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2-Deoxy-D-Glucose Induced Hypothermia: Thermoregulatory Pathways in the Rat /

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Abstract

2-deoxy-D-glucose (2-DG) elicits significant and prolonged hypothermia in a variety of animals when administered either peripherally or centrally. From our current studies it would appear that in high concentrations (250 mg/kg, i.p. or more) 2-DG can act directly on peripheral tissues in the rat by competitively interfering with glucose metabolism and consequently with normal heat producing mechanisms. When a low icrograms concentration of 2-DG (20 µg) is injected centrally, the ensuing glucopenia results in vagal stimulation and subsequent diminuition of peripheral heat production. This is based on studies with atropine which demonstrated a total inhibition of the usual depression in body temperature following the administration of 2-DG into the ventral premammillary nucleus (PMV), a site normally extremely sensitive to this analogue of glucose. Additionally, from studies with PMV-lesioned rats, it was concluded that an intact nucleus is necessary for normal thermoregulation during exposure to either hot or cold environments.

Key Words: hypothermia, 2-deoxy-D-glucose, ventral premammillary nucleus,

thermoregulation



Introduction

In prior publications (5,13,16) we have demonstrated that the administration of 2-deoxy-D-glucose (2-DG) either peripherally or centrally lowers body temperature in both mice and rats. This was evidenced by a precipitous decrease in whole body oxygen consumption, which resulted from 2-DG competitively inhibiting the utilization of glucose. Additionally, while the injection of 2-DG into specific sites of both the anterior and posterior hypothalamus evoked a marked hypothermic response, the ventral premammillary nucleus (PMV) was by far the most sensitive of the areas tested eliciting not only a rapid and marked decrease in core temperature, but also a dosedependent response.

The objective of this paper was to determine whether intraperitoneal (i.p.) administered 2-DG lowered body temperature by directly interfering with peripheral glucose metabolism and consequently, with heat production, by acting indirectly on effector organs via glucose-dependent hypothalamic control centers, or by a combination of both mechanisms. In addition, we wished to characterize further the role of the PMV in the control of basal heat production, and to elucidate the pathway from this area to the thermogenic organs in the periphery.

Materials and Methods

Male albino rats of the Sprague-Dawley strain (Charles River Breeding Laboratories, Wilmington, MA), weighing between 350-450 g, were used in this investigation. The animals were individually housed in a temperature controlled room maintained at 23 ± 1°C, and food and water were freely available. Bilateral vagotomies and sympathectomies were performed cervically, and adrenalectomies were done by the method of Grollman (6) as modified by Shiraishi (14). Lesions were stereotaxically (17) made in the ventral premammillary nucleus (PMV) using stainless steel electrodes (30 ga.) with an applied current of 2.0 mA for 10 seconds. Hypothalamic deafferentations were performed by the method of Halasz and Pupp (7), but with a slightly larger knife (Fig. 1). After the various surgical procedures, the animals were permitted to recover for at least one week at 25°C prior to experimentation at 23°C. Microinjection techniques for the administration of 2-DG and monitoring of core temperature (Tre) have been previously reported (16), as was the colorimetric analysis of plasma 2-DG and the enzymatic determination of plasma glucose (13).

Results

In Fig. 2 is plotted the mean change in body temperature ± S.E. after i.p. injection of 2-DG to intact, bilaterally vagotomized, sympathectomized or adrenalectomized rats. The animals were challenged only once with the drug, and the group size varied from 25 to 34. Only 20% of the vagotomized animals survived post-operatively, and were challenged with 2-DG 3 days after surgery. The other rats were used no sooner than 1 week after surgery. The response of the intact rats to 250 mg/kg of 2-DG (left panel), and 375 mg/kg (right panel) is similar to what we have previously observed and reported (16), i.e. with the smaller dose T decreases approximately 1°C and is still significantly depressed below basal values after 5 hours, while with the larger dose T decreases precipitously, attains a madir of approximately 1.8°C after an hour, and is still approximately 1°C below control values at the end of the 5-hour observation period. The action of 2-DG on T is suppressed when administered to vagotomized rats, since T decreases by only one half as much as the intact animals; in addition, maximum T depression was less than 1°C with both doses of 2-DG. In contrast, adrenalectomy potentiated the hypothermic response to 2-DG at both doses, since a maximum decrease of 2°C was noted with 250 mg/kg after one hour, and a madir of 3.4°C two hours after the higher dose.

In sympathectomized animals, 250 mg/kg of 2-DG elicited a greater depression in T_{re} (1.2°C) than the intact animals, while at the higher dose the nadirs were approximately the same (2.0 vs 1.8°C).

