# SUGAR RECEPTOR SPECIFICITY IN THE FLESHFLY, *SARCOPHAGA BULLATA*

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## INTRODUCTION

The sugar receptor of insects is a useful preparation for studies of receptor specificity compared to the more complex sensors of vertebrates. Unlike the vertebrates, insects appear to respond behaviorally only to carbohydrates. Von Frisch[7] and Dethier[3] using the honey bee, *Apis mellifera*, and the blowfly, *Phormia regina*, respectively, were able to make inferences concerning a common structure for behaviorally attractive and therefore presumably sweet-tasting molecules. They concluded that (1) The size of the sapid molecule is important. Molecules smaller than pentoses are uniformly ineffective; mono- and disaccharides are generally effective whereas only a few trisaccharides are effective. (2) Acyclic polyols such as D-glucitol are ineffective; in this instance, there appears to be a requirement for a ring structure. (3) The ring oxygen is not required; at least one hexahydroxycyclohexane isomer is active. (4) Sugars with $\alpha$-glycosidic linkages are more effective than the corresponding $\beta$-anomers.

Using the blowfly, *Phormia regina*, Evans[5] initiated correlative studies on chemical structure and the gustatory response of insects. The principle conclusion was that sugars interacting with a putative 'glucose site' must be in the pyranose form and that the configuration of the C-3 and C-4 hydroxyl groups determines the responsiveness. Additional interest in this model was generated by the demonstration of electrophysiological responses from insect labellar hairs generally correlated with the positive behavioral response and therefore, by implication, identified as a sweet receptor spike[11]. Subsequent electrophysiological[19,20] and behavioral[4] studies have indicated that in some flies there is only one variety of sweet taste receptor cell, but that it may have multiple receptor sites. Previous studies with the inositol receptor of the silkworm, *Bombyx mori*[15], suggested to us that the cyclitols might be relatively simple and suitable model compounds for study of the stereospecificity of the sugar receptor in the fly. In the present investigation we have in addition measured electrophysiological responses to a number of previously examined as well as many previous-

ly untested sugars using an electrophysiological technique for the labellar sugar receptor response of the fleshfly and have made further inferences regarding the configurational and conformational requirements of effective molecules.

## MATERIALS AND METHODS

The larvae of the fleshfly, *Sarcophaga bullata* (Parker), were grown on a controlled diet of commercial dog food to minimize possible variations in physiological state. The responses of adult *Phormia regina* have been reported to vary as a function of the larval diet[4]. Imagos 2–5 days old were used since during this period, the chemoreceptor cells show little variability in response[21]. The flies were food-deprived from emergence and were given tap water *ad libitum*.

The recording technique was as previously described[15] and similar to that of Hodgson and Roeder[12]. A capillary tube containing about 1 $\mu$l of test sugar in 0.05 *M* NaCl is advanced by means of a micromanipulator over the labellar hair completing the electrical circuit for recording extracellular action potentials by means of a cathode ray oscilloscope and camera. This method was used rather than a sidewall approach[6,17] because it facilitated the study of a large number of hairs per animal. The concentration of NaCl used is below the threshold of the salt receptor[8] as well as that which inhibits the sugar receptor response[18]. All of the experiments in this investigation were conducted with the 'largest' hairs[23]. In *Sarcophaga bullata*, these 'largest' hairs numbered about 8–9 on each of the two labellae. Each hair was first tested with the salt solution. Test solutions were always presented in order of increasing sugar concentration. Following each test solution, each hair was rinsed with 0.1 *M* NaCl followed by a 5 min rest period to permit disadaptation. In a given fly, half of the 'largest' hairs were presented with various concentrations of the test sugar and the remainder were tested with D-glucose and D-fructose standard solutions. In addition, each of the hairs used with the test sugar was ultimately tested with D-glucose as well. On rare occasions, an individual fly had many hairs that did not respond to the glucose and fructose standard solutions, and was rejected.

