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Bernard Jeanrenaud
Minkowski Award, 1970, Warsaw

Bernard Jeanrenaud was born in La Chaux-de-Fonds (Canton of Neuchâtel), Switzerland. He studied medicine at the Neuchâtel and Geneva Universities, Switzerland. Immediately after his M.D. degree, he went to the USA. He was successively Intern at the Mount Auburn Hospital, Cambridge, Mass., USA; Assistant in Medicine at the Peter Bent Brigham Hospital and Research Fellow in Medicine at Harvard Medical School, Boston, Mass.; Guest Investigator and Assistant Physician at the Rockefeller University, New York, N.Y.

He returned to Switzerland in 1960, to be Assistant in Medicine at the "Clinique Universitaire de Thérapeutigue" , Geneva University Hospital, then Instructor at the "Institut de Biochimie Clinique", Geneva University.

He has long been interested in pathophysiological problems, metabolism, endocrinology, and neuroendocrinology. At one point during his career he had to decide between clinical medicine or fundamental research and he chose the latter. He became, in 1970, Professor at the University of Geneva Faculty of Medicine and Head of the "Laboratories de Recherches Métaboliques". His collaborative research deals with experimental endocrinology, experimental diabetes in animals (Type 1 and Type 2 diabetes). He and his colleagues have published about 320 articles in various reputable journals.

Bernard Jeanrenaud has always been interested in the practical therapeutic relevance of the experimental work carried out by his team, therefore he has been keen to establish and maintain a relationship with the Industry. The work of his laboratory has been supported by several Foundations, the "Départment de I' Instruction publique of the State of Geneva"; the Swiss National Research Council and by grants-in-aid from, principally, Nestlé S.A. (Switzerland); Eli Lilly and Company, Indianapolis, Ind., (USA); the "Institut de Recherches Internationales Servier, I.R.I.S,, , Paris, (France); the Foundation Ernst et Lucie Schmidheiny, Geneva (Switzerland); the "Commission pour l'encouragement de la recherche scientifique", Berne (Switzerland); and the Foundation Lord Michelham of Hellingly, Geneva, (Switzerland). Bernard Jeanrenaud is an active member of several scientific societies or associations, the European Association for the Study of Diabetes, the European Association for the Study of Obesity, the American Diabetes Association, the European Neuroscience Association, the Endocrine Society, the Biochemical Society, the American Physiological Society, la Société de Neuroendocrinologie expérimentale, to mention but a few. He received the John Claude Kellion Medal of the Australian Diabetes Society (1983) and was Fellow (1983) of the Japanese Society for the Promotion of Science. In 1990 he was awarded the H.E. Wertheimer Prize and Medal by the International Association for the Study of Obesity, of which he became (1990–1994) President.

Central nervous system and peripheral abnormalities: clues to the understanding of obesity and NIDDM

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Summary To study the impact on glucose handling of the observed hyperinsulinaemia and hypercorticism of the genetically obese fa/fa rats, simplified animal models were used. In the first model, normal rats were exposed to hyperinsulinaemia for 4 days and compared to saline-infused controls. At the end of this experimental period, the acute effect of insulin was assessed during euglycaemic-hyperinsulinaemic clamps. White adipose tissue lipogenic activity was much more insulin responsive in the "insulinized" than in the control groups. Conversely muscles from "insulinized" rats became insulin resistant. Such divergent consequences of prior "insulinization" on white adipose tissue and muscle were corroborated by similar divergent changes in glucose transporter (GLUT 4) mRNA and protein levels in these respective tissues. In the second model, normal rats were exposed to stress levels of corticosterone for 2 days. This resulted in an insulin resistance of all muscle types that was due to an increased glucose-fatty acid cycle, without measurable alteration of the GLUT 4 system. In genetically obese (fa/fa) rats, local cerebral glucose utilization was decreased compared to lean controls. This could be the reason for adaptive changes leading to increased levels in their hypothalamic neuropeptide Y levels and median eminence corticotropin-releasing-factor. Thus, in a third model, neuropeptide Y was administered intracerebroventricularly to normal rats for 7 days. This produced hyperinsulinaemia, hypercorticosteronaemia, as well as most of the metabolic changes observed in the genetically obese fa/fa rats, including muscle insulin resistance. These data together suggest that the aetiology of obesity-insulin resistance of genetically obese rodents has to be searched within the brain, not peripherally. [Diabetologia (1994) 37 [Suppl 2]: S169–S178]

Key words Hyperinsulinaemia, hypercorticosteronaemia, glucose and lipid handling, Neuropeptide Y, corticotropin-releasing factor, autonomic nervous system, insulin resistance, lipogenesis, local cerebral glucose utilization.