In Fig. 3 are depicted the mean changes in plasma 2-DG and glucose following the i.p. injection of 375 mg/kg of 2-DG to other groups of intact, bilaterally vagotomized, sympathectomized, or adrenalectomized rats. The patterns noted for changes in 2-DG and glucose in the intact rat are similar to what has been observed by other investigators, i.e. plasma 2-DG rises and falls rapidly and is essentially back to control levels within 2.5 hours after administration. For the intact animals plasma levels attain approximately 38 mg/100 ml at the 10 minute sampling time and 26 mg/100 ml at 30 minutes. The latter level is comparable to that noted in the vagotomized animals (22 mg/100 ml), sympathectomized (18 mg/100 ml), and adrenalectomized (22 mg/100 ml) animals at 30 min.

In contrast, plasma glucose concentrations after 2-DG administration differed in the surgically treated groups. For the intact animals circulating glucose peaks at approximately 380 mg/100 ml after one hour and levels off at 250 mg/100 ml for the last 1.5 hours of the experiment. The pattern for the sympathectomized animals is similar except they peak at approximately 1.5 hours. The vagotomized animals start at a higher level than the intact rats (220 mg/100 ml vs. 157 mg/100 ml),

and peak at 90 minutes with a plasma level of 332 mg/100 ml. On the other hand, as expected, the adrenalectomized animals display only a minimal increment in plasma glucose at 30 to 60 minutes, with an increase from 132 to 176 mg/100 ml.

As previously described, surgical vagotomy attenuated the T depression after i.p. injection of 2-DG (Fig. 2). However, interpretation of data after this treatment is speculative at best, since the lethality of the surgical procedure is high. Accordingly chemical vagotomy with atropine was used to further delineate the central and peripheral effects of 2-DG on heat production. In Fig. 4 are the results of experiments with atropine (1 mg/kg, i.p.) plus 2-DG (375 mg/kg, i.p.) administered to a group of intact rats, and the data obtained for groups of controls. Note that saline alone and atropine plus saline minimally reduced T (upper 2 curves), while 2-DG alone and atropine plus 2-DG both elicited an intense hypothermia (lower 2 curves). However, while with 2-DG alone the Tre remained about 1°C below baseline values at the end of the 5 hour observation period, the atropine plus 2-DG treated animals displayed T values approaching basal levels. Thus, not surprisingly, the areas under these curves for the last 2 1/2 hours are significantly different from one another (p<.02).

In Fig. 5 are the mean changes in rectal temperature following i.p. administration of saline and 375 mg/kg of 2-DG to rats 3 weeks after bilateral lesions in the PMV nucleus. While the nadir is not as

sharp as for intact rats, the overall response is not significantly different from what is usually noted with intact animals. In Fig. 6 are photographs of histological sections after Nissl staining of these lesioned animals.

In Fig. 7 are the mean changes in core temperature after i.p. injection of saline, 250 mg/kg of 2-DG, and 375 mg/kg of 2-DG to rats 28 days post hypothalamic deafferentation. Note that generally the patterns noted are similar to what had been previously observed for intact animals; however, the response to the lower dose seems to be slightly facilitated.

In Fig. 8 are plotted the mean changes in rectal temperature for hypothalamic deafferentated and intact rats after the microinjection of 20 μ g/2 μ L of 2-DG into the PMV nucleus. Note, that for the intact animals a nadir of about 1.5° C was attained after 1 hour and a return to baseline values after 4 hours, which is similar to what we have previously reported (16); however, the deafferentated animals displayed no hypothermic response.

In Fig. 9 are the mean changes in body temperature of intact rats and chemically vagotomized rats administered 5 μ g i.v. of atropine immediately prior to the microinjection of 20 μ g/2 μ L of 2-DG into the PMV nucleus. This dose and route of administration for atropine had been used previously, and was effective in blocking gastric acid secretion

following microinjection of 2-DG into the hypothalamus (15). Note again the abolition of the T_{re} depression usually noted for the intact animal. Thus, treatments which only had a partial effect on i.p. 2-DG, completely negated the effects of microinjection of 2-DG in the PMV.

To determine whether PMV-lesioned and hypothalamic deafferentated rats displayed the normal diurnal cyclicity in body temperature, groups of these and intact animals were monitored for core temperature for 72 hours while maintained at an environmental temperature of $21 \pm 0.5^{\circ}$ C (Fig. 10). There are no significant differences among these groups, and all of them display an approximate 1° increase in T_{re} AM to PM.

In Figs. 11, 12 and 13 are plotted, for the same group of animals, the T_{re} levels \pm S.E. of intact, PMV-lesioned and hypothalamic deafferentated rats when exposed to a hot $(35.5 \pm 0.2^{\circ}C)$ and a cold $(5 \pm 0.5^{\circ}C$ and $10 \pm 0.5^{\circ}C)$ environment. After 2 hours at $35.5^{\circ}C$ the core temperature of all three groups of animals rose about $1^{\circ}C$ or more; thereafter, the intact animals maintained their T_{re} while the PMVlesioned and deafferentated rats continued to increase (Fig. 11). Thus, after 3 hours these groups were approximately $0.7^{\circ}C$ higher than the intact animals, and $1.6^{\circ}C$ after 4 hours (p<.001). After one hour at $25.0^{\circ}C$ all the animals returned to baseline values, and after 2 hours were below their initial levels.

