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## Hypoglycaemia associated syndrome

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Severe hypoglycaemia is a state in which cognitive function is so disturbed the victim is unable to take corrective action and requires assistance from another individual [1]. Occasionally, severe hypoglycaemia is defined more rigorously as a state in which coma occurs or in when the conscious level is so suppressed that parenteral therapy (intravenous glucose or intramuscular glucagon) is required [2]. It occurs because the brain is normally dependent on glucose to sustain its metabolism, and therefore its function, but it does not store significant quantities. Brain metabolism is therefore dependent on a constant supply of new glucose from its circulation.

Severe hypoglycaemia does not occur in health because of the efficiency of the body's endogenous mechanisms for blood glucose control. In response to an increased demand for glucose or diminished availability (e.g. during fasting), the mechanisms of glucose counterregulation are stimulated. Endogenous insulin secretion is reduced and pancreatic glucagon increased [3, 4], with the net result of increasing endogenous glucose production; more extreme hypoglycaemia is detected centrally and stimulates a systemic neurohumoral response including activation of the sympathetic nervous system and adrenal medulla, with release of catecholamines, and, slightly later, the adrenal cortex and pituitary, with release of cortisol and growth hormone [4]. These neurohumoral responses diminish peripheral glucose uptake, and increase endogenous glucose production, particularly via gluconeogenesis by elevating circulating gluconeogenic substrates. Only in extreme

circumstances (such as excessive exercise) can these responses be overcome in health. In disease however, where the hypoglycaemic drive is artificially elevated (e.g. insulin and sulphonylurea treatment of diabetes, tumours secreting insulin or insulin-like growth factors) or counterregulatory mechanisms severely disrupted (alcohol, especially in association with chronic malnutrition; hormone deficiencies such as Addison's disease; hypopituitarism), severe hypoglycaemia can occur. The first of these pathologies, pharmacological treatment of diabetes, is the most common. Severe hypoglycaemia is the most important side effect of insulin therapy and fear of it ranks in the patients' minds, alongside fear of blindness or renal failure [5]. Although less obvious a problem, sulphonylurea therapy can also cause severe hypoglycaemia, especially in the elderly or frail [6–8].

In diabetes, the deficiencies in counterregulation are not just the artificial elevation of hypoglycaemic drive by exogenous insulin or insulin secretagogues. In type 1 diabetes, glucagon responses are lost within the first 1 to 5 years of the disease [9]. A recent study suggests this defect might be delayed by intensive therapy starting immediately after diagnosis [10], but it is not clear whether this is associated with the preservation of endogenous insulin secretion. There is certainly evidence to suggest that the pancreatic  $\alpha$ - and  $\beta$ -cells communicate [11]. With increasing duration of disease, many diabetic patients also show defects in their catecholamine responses to hypoglycaemia [9]. This is associated with a loss of symptom generation in response to early hypoglycaemia [12]. The resulting syndrome of hypoglycaemia unawareness is strongly associated with increased frequency of severe hypoglycaemia [13, 14].

Frequency of severe hypoglycaemia is difficult to determine, especially retrospectively when recall is poor. It also depends on which definitions of severe hypoglycaemia are used, with much lower levels being described if the definition requires coma and/or parenteral therapy, e.g. [15] compared with [2]. It also depends on the age of the population studied [16, 17], their duration of diabetes [16] and, most topically, their degree of glycaemic control [1, 2, 15, 16].

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Intensified insulin therapy can be associated with a threefold increase in the incidence of hypoglycaemia without symptoms [18] and in the incidence of severe hypoglycaemia [15]. These phenomena are associated with easily demonstrable defects in counterregulation and counterregulatory responses [12, 19]. Both the magnitude of the symptomatic and humoral responses to hypoglycaemia and the glucose level for triggering them are lowered in intensified insulin therapy [20–22], creating a syndrome of defective counterregulation, hypoglycaemia unawareness and increased risk of severe hypoglycaemia. There is also evidence to suggest that there is diminished sensitivity to the residual autonomic activation and adrenaline secretion, exaggerating the affect [23]. It is important to realise that this syndrome, although more common in intensified diabetes therapy, is not restricted to it [12, 24]. Defective counterregulation is found (when sought) in all types of hypoglycaemia unawareness and may be necessary for severe hypoglycaemia, especially recurrent severe hypoglycaemia, to occur.