The concept that obesity syndromes in animals, at least in some, are due to central nervous system abnormalities, originates from the observation that lesions of the ventromedial hypothalamic area (VMH) in normal rats produce hormonal and metabolic disorders that are similar to those observed in genetically obese rodents [1–34]. From this research, summarized inTable 1, it was concluded for both animal models of obesity (i.e. hypothalamic obesity obtained by lesion of the VMH or genetic obesity), that the main initial defect(s) appeared to be an abnormal central nervous system regulation of the autonomic nervous system. It was striking to observe, in particular, that hyperinsulinaemia both in genetically preobese rats or in acutely VMH-lesioned rats occurred early and was a vagus-nerve mediated process [3, 7, 14–16, 20]. During the course of many studies carried out in the genetically obese (fa/fa) rat, hyperinsulinaemia was thought, albeit indirectly, to play a role in several of the abnormalities observed. Thus, the impact of hyperinsulinaemia on some of these alterations was investigated, using a simplified animal model [35].

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Abbreviations: VMH, Ventromedial hypothalamic area; GLUT 4, insulin responsive glucose transporter; HPA, hypothalamo-pituitary-adrenal; NPY, neuropeptide Y; CRF, corticotropin-releasing factor; i.c.v., intracerebro-ventricularly.

Hyperinsulinaemia imposed on normal rats

To mimick a state of hyperinsulinaemia, awake normal rats were infused with insulin for 4 days via minipumps ("insulinization"), and compared to saline-infused rats. Euglycaemia of the "insulinized" animals was maintained by a superimposed infusion of glucose [35]. The in vivo glucose uptake by individual tissues was then measured during euglycaemic-hyperinsulinaemic clamps [36] using the 2-deoxy-[1-^{3}H]-D-glucose technique [37]. The rat was killed and the parametrial white adipose tissue and different muscles (e.g. the tibialis) were removed and their content in 2-deoxy-[1-^{3}H]-glucose 6-phosphate (an in-

Table 1. Main disorders common to hypothalamic lesioned rats and genetically obese (fa/fa) rats

1. Increase food intake (not always)
2. Hyperinsulinaemia-hyperglucagonaemia of early onset and vagus nerve mediated (present even in the absence of hyperphagia)
3. Decreased energy dissipation as heat of early onset and mediated by decreased sympathetic efferent(s)
4. For adipose tissue glucose uptake and lipogenesis therefrom: evolution from a state of initial insulin over-responsiveness to a later phase of insulin resistance. Insulin resistance usually does not bear on the adipose tissue lipoprotein lipase-mediated process responsible for circulating triglyceride uptake. This process remains insulin over-responsive
5. For muscles: evolution from a transient state of insulin over-responsiveness to a state of insulin resistance
6. For hepatic glucose production: evolution from a state of normal insulin responsiveness to a state of insulin resistance
7. Overactive liver and adipose tissue lipogenic activities that do not frequently become insulin resistant
8. Defects no. 1, 2, 3, 4, 7 are responsible for the occurrence of obesity
9. Defects no. 5 and 6 are responsible for a glucose intolerance of varying degree, initially associated with hyperinsulinaemia
10. Endocrine pancreas secretory failure with relative or absolute decrease in insulin output, long-term kidney and ocular complications, thus evolution toward NIDDM

Based on [1–34, 57]

dex of glucose uptake and phosphorylation) was determined. The mean steady-state insulinaemia values achieved during the clamps were about 1000 μU/ml for both controls and "insulinized"rats [35, 38] These values of insulinaemia enabled the study of tissue responsiveness (i.e. maximal response) to the hormone. Other rats were killed at the end of the same treatments (saline-infused control vs "insulinized", rats) and the parametrial white adipose tissue and the tibialis were removed for measurements of insulin responsive glucose transporter (GLUT 4) mRNA and GLUT 4 protein levels. Arbitrary units refer to optical density ratio of GLUT 4 mRNA over actin mRNA. Immunodetection and quantification of glucose transporters were carried out with a monoclonal GLUT 4 antibody [35, 38–40].

In additional experiments, lipid synthesis was studied in saline-infused control or "insulinized" rats, again during euglycaemic-hyperinsulinaemic clamps, via the incorporation of ^3H, from ^3H_2O given as a bolus, into lipids of white adipose tissue and liver [35, 38].

As can be seen by Figure 1, the glucose utilization index of white adipose tissue (i.e. the acute tissue responsiveness of this process to insulin) was much higher in rats previously "insulinized" for 4 days than in saline-infused controls. This was accompanied by an increase (in the "insulinized" group relative to controls) in the abundance of mRNA coding for the insulin-responsive glucose transporter GLUT 4 and by an increase in the amount of GLUT 4 protein, as further depicted by Figure 1 [35, 40].

In marked contrast, the insulin-stimulated glucose utilization index (2-deoxy-D-glucose uptake) of five muscles of different fibre composition, that of tibialis for example, was much lower in the "insulinized" group than in controls. This was accompanied by a decrease in the abundance of tibialis GLUT 4 mRNA and GLUT 4 protein levels (Fig. 1) [35, 38, 40].