When exposed to 5° C, the intact animals increased their T_{re} to approximately 38° C and remained at this level for the entire 6 hours of cold exposure (Fig. 12). The lesioned and deafferentated animals were unable to increase their body heat stores, and in fact the temperature differences between the groups steadily grew larger with time. Thus, after 5 hours the T_{re} difference was 1° C (p<.001), after 6 hours the deafferentated group differed from the intact animals by 1.5° C and the lesioned rats by 1.8° C (p<.001).

The T_{re} differences between these groups was not as great when these animals were exposed for 6 hours to an environmental temperature of $10^{\circ}C$ (Fig. 13); however, the pattern was distinctly similar. The lesioned animals were $0.8^{\circ}C$ lower than the intact group after both 5 and 6 hours of their cold exposure (p<.001), while the deafferentated animals were $0.6^{\circ}C$ and $0.9^{\circ}C$ lower at the same time intervals (p<.001).

Discussion

2-deoxy-D-glucose elicits in rats significant and prolonged hypothermia when injected into either selected intrahypothalamic sites or intraperitoneally. From our current investigations, it would appear that the injection of micro-quantities of 2-DG into the PMV results in a neuronal discharge via parasympathetic pathways, and thus diminishes heat production. These postulates are based primarily on our studies with atropine (Fig. 9) which demonstrated a total inhibition of

the usual depression in body temperature following the administration of 2-DG into the PMV, a site normally extremely sensitive to this analogue to glucose. One might speculate that the mechanism of action of 2-DG centrally is related to an inhibition of glucose metabolism in the PMV, resulting in vagal stimulation and subsequent diminuition of heat production in the periphery. The involvement of vagal pathways in this phenomenon is not surprising, considering their well-known role in the stimulation of gastric acid secretion in the rat following the administration of 2-DG into the hypothalamus (11,14,15). Additionally, Ball (1) has reported that eating and self stimulation produced in rats by lateral hypothalamic stimulation are markedly inhibited by subdiaphragmatic vagotomy. In addition, in high concentrations (250 mg/kg i.p. or more) 2-DG can act directly on peripheral tissue interfering with glucose metabolism and normal heat producing mechanisms. Accordingly, we observed hypothermic responses after the i.p. administration of 2-DG in chemically vagotomized, PMV-lesioned, or deafferentated animals (Fig. 4,5,7).

In 1913 Myer (12) postulated the presence of interconnecting and reciprocal thermoregulatory centers in the hypothalamus. One site in the supraoptic and anterior hypothalamic region was principally concerned with heat loss, but also was capable of exerting an inhibitory influence upon the center for heat production. The other center was in the posterior hypothalamus and was concerned with heat production, but

whose ablation had no influence upon the animal's ability to thermoregulate in the heat. Through the years many investigators have confirmed this theory, and their work has been described and summarized in several recent reviews (2,8,9,10). More recently, Chowers et al. (3) have reported on the effect of hypothalamic disconnection on temperature regulation and pituitary-adrenal activity during exposure to cold. At 0°C none of their animals, initially, were able to maintain their body temperature, however, the anterior or posterior disconnected rats were able to compensate better for heat loss than the intact rats or those with complete or posterolateral disconnection. They suggested that the major stimulus for ACTH release after cold exposure depend on neural input through the posterior hypothalamus. It should be noted that in our investigations the deafferentated and PMV-lesioned rats were exposed to 5 and 10.5°C, an environmental temperature that did not evoke discernable shivering in our animals. As a consequence of their altered state, efferent impulses to the periphery for increased metabolic activity and its resultant heat production were interrupted; however, they did display the normal diurnal cyclicity in core temperature. Similarly, the inability of the deafferentated animals to thermoregulate in the heat (35.5°C) as did the intact rats, is readily understandable, since the total thermoregulatory center is separated; however, the parallel hyperthermia exhibited by the PMV-lesioned animals cannot be interpreted as simplistically, and one must assume that integrated thermoregulatory signals from the hypothalamus require that this small area be intact.