Cyclitols* were the generous gifts of Dr. S. J. Angyal, University of New South Wales, Australia and Dr. L. Anderson, University of Wisconsin, U.S.A. For evaluation of purity of the cyclitols, they were derivatized and analyzed by gas–liquid chromatography[15]. D-Glucose was obtained from J. T. Baker Chemical Company (Phillipsburg, N.J.), methyl $\alpha$-D-glucopyranoside, 3-*O*-methyl-D-glucose, L-glucose and methyl $\alpha$-D-xylopyranoside were purchased from Pfanstiehl Laboratories (Waukegan, Ill.), sucrose, methyl $\beta$-D-glucopyranoside, methyl $\alpha$-D-mannopyranoside and 2-deoxy-D-*arabino*-hexopyranose were the product of Allied Chemical (Morristown, N.J.). *Myo*-inositol was purchased from Nutritional Biochemical Corporation (Cleveland, Ohio). 1,5-Anhydro-D-glucitol, D-allose, methyl $\alpha$-D-allopyranoside, methyl $\beta$-D-allopyranoside, 3-deoxy-D-*ribo*-hexopyranose and methyl $\alpha$-L-sorbo-

* IUPAC-IUB tentative cyclitol nomenclature rules were used where applicable, *Biochem. J.*, 112 (1969) 17–28.

pyranoside were the gift of Dr. N. K. Richtmyer, National Institutes of Health (Bethesda, Md.). 6-Deoxy-D-glucose was purchased from Ash Stevens Inc. (Detroit, Mich.). α-D-Thioglucopyranose was a gift of Dr. R. L. Whistler of Purdue University (Lafayette, Ind.). D-Fructose was obtained from Eastman Kodak Co. (Rochester, N.Y.). The following sugars were available in the laboratory of one of us (I.J.G.): 2-*O*-methyl-D-glucose, methyl 2-amino-2-deoxy-α-D-glucopyranoside, methyl 2-acetamido-2-deoxy-α-D-glucopyranoside, methyl α-D-galactopyranoside, 4-*O*-methyl-D-glucose, methyl α-L-glucopyranoside, 6-*O*-methyl-D-glucose, methyl β-D-fructopyranoside, methyl α-D-fructopyranoside, methyl α-D-fructofuranoside, methyl β-D-fructofuranoside and 3-*O*-methyl-D-fructose. Methyl β-L-glucopyranoside was prepared by Cheryl McBroom, Department of Biological Chemistry, University of Michigan. Purity of these compounds was determined by appropriate paper chromatographic or thin-layer chromatographic techniques.

## RESULTS

In the labellar chemosensory hair of the fleshfly (*Sarcophaga bullata*, Parker), the spike heights of the sugar, salt and water receptors were found to differ sufficiently to allow classification of each spike as belonging to the appropriate receptor cell[14,16]. A typical record (Fig. 1) shows that when 0.05 *M* NaCl was presented alone, a very small spike was elicited while when D-glucose was added, an easily distinguished larger spike appeared. The sugar spike for a given cell could be further distinguished by its increasing frequency with increasing sugar concentration. When on occasion, a water spike and sugar spike occurred simultaneously they summated to produce a slightly larger spike. Large salt spikes were seldom seen at the concentration of salt used and were readily identified. The water spike was often so small that it was barely discernible in the baseline noise.

While responses of a population of flies showed some variability, the responses of a single fly to repeated applications of a given sugar were remarkably constant (Fig. 2). In the present study, the response measured was the number of action potentials occurring during the last 400 msec of a 500 msec stimulation. The receptors were tested periodically with 0.3 *M* D-glucose for reproducibility of the response. The results of most of the experiments reported here are expressed as maximal rates relative to the maximal response of D-glucose in the same cell. While one can calculate an affinity constant from a reciprocal plot of the response or alternatively, compare threshold concentrations it has been our experience that maximal rates are more reproducible and are directly comparable. Since most of the sugars tested have either no effect or 50% or more of that of D-glucose, this method would seem to adequately separate efficacious from non-efficacious molecules. It should be noted that in each instance, the sugar was tested at a range of concentrations and was shown to have achieved the maximal rate. The results in Fig. 2 show the order of effectiveness at maximal stimulatory levels is sucrose > glucose > fructose, although below 0.13 *M* it can be seen that the order is changed to sucrose > fructose > glucose. Although the concentration of the intersection of the glucose and fructose curves