As shown by the data in Table 2, it was further observed that the stimulation of lipogenesis produced by insulin during the clamps was higher in the liver from "insulinized" rats than in that from saline-infused controls. Similar results were obtained for white adipose tissue lipogenesis of "insulinized" rats compared to that of saline-infused controls. These observations were in keeping with the increase in body weight and total inguinal fat pad weight of "insulinized" rats compared to controls (Table 2) [35].

Data accrued from such experiments on control and "insulinized" rats show that hyperinsulinaemia per se produces divergent changes in glucose transport and glucose transporter mRNA in white adipose tissue and muscles that are accompanied, although not always for muscles, by analogous changes in the corresponding glucose transporter protein [40]. This also indicates that, by mechanisms yet to be determined, hyperinsulinaemia up-regulates the adipose tissue glucose transport and transporter system, while down-regulating those of muscles. This favours the view that a state of hyperinsulinaemia, even of short duration, can be one of the driving forces responsible for increased white adipose tissue (and liver) metabolic activity, ultimately leading to obesity, together with producing muscle insulin resistance (Fig. 1, Table 2) [35]. A hyperinsulinaemia of 4 days does not, however, bring about insulin resistance of the hepatic glucose production process [35].

The data just summarized may explain why a state of increased insulin responsiveness of some metabolic pathways in certain tissues (i.e. liver and adipose tissue lipogenesis), together with a state of insulin resistance of others (e.g. muscles) often coincide in animal models of hyperinsulinaemia and obesity [6, 22–24, 29].

A feature of genetically obese animals, the obese (fa/fa) rat in particular, is non-detectable hypoglycaemia, despite early and subsequently sustained hyperinsulinaemia [15, 20]. This could be partly attributed to the early occurrence of muscle insulin resistance [29, 33]. In addition, as insulin is a powerful hormone, it was hypothesized that hypoglycaemic effects of hyperinsulinaemia could be prevented by a

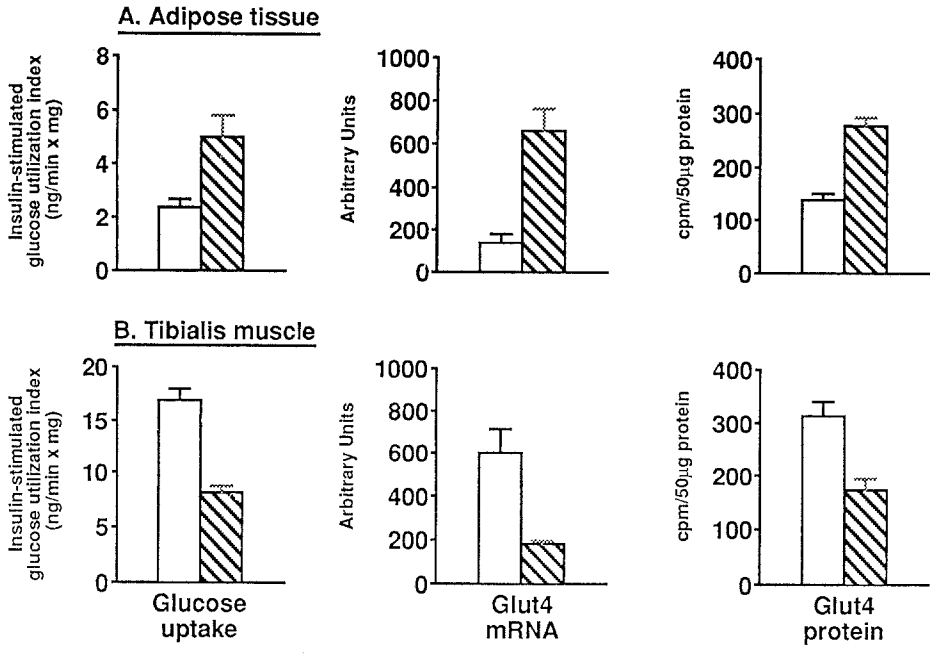

Fig. 1 A, B. Effects of a 4-day insulin-administration (2 U/day) together with a glucose infusion to maintain euglycaemia in normal rats („insulinized„ rats) on the acute effect of insulin on glucose uptake by white adipose tissue (**A**) and tibialis (**B**) measured during euglycaemic-hyperinsulinaemic clamps associated with the 2-deoxy-D-glucose technique (left panels). At the end of another 4-day experimental period, the same tissues were removed from another series of animals for measurements of the insulin-responsive GLUT 4 mRNA and protein levels (middle and right panels; saline-infused controls: □; "insulinized" rats: ▨. Mean of 5–6 experiments ± SEM, all differences $p < 0.01$ [35, 38, 40]

prevailing adaptive activation of the hypothalamo-pituitary-adrenal (HPA) axis [41]. Concomitant to these data the HPA was hypothesized to be responsible for muscle insulin resistance.