In conclusion, our studies indicate that the resultant hypothermia of 2-DG administration is initiated centrally, probably the result of a glucopenia in the ventral premammillary nucleus. Efferent signals are transmitted via the vagi to effector organs in the periphery, inhibiting heat producing reactions which probably also require metabolizable carbohydrate. Recently, however, Fiorentini and Muller (4) have reported that 2-DG induced hyperglycemia and hypothermia can be prevented by the presence of substrate which can support high metabolic rates e.g. D-fructose, fumarate, or glutamate. It should be noted that no definitive work has, to date, identified all the exothermic reactions that are involved in basal heat production, and which contribute to core temperature. These chemical reactions may be different or the same as those that are operative during acute cold exposure, or after the establishment of non-shivering thermogenesis in certain animals. Other studies should be focused on the simpler question regarding which peripheral site(s) decrease its basal heat production as a consequence of central glucopenia.

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Figure Legend

<u>Fig. 1</u>. In the left panel 'A' is a schematic sagittal section drawing of a complete deafferentation of the hypothalamus. The dotted line indicates the cut, while drawing 'B' is a schematic illustration of the knife used for this procedure.

'C' is an enlarged drawing of the area inside the cut. Abbreviations -OC: optic chiasma, NAH: anterior hypothalamic nucleus, SC: suprachiasmatic nucleus, PV: paraventricular nucleus, VM: ventromedial nucleus, ARC: arcuate nucleus, MM: medial mammillary nucleus.

'D' is a coronal section indicating the cut, while 'E' is a histological section with the arrows pointing to the separated hypothalamic area.

Fig. 2. Change in rectal temperature after i.p. administration of 250, or 375 mg/kg of 2-DG to intact, bilaterally vagotomized, sympathectomized, or adrenalectomized rats. Each point represents the mean ± S.E. of 25 to 34 animals.

Fig. 3. Plasma 2-DG and glucose levels following i.p. injection of 375 mg/ kg of 2-DG to intact, vagotomized, sympathectomized or adrenalectomized rats. Each point represents the mean \pm S.E. of 12 intact rats, while for the other animals n=7.

Fig. 4. Mean change in rectal temperature \pm S.E. of intact rats following the i.p. injection of saline (n=5), atropine (1 mg/kg) plus saline (n=5), 375 mg/kg of 2-DG (n=6), and atropine (1 mg/kg) given 30 minutes prior to 375 mg/kg of 2-DG (n=10).

<u>Fig. 5</u>. Mean change \pm S.E. in rectal temperature following i.p. administration of 375 mg/kg of 2-DG (n=6) and saline (n=6) to rats 21 days after lesions were placed in the ventral premammillary nucleus.

Fig. 6. Macro-, and microphotographs of bilateral lesions in the ventral premammillary nucleus. Nissl staining was used to discern the tracks of electrodes and the lesions. Magnifications: A: x 11, B: x 13, C: x 9, D: x 15, E: x 14 and F: x 35.

Fig. 7. Mean change \pm S.E. in rectal temperature after i.p. injection of 2-DG: 250 mg/kg (n=7), 375 mg/kg (n=6), or saline (n=6) to rate 28 days after hypothalamic deafferentation.

Fig. 8. Change in rectal temperatures after the microinjection of 2-DG (20 μ g/2 μ L) into the ventral premammillary nucleus of intact (n=9) and hypothalamic deafferentated (n=5) rats. Each point represents mean ± S.E.

Fig. 9. Effects of microinjection of 2-DG (20 μ g/2 μ l) into the ventral premammillary nucleus on body temperature after chemical vagotomy with 5 μ g atropine, i.v. (n=5) as compared to intact rats (n=9). Each point represents mean ± S.E.

Fig. 10. Rectal temperature levels in intact (n=11), ventral premammillarylesioned (n=14), and hypothalamic deafferentated (n=13) rats maintained at an environmental temperature of $21 \pm 0.5^{\circ}$ C for 72 hours. Each point is the mean \pm S.E. <u>Fig. 11</u>. Effect of hot environment $(35.5 \pm 0.2^{\circ}C)$ on the rectal temperature of intact (n=11), ventral premammillary-lesioned (n=14), and hypothalamic deafferentated (n=13) rats. Each point represents mean \pm S.E.

Fig. 12. Effect of cold environment (5 \pm 0.5°C) on the rectal temperature of intact (n=11), ventral premammillary-lesioned (n=14), and hypothalamic deafferentated (n=13) rats. Each point is mean \pm S.E.

Fig. 13. Effect of cold environment (10 \pm 0.5°C) on the rectal temperature of intact (n=11), ventral premammillary-lesioned (n=14), and hypothalamic deafferentated (n=13) rats. Each point is mean \pm S.E.

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stimulation and subsequent diminuition of peripheral heat production. This is based on studies with atropine which demonstrated a total inhibition of the usual depression in body temperature following the administration of 2-DG into the ventral premammillary nucleus (PMV), a site normally extremely sensitive to this analogue of glucose. Additionally, from studies with PMVlesioned rats, it was concluded that an intact nucleus is necessary for normal thermoregulation during exposure to either hot or cold environments.

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