drinks, yeast extracts, sea-foods, and chocolate. Hanington (1967) noted that those tyramine-containing foods, known to interact with monoamine oxidase inhibitors, were the same foods recognized to precipitate migraine. This observation was challenged by experiments in which tyramine taken by mouth was shown to precipitate migraine in those individuals whose attacks were provoked by tyramine-containing foods (Hanington, Horn & Wilkinson, 1970). Chocolate is a clear exception, being a common migraine precipitant, but containing little tyramine. It does, however, contain large amounts of β-phenethylamine (β-PEA; Sandler, Youdim & Hanington, 1974) a sympathomimetic amine of low potency. Since Ghose, Coppen & Carroll (1977) found that tyramine-sensitive migraine can be prevented by pretreatment with the α-adrenoceptor blocking drug indoramin in low dosage it becomes important to discover whether β-PEA also acts like tyramine to release noradrenaline from nerve-endings.

Agonist-antagonist experiments were made on the rabbit isolated aortic spiral preparation and rat and guinea-pig vasa deferentia.

On the rabbit aorta increasing concentrations of phentolamine displaced the dose response-lines of both β-PEA and noradrenaline to the right in a parallel manner, indicating competitive antagonism. The antagonism was quantified on the rat vas deferens by the method of Arunlakshana & Schild (1959): the pA_2 value for phentolamine against noradrenaline was 7·3 and for phentolamine against β-PEA it was 7·4. These experiments implied that both drugs acted through a common receptor site, but the possibility that β-PEA was releasing noradrenaline from nerve endings had to be excluded.

In a separate group of experiments contractions of equal magnitude were induced on the rat vas deferens by noradrenaline, β-PEA, tyramine and electrical transmural stimulation. Guanethidine (10^{-5}M) markedly inhibited the response to tyramine whereas the responses to noradrenaline and β-PEA were potentiated by 78 and 42% respectively. On the Finkleman preparation of the rabbit duodenum similar relaxant responses were induced by noradrenaline, β-PEA and electrical stimulation of the periarterial sympathetic nerves. The preparation was then perfused with Krebs solution containing guanethidine (10^{-5} to 10^{-3}M) which eventually completely blocked the relaxation to periarterial electrical stimulation. At this time the noradrenaline and β-PEA responses were slightly but equally reduced by about 20%. This evidence is consistent with an action of both β-PEA and noradrenaline on postsynaptic α-adrenoceptors.

β-PEA (0·1 mg, i.v.), noradrenaline (0·1 μg, i.v.) and tyramine (0·1 mg, i.v.) all increased the carotid arterial systolic and diastolic pressures of the urethane-anaesthetized rat to a similar extent. After guanethidine (1 mg kg^{-1}, i.v.) the blood pressure responses to both β-PEA and noradrenaline were increased, whereas those to tyramine were reduced by rather more than half. After phentolamine, noradrenaline caused a slight fall in blood pressure whereas β-PEA and tyramine had no effect.

Additional experiments on the guinea-pig vas deferens revealed that neither atropine nor mepyramine in concentrations which blocked the actions of acetylcholine and histamine affected the responses to β-PEA or noradrenaline indicating that neither amine exerted its effects through postsynaptic acetylcholine or histamine receptors.

In conclusion, β-PEA has the properties of a sympathomimetic agonist which exerts its action directly on phentolamine-sensitive α-adrenoceptors, and not indirectly by releasing endogenous noradrenaline from neuronal stores.

These experiments provide a rational basis for the prophylaxis of β-PEA-sensitive migraine with α-blocking drugs.

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