Indeed, it was found that genetically obese (fa/fa) rats had increased adrenocorticotropic hormone (ACTH) and/or corticosterone output following various forms of stress (e.g. immobilization) [41, 42]; greater 24-h urinary corticosterone output [43], and higher than normal plasma corticosterone levels (accompanying those of insulin) during a meal (unpublished observation). It has been estimated that genetically obese rodents are exposed, on a daily basis, to plasma concentrations of corticosterone at least twice that of their lean littermates [43–45]. Thus, obese animal models have an overactive HPA axis with resulting hypercorticosteronaemia [41–45].

Hypercorticosteronaemia imposed on normal rats

Experiments with a similar paradigm were carried out with corticosterone. This was studied by imposing normal rats for 2 days to stress levels of the hormone by the subcutaneous route. Euglycaemic hyperinsulinaemic clamps and in vivo insulin-stimulated glucose utilization index (using the labelled 2-deoxyglucose method) of individual tissues were then measured as described above with subsequent detection of GLUT-4 mRNA and protein, by Northern and Western blot analysis [46].

Corticosterone administration for 2 days resulted in stress levels of the hormone of about 500–600 ng/ml. Increased plasma non-esterified fatty acid (NEFA) levels were also observed (controls: 0.36 ± 0.5; corticosterone administration: 1.04 ± 0.10, $p < 0.001$). The glucose infusion rate necessary to maintain euglycaemia during the clamp was 50 % lower in corticosterone-administered rats than in controls, predominantly due to decreased insulin-stimulated total glucose utilization and to partial lack of inhibition of hepatic glucose production process.

As illustrated by Figure 2, (red gastrocnemius) insulin-stimulated glucose utilization index was markedly decreased by 2-day corticosterone administration. In fact this occurred in all of the eight muscles studied (mean decrease: 62 ± 6 %) indicating that all muscles became insulin resistant, whatever their fibre composition [46].

Somewhat surprisingly, muscle GLUT 4 mRNA and protein levels were either unchanged or increased by corticosterone administration [46, 47]. Glycogen content was also increased by corticosterone administration in seven out of the eight muscles

Table 2. Effects of imposed hyperinsulinaemia to normal rats ("insulinization") on lipid handling

Groups of rats	Body weight gain (g)	Fat pad weight (g)	De novo lipogenesis	
			Liver	adipose tissue
			(µg-atoms/h · g^{-1})	
Controls	5.2 ± 0.5	1.8 ± 0.5	58.1 ± 4.8	56.2 ± 11.3
"Insulinized"	9.8 ± 1.4[a]	2.8 ± 0.1[a]	89.6 ± 7.7[a]	133.8 ± 27.9[a]

Hyperinsulinaemia was imposed to normal rats via subcutaneously implanted minipumps delivering the hormone for 4 days, while maintaining euglycaemia by a superimposed glucose infusion. Controls were saline-infused. At the end of the 4 experimental days the measurements were made. De novo lipogenesis was assessed by incorporation of ^3H, from ^3H_2O, into long chain fatty acids during euglycaemic-hyperinsulinaemic clamps. Mean ± SEM of 5–7 experiments, [a] p at least < 0.05 [35]

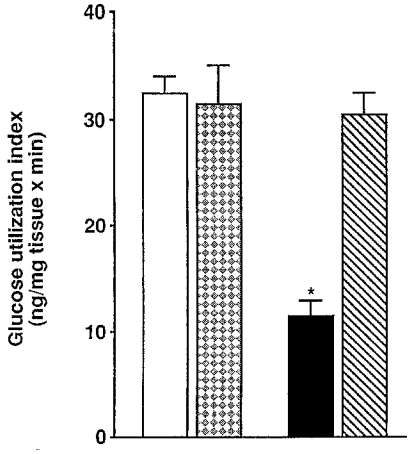

Fig. 2. Effects of a 2-day corticosterone administration to normal rats (to reach stress levels of the hormone) on the acute effect of insulin on glucose uptake by a skeletal muscle measured during euglycaemic-hyperinsulinaemic clamps associated with the 2-deoxy-D-glucose technique (untreated control rats: ▨; corticosterone administered rats: ■). The corticosterone effect seen was prevented by Etomoxir treatment (an inhibitor of fatty acid oxidation) given during the 2-day corticosterone administration (control rats Etomoxir administered: □; corticosterone + Etomoxir administered rats: ▧). Mean ± SEM of 4–8 experiments (control vs corticosterone administration, $p < 0.05$). Similar results were obtained in several muscles of different fibre composition [46]

studied (by 21 to 110 %), a finding that was compatible with an increased glucose fatty acid (Randle) cycle related to high rates of corticosterone-induced lipolysis in adipose tissue with subsequent increases in NEFA release. It was striking to observe that NEFA levels were high in corticosterone-administered rats and did not decrease during the euglycaemic-hyperinsulinaemic clamp as they did in control rats [46].

