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Pharmacologic Action of β-Phenylethylglucosamine.* (19958)

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The quantitative difference in activity between the optical isomers of various sympathomimetic amines has been widely investigated. The present report concerns the changes in pharmacologic activity of optically inactive β-phenylethylamine which result when it is conjugated with an optically active sugar moiety.

Materials and methods. β-Phenylethylglucosamine (PEGA) was prepared by the method of Pigman *et al.*(1). It was a white crystalline solid (M.P. 82°) which gradually darkened on standing. *Analysis.* Calculated for $C_{14}H_{19}O_5N$; N, 4.98. Found: N, 5.06. Mutarotation studies of PEGA in water were performed with standard polarimetric technics. Freshly prepared aqueous solutions of PEGA had a specific rotation $\alpha\,]_d^{20}$ −21° however; upon standing at room temperature for 15 minutes, the value fell to $\alpha\,]_d^{20}$ −15° and remained constant over a period of 2 hours. Heating the solution for 1 hour at 50° yielded a value of $\alpha\,]_d^{20}$ +8° which remained constant over a period of 1 hour. Heating PEGA solutions at temperatures of above 60°C, however, very quickly hydrolyzed the glucosamine. Toxicities were calculated by the method of probits following intraperitoneal injections of aqueous solutions in groups of 20-30 white mice. The effects on carotid arterial blood pressure were determined in pentobarbitalized dogs following intravenous injections of aqueous solutions of the drugs.

Results. The toxicities of the two forms of PEGA (+8 and −15) and of β-phenylethylamine hydrochloride (PE) are compared in Table I on both a milligram and molar basis. Whereas PEGA (+8) and PE were apparently not different, PEGA (−15) was definitely less toxic. The observable responses in the mice were essentially the same for all materials although PE appeared to exert its effects more rapidly than either form of PEGA. Following the injection of lethal doses of all materials the mice initially were quite aggressive† then followed a period of relative inactivity which merged into fine tremors, later coarse tremors and finally asymmetrical convulsions. Upon cessation of respiration, opening the chest cavity revealed the heart was still beating.

TABLE I. Acute Toxicity Study.

Compound	LD_{50} (mg/kg)	LD_{50} moles $\times 10^3$/kg
PE	366	1.47
PEGA (+8)	426	1.53
PEGA (−15)	535	1.89

In their effects on the dog's blood pressure, PEGA (+8) and PE produced qualitatively and quantitatively similar pressor responses and were roughly 1/300 as potent on a weight basis as epinephrine. PEGA (−15), however, appeared to be only about ⅓-⅕ as active. Qualitatively, PEGA (−15) in low dosage ranges (up to 2 mg/kg) produced a more prolonged rise in pressure than did PEGA (+8) or PE at a dose of equal pressor height. Doses of PEGA (−15) in high dosage ranges (5 mg/kg and larger) gave responses qualitative-

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† The term 'aggressive' here denotes the fact that mice were observed to run about the cage biting one another.

ly like those of PEGA (+S) and PE. The blood pressure responses to epinephrine were unchanged by the prior administration of any of these materials.

Discussion. The combination of glucose with β-phenylethylamine appears to change the qualitative toxicity of PE relatively little. However, quantitatively, the combination does appear to delay the onset of toxicity effects, and in the case of the levorotatory compound, PEGA (−15), molar toxicity is actually decreased. The blood pressure studies tend to confirm that PEGA (−15) is less active and more prolonged in its action than PE or PEGA (+8).

The quantitative change in activity that occurs in PEGA (−15) may be contrasted with the results of Swanson *et al.*(2). These workers in a study of the effect of optically active isomers of acids in combination with sympathomimetic amines, concluded that the configuration of the acid did influence the activity of optically active amine salts but did not influence the activity of optically inactive PE. While the degree of dissociation (ionization) of the amine salt as contrasted with the relatively undissociable covalent linkage of the glucosamine is great the glucosyl group does not act in the same manner as simple nitrogen substituents. Bovet(3) reports that all N-substituted PE derivatives in which the substituent was ethyl or larger were sympatholytic; none of the present materials is sympatholytic.

Summary. The glucosyl derivatives of β-phenylethylamine have been synthesized and compared with β-phenylethylamine with respect to toxicity and pressor effects. The levorotatory β-phenylethyl glucosamine is less toxic and more prolonged in its action than β-phenylethylamine or the dextrorotatory glucosamine.

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Distribution of P^{32} in Tissues of Normal Animals.* (19959)

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Many investigators are using radioactive phosphorus in biological studies but there is very little recent data available on the distribution of P^{32} in the various tissues. The most extensive investigations available up to the present time deal with the use of radioactive phosphorus in connection with the phospholipid metabolism, which was summarized by Chaikoff(1). As a preliminary study in connection with the effect of selenium poisoning on phosphorus metabolism we have investigated the distribution of P^{31} and P^{32} in the tissues of normal animals. In this review we would like to report our findings. Detailed studies on liver, kidney, spleen, heart, and brain will be given in subsequent reports.

Methods. Normal adult Sprague-Dawley male and female rats were used as experimental animals and injected intraperitoneally with 2.6684×10^8 counts per minute of P^{32}. The P^{32} (H_3PO_4) was received from Oak Ridge in weak HCl solution which contained 0.024 mg P per millicurie and was neutralized with NaOH before injection. Animals were sacrificed under nembutal anesthesia at 1, 2, and 12 hours after the administration of the isotope. The results are the average of 5 or

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