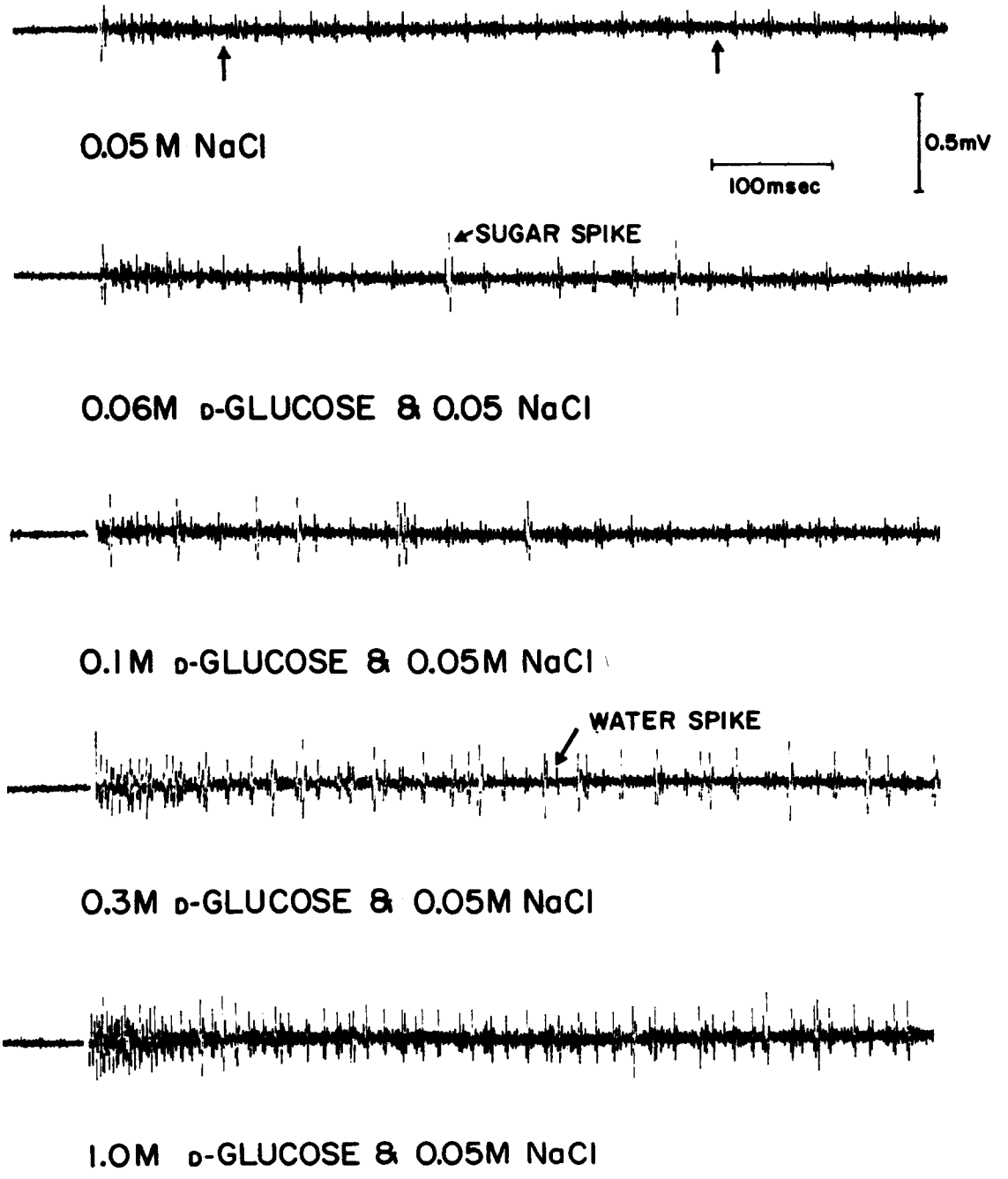


Fig. 1. A typical recording from a single labellar chemosensory hair responding to increasing concentration of D-glucose. The arrows in the top record are 400 msec apart. Note the artifact at the beginning of most of the records indicating the onset of stimulation.