Evidence of a possible effect of increased NEFA oxidation on glucose metabolism (and hence on muscle insulin resistance elicited by corticosterone administration) was investigated in control and corticosterone-administered rats treated with Etomoxir, an inhibitor of fatty acid oxidation. As further shown by Figure 2, Etomoxir treatment prevented the corticosterone-induced decrease in insulin-stimulated glucose utilization index of the gastrocnemius muscle which was representative of all muscles studied. Etomoxir treatment had no or little effect on muscles obtained from control rats. Glycogen accumulation observed in most muscles following corticosterone administration was also prevented by Etomoxir treatment [46].

Taken together, these results demonstrate that increased lipid oxidation is responsible for glucocorticoid-induced muscle insulin resistance. It thus seems likely that an excessive NEFA oxidation induces muscle insulin resistance at the level of glucose uptake by altering glucose transport, either via an increased glucose fatty acid cycle as proposed by Randle et al. [48], or via the alterations of glucose transporter translocation and/or activation. At this point we suggested that animal obesity was associated with hyperinsulinaemia, with the likely consequences summarized in Figure 1 and Table 2, together with and perhaps reinforced by moderate hypercorticosteronaemia and its metabolic consequences (Fig. 2). We thus searched for a potential link between hyperinsulinaemia, hypercorticosteronaemia and muscle insulin resistance.

Intracerebro-ventricular administration of neuropeptide Y to normal rats

Neuropeptide Y was considered as a prime candidate in this link for the following reasons: NPY is a 36 amino-acid peptide initially isolated from pig brain. It is named "Y" for the single-letter code identifying the tyrosine residues found at the C- and N-terminals, as well as at three other positions in the molecule. Most of the metabolic effects of NPY appear to be mediated via the hypothalamic area [49]. NPY administered intracerebro-ventricularly (i.c.v.) has been shown by others to be a potent stimulator of food intake in normal rats [49]. It produces obesity when administered for several days [50]. Acute central NPY administration to normal rats has also been shown to increase plasma insulin levels, thought to be mediated via the vagus nerve [51, 52] and to inhibit the thermogenic capacity of brown adipose tissue [53], a sympathetic nerve mediated process.

Studies by this and other laboratories have shown that hypothalamic NPY mRNA and NPY protein content are increased in genetically obese rodents [54, 55], animals which have increased food intake, plasma insulin levels, hepatic and adipose tissue lipogenic activities, alongside decreased energy dissipation [24].

The aim of subsequent studies was to investigate whether a chronic (7-day duration) i.c.v. administration of NPY to normal rats would result in hormonal and metabolic defects similar to those of genetically obese fa/fa rats. The impact of i.c.v. NPY in the absence of hyperphagia (pair-feeding experiments) on hormone output, as well as glucose and lipid handling by liver, muscles and adipose tissue was also investigated to establish the NPY-induced changes that were not linked to hyperphagia [56].

In all experimental groups, animals treated with i.c.v. NPY received 10 μg/day of the peptide. In the first experimental group, control and i.c.v NPY-administered animals were allowed to eat ad libitum throughout the 7-day experimental period. In the second group, animals were allowed to eat ad libitum for the first 3 days after the treatment. Subsequently, NPY-treated rats were pair-fed to vehicle-treated control animals for the remaining 4 days of NPY administration. This enabled diagnosis of successful

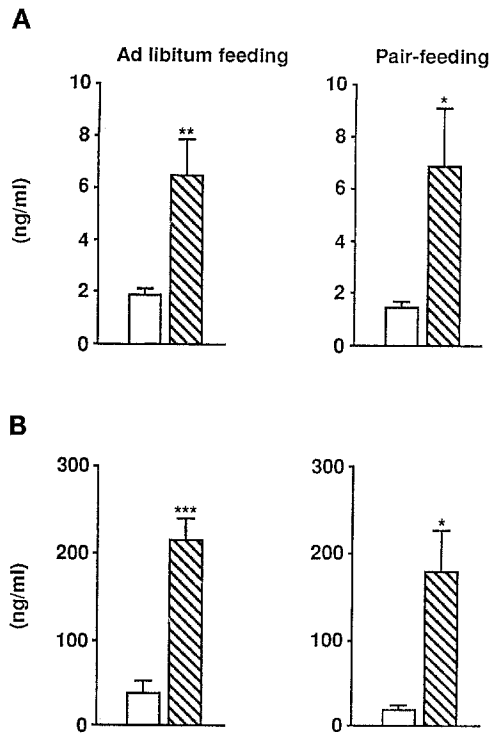

Fig. 3 A, B. Effects of 7-day i.c.v. NPY (10 μg/day) administration to normal rats on **A** basal (i.e. 2 h after the last meal) plasma insulin and **B** morning plasma corticosterone levels (vehicle-infused controls: □; i.c.v. NPY-infused rats: ▨). The animals were fed ad libitum or pair-fed, as indicated. Each bar is the mean ± SEM of 5–8 (insulinaemia) and of 6–9 experiments (corticosteronaemia) with * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ [56]

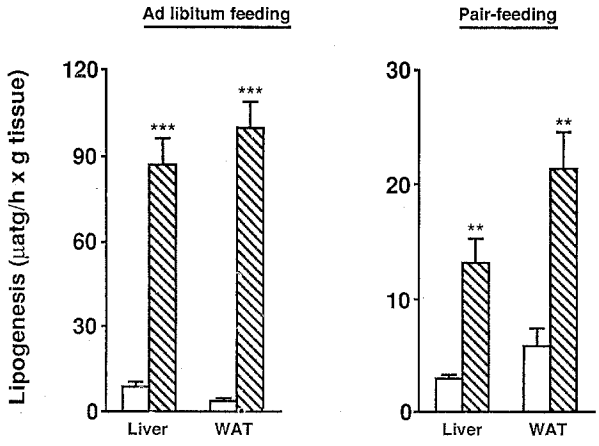

Fig. 4. Effects of 7-day i.c.v. NPY (10 μg/day) administration to normal rats on lipogenesis (measured via ^3H incorporation, from ^3H_2O, into long chain fatty acids) in the liver and in the white adipose tissue (WAT) of normal i.c.v. vehicle-treated or i.c.v. NPY-treated rats, fed ad libitum or pair-fed, as indicated (vehicle-infused controls: □; i.c.v. NPY-infused rats: ▨). Each bar is the mean of 4–8 experiments ± SEM. ** $p < 0.01$; *** $p < 0.005$ [56]

Table 3. Effects of 7-day intracerebro-ventricular NPY administration to normal rats on peripheral metabolism

1. Liver lipogenesis: increased
2. Liver acetyl CoA carboxylase activity: increased
3. Adipose tissue lipogenesis: increased
4. Glucose uptake by adipose tissue: increased
5. Adipose tissue acetyl CoA carboxylase activity: increased
6. Adipose tissue lipoprotein lipase activity: increased
7. Circulating triglycerides: increased
8. Muscle glucose utilization (several muscles of different fibre composition): decreased by mechanisms involving an increased glucose-fatty acid cycle, with normal GLUT 4 mRNA and GLUT 4 protein levels

These alterations are observed, sometimes to different extent for some parameters, whether the animals are fed ad libitum or pair-fed. This underlies a role of NPY per se in producing the effects summarized. These data complete the i.c.v. NPY effects shown by Figures 3 and 4 [56, 58]

NPY administration as seen by an initial increase in food intake, then ruling out hyperphagia as a complicating factor in interpretation of results [56].

As shown by Figure 3, basal plasma insulin levels were markedly elevated in NPY-treated groups, whatever the feeding conditions used. Morning plasma corticosterone levels were also found to be increased in both the ad libitum fed and the pair-fed NPY-treated animals compared to their respective controls. Thus, high concentrations of NPY in the brain of normal animals produces two major alterations that are present in genetically obese rodents, namely hyperinsulinaemia and hypercorticosteronaemia [56]. The latter effects of i.c.v. NPY administration on hyperinsulinaemia are possibly mediated via the para-sympathetic nervous system, and via the stimulation of corticotropin-releasing factor (CRF) for hypercorticosteronaemia, as has previously been suggested with acute experiments (referred to in [56]).

Moreover, the present study contributes to support the existence of functional relationships between NPY and insulin, whereby central NPY stimulates insulin release. As insulin down-regulates central NPY levels in normal rats, this regulation would be abnormal in genetically obese (fa/fa) rats, thereby explaining their elevated hypothalamic levels of the peptide [49, 54, 55, others referred in 56].

It has been mentioned above that the genetically obese fa/fa rat as well as other genetic models of obesity in rodents are characterized by hyperphagia, hyperinsulinaemia, increased liver and adipose tissue lipogenic activities, varying degrees of insulin resistance, and of hypercorticism, together with decreased energy expenditure [24, 25, 41, 57]. It is therefore of interest to note that many of the hormonal and metabolic defects of the genetically obese rodents were mimicked, in the present study, by the chronic i.c.v. administration of NPY to ad libitum