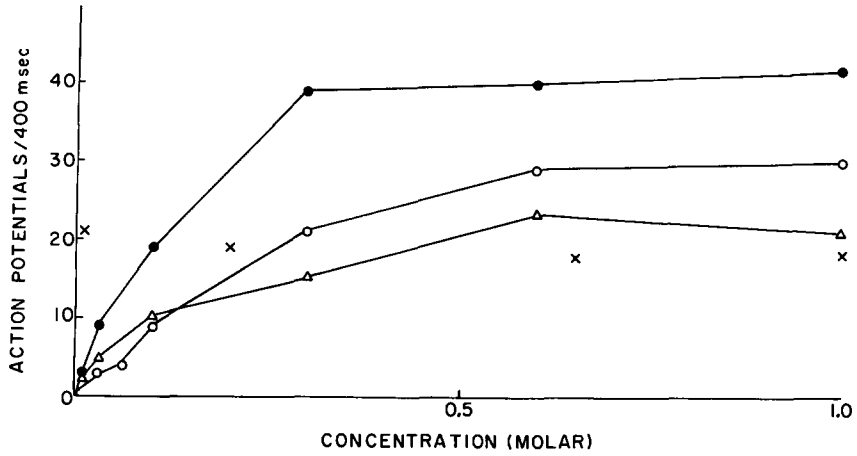


Fig. 2. Comparison of response–concentration relation in stimulation by sucrose (●), glucose (○) and fructose (△) of a single receptor. Reproducibility of the response was tested with 0.3 *M* D-glucose (×).

varied from animal to animal, crossing was always seen. The results of tests with different sugars are presented in Table I.

## DISCUSSION

The sugar receptor of the fly is extremely variable in its response to different carbohydrates. The present study has extended considerably the number of sugars tested and has extended information available on the sugar–receptor interaction. It would appear that there is a D-glucopyranoside receptor site as has previously been proposed[5] and that while positions C-2, C-3 and C-4 of the pyranose ring are most effective when there are equatorial hydroxyls, an axial hydroxyl is favored at C-1. A methyl substituent on the axial C-1 hydroxyl as in methyl α-D-glucopyranoside may even enhance activity. In contrast to behavioral observations[3,5], methyl β-D-glucopyranoside is active, but at a much reduced level. The equatorial methyl group may represent a steric effect, since β-D-glucopyranose, freshly dissolved and tested prior to significant expected mutarotation was as effective as the equilibrium mixture. As has been observed in behavioral experiments[5], an hydroxyl group on the C-1 position (1,5-anhydro-D-glucitol) was not required for activity. *Scyllo*-inositol, which resembles β-D-glucopyranose in that it has an equatorial hydroxyl corresponding to the C-1 hydroxyl group of β-D-pyranose, is completely ineffective at the highest concentration permitted by its limited solubility (0.2 *M*), while *myo*-inositol, corresponding to the α-anomer, was effective. These results are taken to indicate that the effectiveness of a sugar is blocked by the presence of an equatorial hydroxyl rather than the absence of an axial hydroxyl at C-1. Sucrose, an effective sugar, may be considered a C-1 substituted α-D-glucopyranoside.