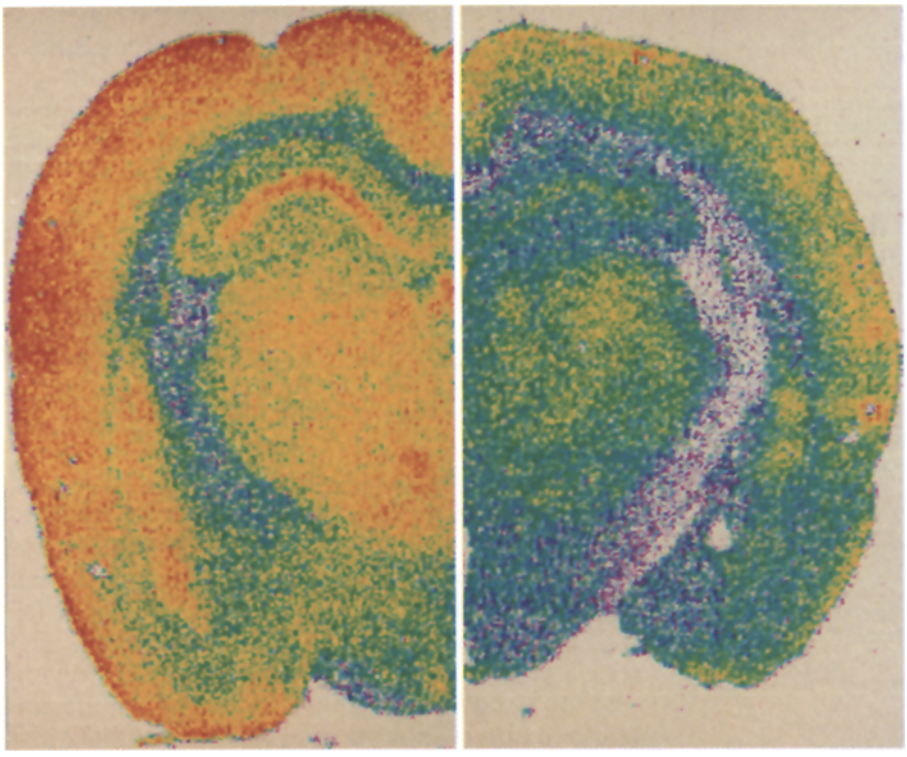

Fig. 5. Local cerebral glucose uptake (measured by the labelled 2-deoxy-D-glucose method of Sokoloff) of adult lean (left) and genetically obese (right) fa/fa rats. Each representation has the same calibration scale to allow direct comparison of the colour-coded autoradiographs. Mean of 5–6 rats per group, with at least 6 measurements for each brain area. Local cerebral glucose uptake is expressed as μmol/100 g ·min^{-1} [61]

fed or pair-fed normal rats [56]. Thus, as shown by Figure 4, i.c.v. NPY administration to normal rats resulted in increases in liver and white adipose tissue de novo lipogenesis. Also shown in Figure 4, such increases were greatest in the NPY-treated group having the highest availability of substrates, i.e. the ad libitum fed group [56]. Further measurements were made in i.c.v. NPY-administered animals, with preliminary results summarized by Table 3. It was observed that i.c.v. NPY-treated normal rats, whether fed ad libitum or pair-fed, were characterized by increased liver and white adipose tissue lipogenic activity, together with concomitant muscle insulin resistance (Table 3) [56, 58].

It is important to realize that the hormonal and metabolic changes brought about by i.c.v. NPY administration to normal rats can be observed in the absence of hyperphagia [56, 58]. This indicates the existence of genuine NPY effects within the brain, that are able to modify the peripheral homeostasis. The routes suggested above for these NPY-induced peripheral changes (concomitant increase in the efferent parasympathetic and/or HPA axis activities) actually remain to be demonstrated. NPY-induced hyperphagia would, by increasing substrate availability, be only an aggravating factor rather than a necessary one in the establishment of the alterations described in this study (Figs. 3, 4, Table 3). This may also be the case in genetically obese rodents, in which the NPY'ergic system in the hypothalamus is reportedly overactive and could be responsible for several features of such an obesity syndrome [cited in 56].

Hypothalamic NPY levels in genetically obese rodents

We posed the question as to why genetically obese rodents had high levels of hypothalamic NPY [54, 55], and high CRF levels responsible for the overactive HPA axis mentioned above [42]. We were particularly struck by the observations of others that rats placed in situations of transient energy lack, such as fasting [59] were characterized by increased hypothalamic NPY levels. This was considered as an adaptative mechanism enabling the animal to obtain food (NPY-induced hyperphagia) and to store energy when nutrients became available (NPY-induced hyperinsulinaemia and concomitant increased lipogenesis). It is also noteworthy that the HPA axis could be triggered by central hypoglycaemia [60].

Local cerebral glucose utilization in lean and genetically obese rats

It was further considered whether the high central NPY and CRF levels of genetically obese animals could be the result of some central lack in energy substrates. To test this posssibility, lean and genetically obese animals received an i.v. bolus injection of a trace amount of ^{14}C-2-deoxy-D-glucose. After 45 min they were killed, their brain removed, sliced and autoradiographed to measure the amount of labelled 2-deoxy-D-glucose taken up by specific brain regions (an index of local cerebral glucose utilization), using a quantitative autoradiographic method [61].