Absence or *O*-methylation of the hydroxyl at C-2 changed the effectiveness of

TABLE I

MAXIMUM RECEPTOR ACTIVITY OF SINGLE LABELLAR HAIRS EVOKED BY THE STIMULATION WITH VARIOUS SUGARS

| *Compound* | *Maximum relative effectiveness (to D-glucose)* | *No. of hairs tested electrophysiologically* |
|---|---|---|
| D-Glucose (equilibrium mixture) | 1.00 | 462 |
| Methyl α-D-glucopyranoside | 1.10 | 15 |
| Sucrose (β-D-fructofuranosyl-D-glucopyranoside) | 1.43 | 18 |
| *Myo*-inositol (0.7 *M*)* | 0.50 | 19 |
| Methyl β-D-glucopyranoside | 0.30 | 21 |
| 1,5-Anhydro-D-glucitol | 0.90 | 17 |
| *Scyllo*-inositol (0.2 *M*)* | 0 | 13 |
| Methyl α-D-mannopyranoside (0.6 *M*)* | 0 | 18 |
| L-*Chiro*-inositol | 0 | 27 |
| *Muco*-inositol | 0 | 16 |
| 2-Deoxy-D-*arabino*-hexopyranose | 0.23 | 14 |
| (+)-Quercitol (1L-1,3,4/2,5-cyclohexane pentol) | 0 | 13 |
| 2-*O*-Methyl-D-glucose | 0.53 | 18 |
| Methyl 2-amino-2-deoxy-α-D-glucopyranoside | 0.63 | 17 |
| Methyl 2-acetamido-2-deoxy-α-D-glucopyranoside | 0 | 12 |
| D-Allose | 0.33 | 14 |
| Methyl α-D-allopyranoside | 0.17 | 18 |
| Methyl β-D-allopyranoside | 0 | 14 |
| *Epi*-inositol | 0 | 13 |
| 3-Deoxy-D-*ribo*-hexopyranose | 0 | 21 |
| 3-*O*-Methyl-D-glucose | 0.17 | 16 |
| Methyl α-D-galactopyranoside | 0 | 10 |
| *Allo*-inositol | 0 | 12 |
| 4-*O*-Methyl-D-glucose | 0 | 16 |
| L-Glucose | 0.70 | 15 |
| Methyl α-L-sorbopyranoside | 0 | 16 |
| Methyl α-L-glucopyranoside | 0 | 18 |
| Methyl β-L-glucopyranoside | 0 | 12 |
| Methyl α-D-xylopyranoside | 0.50 | 15 |
| 6-Deoxy-D-glucose | 0.50 | 13 |
| 6-*O*-Methyl-D-glucose | 0.73 | 11 |
| D-*Chiro*-inositol | 0.17 | 14 |
| α-D-thioglucopyranose | 0.77 | 15 |
| D-Fructose | 0.77 | 458 |
| Methyl β-D-fructopyranoside | 0 | 24 |
| Methyl α-D-fructopyranoside | 0 | 17 |
| Methyl α-D-fructofuranoside | 0 | 15 |
| Methyl β-D-fructofuranoside | 0 | 19 |
| 3-*O*-Methyl-D-fructose | 0 | 13 |

* Maximum concentration tested; in all others the maximum concentration was 1 *M*.

tested compounds dramatically. 2-Deoxy-D-*arabino*-hexopyranose (2-deoxy-D-glucose) and 2-*O*-methyl-D-glucose showed similar degrees of reduced effectiveness. (+)-Quercitol (1L-1,3,4/2,5-cyclohexane pentol), which lacks an hydroxyl at the comparable position, was inert. The inactivity of (+)-quercitol might, alternatively, be attributed to the presence of an axial hydroxyl in the position comparable to the ring

oxygen in pyranosides. An axial hydroxyl over the ring position does not however preclude activity. D-*Chiro*-inositol, which corresponds to the α-D-glucopyranose configuration in every other way (axial hydroxyl at C-1, and equatorial hydroxyls at C-2, C-3, C-4 and C-5), does have some slight activity. The absence of an hydroxyl at C-2 may then additionally disfavor receptor activity of (+)-quercitol. Replacement of the C-2 hydroxyl group of α-D-glucopyranose with an amino group (methyl 2-amino-2-deoxy-α-D-glucopyranoside) yielded a relatively effective molecule. However, a bulkier substituent, as in methyl 2-acetamido-2-deoxy-α-D-glucopyranoside, rendered the molecule completely ineffective. The presence of an axial C-2 hydroxyl as in methyl α-D-mannopyranoside also renders the molecule inactive. Additional support for the importance of the equatorial substituent at C-2 is indicated by the ineffectiveness of L-*chiro*-inositol and *muco*-inositol. When the axial hydroxyl at C-2 of L-*chiro*-inositol and the C-2 of *muco*-inositol is superimposed over the C-1 of α-D-glucopyranose, they both may be considered to have axial hydroxyls at the C-2 position of the α-D-glucopyranose.