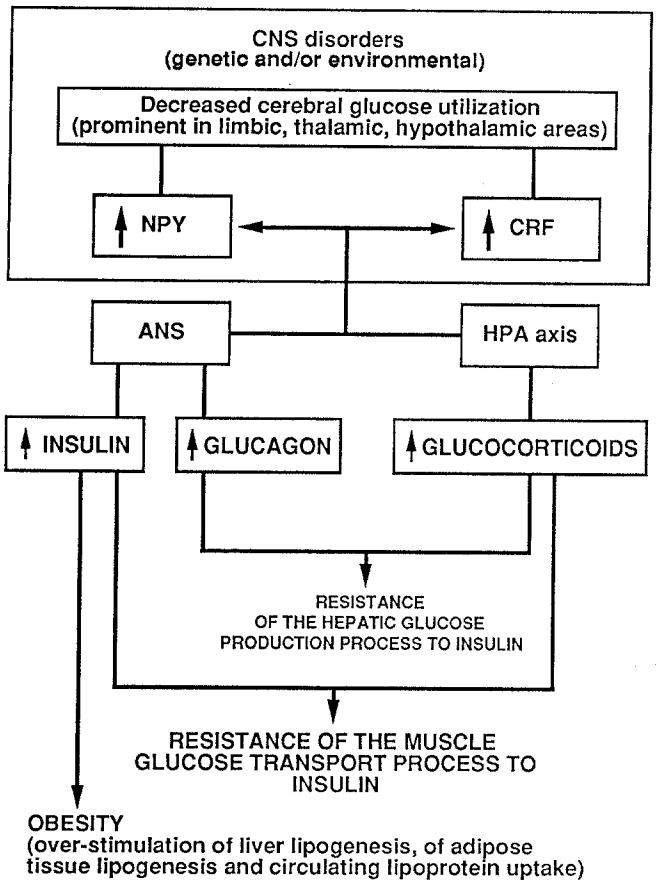

Fig. 6. Moderate decrease in cerebral glucose utilization would result in increased brain NPY and CRF levels, concomitantly producing dysfunctions of the brain regions mentioned. NPY might modulate the autonomic nervous system with resulting hyperinsulinaemia, as well as (together with CRF) the HPA axis, with resulting hypercorticosteronaemia. Hyperinsulinaemia is responsible for the occurrence of obesity and muscle insulin resistance (see Fig. 1, Table 2). Hypercorticosteronaemia is also responsible for insulin resistance (see Fig. 2), albeit by mechanisms different from those brought about by hyperinsulinaemia. CNS, central nervous system; ANS, autonomic nervous system

The main observations were that glucose utilization of all grey matter brain regions studied in the genetically obese (fa/fa) rats was decreased when compared to that of lean rats, although the extent of this decrease was not uniform, as shown by Figure 5 [61].

The areas that had the greatest decrease in cerebral glucose utilization were associated with four specific systems of the brain: the limbic region related, in particular, to behavioural regulation, arousal during a meal, as well as regulation of the HPA axis; the thalamic region, related in particular, to taste perception and learning; the hypothalamic region, whose nuclei regulate the autonomic nervous system, feeding, various endocrine systems, including the HPA axis; as well as the autonomic nervous system [61].

Despite their novelty, the present findings cannot yet be explained on a clear pathophysiological basis. They strongly suggest, however, that in the genetically obese fa/fa rat syndrome, all brain regions, crucial ones known to be of importance in the obesity syndrome in particular, may be inadequately supplied by the primary brain fuel, glucose. This could be one of the causes for increased central levels of both NPY and CRF.

Conclusions

The data summarized in Figures 1–5 and Tables 1–3, at present and until the protein(s) for which the fa gene is encoding are discovered can be schematized by the flow chart proposed in Figure 6.

Genetic, or environmental alterations, or both would produce a decrease in cerebral glucose utilization. Environmental alterations may be moderate as obese rats display no sign of cerebroglucopenia – but may be the reason why hypothalamic NPY and CRF levels are increased in genetically obese rodents. Decreased cerebral glucose utilization (partly compensated for by increased cerebral lactate utilization, unpublished observation) is most prominent in the limbic, thalamic and hypothalamic regions, and is likely to produce abnormalities of the respective functions of these areas. Increased efferent parasympathetic and decreased sympathetic activities of the obese animal could be elicited by the increased hypothalamic NPY levels, with resulting hyperinsulinaemia (and hyperglucagonaemia). Hyperinsulinaemia would be responsible for both obesity and muscle insulin resistance (Fig. 1, Table 2). Increased central CRF would result in hypercorticosteronaemia. The latter, probably in concert with hyperglucagonaemia [20] could be responsible for the insulin resistance of the hepatic glucose production [46]. It also produces, as shown by Figure 2, muscle insulin resistance by mechanisms different from those brought about by hyperinsulinaemia [46].

If the abnormalities proposed in Figure 6 apply, at least in part, to some types of human obesity, it may be appreciated why a decrease in body weight and amelioration of insulin resistance cannot be maintained on a long-term basis. The argument is that these abnormalities are present permanently, thereby being potentially ready at all times to favour abnormal channeling of incoming nutrients.

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