A requirement for a C-3 equatorial is inferred from the ineffectiveness of 3-deoxy-D-glucose (3-deoxy-D-*ribo*-hexopyranose). *O*-Methylation of the equatorial hydroxyl at C-3 also results in an inactive compound. D-Allose, having an axial hydroxyl at C-3 is much less effective than D-glucose while methyl α-D-allopyranoside is even less effective than D-allose but somewhat more active than methyl β-D-allopyranoside. These findings support the view that even with an unfavored configuration about C-3 the axial hydroxyl at C-1 contributes to receptor activation. It should be noted that *epi*-inositol which may be compared to methyl α-D-allopyranoside as *myo*-inositol is analogous to methyl α-D-glucopyranoside is inactive: further evidence for a rather stringent requirement for an equatorial hydroxyl at C-3.

Although the 4-deoxy-D-glucose derivative was not available, we found 4-*O*-methyl-D-glucose to be inactive. Methyl α-D-galactopyranoside, which resembles the corresponding glucoside except for an axial hydroxyl at C-4, was also inactive. *Allo*-inositol may have been less active than D-*chiro*-inositol for the same reason.

Methyl α-L-sorbopyranoside resembles 1,5-anhydro-D-glucitol with the exception that it possesses, in addition, an axial $OCH_3$ group at C-2, corresponding to C-5 of α-D-glucopyranose. It was ineffective in stimulating the receptor. *Epi*-inositol may be considered as an analog of *myo*-inositol which has an axial hydroxyl at position C-3 or C-5 of α-D-glucopyranose, depending on its manner of superposition. It was also ineffective.

The substituent requirement at C-6 appears to be less stringent. Substitution of the C-6 hydroxymethyl group by hydrogen (methyl α-D-xylopyranoside) or by a methyl group (6-deoxy-D-glucose) produced only a 50% loss in activity, and the presence of a methoxymethyl (6-*O*-methyl-D-glucose) group gave 73% of that obtained with D-glucose.

An estimate of the significance of the ring oxygen can be made by using cyclitol derivatives. *Myo*-inositol, which resembles α-D-glucopyranose more closely than does any other cyclitol, gave the highest activity of cyclitols tested. When D-*chiro*-inositol is superimposed over α-D-glucopyranose with the axial C-2 hydroxyl

at C-1 of α-glucopyranose, it has an axial hydroxyl in a position superimposable on the ring oxygen, and is somewhat less effective. The reduced effectiveness of α-D-thioglucopyranose is perhaps attributable to the replacement of the oxygen by a sulfur atom.

The experiments with L-glucose and its methyl pyranosides was of some interest since these sugars have not previously been tested with the insect receptor. The positive response with L-glucose was somewhat surprising since it, in all likelihood, occurs in the IC conformation in contrast to most D-sugars[22]. However, it has previously been shown that *Phormia regina* responds to the L-sugars, L-fucose and L-xylose[10]. Caspary and Crane[2] have pointed out that the IC and CI chair forms may be superimposable; D- and L-glucose differ only in the interchange of two substituents—thus the equatorial hydroxymethyl group at the C-6 position of L-glucose may be superimposed with the C-1 hydroxyl group of D-glucose (in the β-anomeric form) while the β-L-anomeric carbon is superimposed over the C-6 hydroxymethyl group of D-glucose. We are still unable to account for the inactivity of methyl β-L-glucopyranoside.

The present study has then extended our knowledge of substances that activate the sugar receptor. We have confirmed and extended the previous conclusion[5] that equatorial hydroxyls at C-3 and C-4 of D-glucose are required for it to be stimulatory. Considering differences in species tested and in methods used, *i.e.* behavioral *versus* electrophysiological, there is surprising agreement. How many different sugar receptor sites are present in a single cell remains unknown. In some instances, kinetics closely resembling that for the enzyme–substrate complex can be derived from a concentration curve[1]. On the other hand, deviations from the idealized case are notable and many explanations have been put forward to account for these results including allosteric mechanisms[19] and the presence of two receptor sites for the same compound[19,20]. Of particular biological interest is the reception of sucrose. Behaviorally, this molecule appears a magnitude more detectable than glucose[5], while it is less than twice as effective electrophysiologically. Our study would suggest that the α-D-glucopyranosyl moiety is responsible for its efficacy. To examine whether the β-D-fructofuranosyl moiety of sucrose also participates at this receptor site, its 4 methyl glycosides were tested but were found to be inactive. In fact, both the α- and β-anomers of D-fructofuranoside and D-fructopyranoside were inactive whereas free D-fructose is stimulatory. These results do not explain the higher activity of sucrose compared to α-methyl glucoside. The possibility that the β-D-fructofuranoside is acting allosterically would appear to be ruled out by an experiment in which the latter was added together with α-D-glucose. It did not enhance the response, and was in fact found to be slightly inhibitory. Since methyl α-D-glucopyranoside is more effective than free D-glucose or 1,5-anhydro-D-glucitol, a bulky group in the C-1 axial position appears to enhance receptor activity. Perhaps the bulky fructofuranoside substituent is bound still more effectively. D-Mannose is known to inhibit the fructose response[19,20] but not that of sucrose[20] (or very little[19]), suggesting further the existence of at least two different receptor sites, one for glucose and one for fructose. More direct evidence comes from the activity of free fructose. Since in solution the β-pyranose form pre-

dominates[9], the data suggest that methyl β-D-fructofuranoside is inactive because of the glycosidic *O*-methyl group at C-2. The possibility that sucrose is hydrolyzed at the receptor site cannot be ruled out. Turanose (3-*O*-D-glucopyranosyl-D-fructose) has been reported to stimulate the sugar receptor[3,20]. Yet, substitution of the C-3 hydroxyl group of D-fructose by a methoxy group completely inactivates the sugar; hence the α-D-glucopyranosyl moiety rather than the 3-substituted D-fructopyranose in turanose is likely responsible for its activity.

The use of cyclitols proved useful in verifying the positional specificities. The results with the sugar receptor of the fly are in contrast to those seen with the inositol receptor of the silkworm larva. Most strikingly, the inositol receptor is sensitive to much lower concentrations of *myo*-inositol than the fly sugar receptor (it is saturated at about 0.01 *M*, and responds to 0.0001 *M*)[15] and is relatively insensitive to sugars[13]. The silkworm inositol receptor responds only to *myo*-inositol and *epi*-inositol; the fly is insensitive to *epi*-inositol and to a small degree, to D-*chiro*-inositol. It is apparent that the sugar detector responds only to those cyclitols closely resembling the α-D-glucopyranoside structure.

SUMMARY

Various carbohydrates were tested for stimulating activity of the sweet receptor of *Sarcophaga bullata*. Efficacy appears to be highest in D-pyranosides having equatorial substituents at C-2, C-3, C-4 and C-5, with the exception of the C-1 position where equatorial substituents detract. Similarly, *myo*-inositol, having 5 equatorial and 1 axial hydroxyl, is the most stimulatory of the cyclitols tested. The anomalous action of several compounds remains unexplained. L-Glucose is stimulatory, while its α- and β-pyranosides are not. Similarly, free fructose, an extremely potent sugar, is completely inactive as its α- or β-furanoside or its α- or β-pyranoside. This finding is discussed in relation to the stimulatory action of sucrose.

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