The principal defect in counterregulation in hypoglycaemia unawareness is a substantial lowering of the glucose concentration required to stimulate protective symptomatic neurohumoral responses [22]. Similar defects can be induced transiently in healthy volunteers by recent prior exposure to hypoglycaemia and it is important to note that this antecedent hypoglycaemia need not be very profound [25]. Two episodes of exposure to a plasma glucose concentration of 3 mmol/l will induce defects in normal counterregulation to more severe hypoglycaemia the next day [26]. These experimental data support the hypothesis that defective glucose counterregulation is a response to prior hypoglycaemic experience. The clinical relevance of this is strongly supported by the demonstration that normal [24] or near-normal [27] neurohumoral responses and, more importantly, subjective awareness [22, 27] of hypoglycaemia, can be restored in hypoglycaemia unaware diabetic subjects by a strict policy of hypoglycaemia avoidance in daily life. The critical glucose level appears to be 3 mmol/l – avoidance of glucose levels below this is associated with a restoration of defective counterregulatory responses in short- [27] and long-duration [24, 28] diabetes and in patients with recurrent severe hypoglycaemia associated [24, 27], or not [24], with tight metabolic control. Only one study has failed to demonstrate any restoration of hormonal counterregulation with hypoglycaemia avoidance in hypoglycaemia-unaware type 1 diabetic subjects and this study did show restoration of symptom generation [29]. This is difficult to explain but the failure to restore hormonal responses may relate to an inability to eradicate antecedent hypoglycaemia completely, and the success of restoring symptoms may have been due to changes in sensitivity to residual autonomic activation.

Lowering of the plasma glucose concentrations required to stimulate counterregulatory responses is also seen during intensification of therapy in type 2 diabetes, at least if insulin is used [30]. Allowing for the older age of these patients, the change appeared to be essentially exaggerated counterregulatory responses associated with chronic hy-

perglycaemia being restored to normal; however, the increased tendency to cognitive dysfunction during hypoglycaemia in the older subject [31] makes this regression to normality potentially dangerous in the setting of diabetes drug therapy.

Detection of hypoglycaemia and initiation of the systemic and symptomatic responses are functions of the central nervous system – in rodents at least of the ventromedial hypothalamus (VMH) [32, 33]. Glucose sensing also occurs in the hepatic portal vein and preservation of glucose levels in the portal vein during systemic hypoglycaemia in experimental models in animals does diminish counterregulatory hormone responses [34]. It is likely that these portal sensors are involved in modulating gluco-regulation in response to feeding.

The trigger for counterregulation is a fall in tissue metabolic rate – counterregulatory responses can also be diminished by supplying non-glucose metabolic substrates for neuronal metabolism such as lactate, either systemically [35] or directly into the VMH in laboratory rodents [36]. Using invasive arterio-venous difference techniques, Boyle and colleagues [37] were able to measure a fall in brain glucose uptake in human subjects at the time of or before any measurable counterregulatory hormone or symptom responses. Interestingly, this group were also able to demonstrate preservation of global brain glucose uptake during moderate hypoglycaemia in normal volunteers after exposure to prolonged moderate hypoglycaemia [37] and in intensively treated hypoglycaemia unaware diabetic subjects [38]. Clearly the human brain can adapt to hypoglycaemia by increasing the efficiency of its ability either to take up or to metabolise glucose, thus delaying the onset of impaired glucose metabolism and brain dysfunction (including triggering of counterregulation) when next exposed to hypoglycaemia. One hypothesis is that the human brain can upregulate glucose transporters, as has been demonstrated in animal models in response to more prolonged or profound hypoglycaemia [39], but this has not been proven and other possibilities exist.

If the human brain can defend itself against hypoglycaemia as just described, hypoglycaemia adaptation should be able to defend diabetic patients against severe hypoglycaemia rather than increase the risk. Boyle's experiments measure a global increase in brain glucose uptake in the hypoglycaemia-experienced subject – this should be associated with a delayed onset of cortical dysfunction as well as a delayed onset in triggering counterregulatory responses. Testing of cognitive function during acute hypoglycaemia is a controversial area. My group has favoured the use of one very hypoglycaemia-sensitive complex task (the four-choice reaction time [40, 41]), with obvious relevance to task performance in daily life such as driving or operating machinery or being in potentially dangerous situations such as on scaffolding, as a marker for cognitive function. Such an approach has the advantage of high sensitivity to hypoglycaemia, reproducibility and, by virtue of its simplicity and brevity, the ability to be measured at a discrete glucose level and repeatedly during experiments

of acute induced hypoglycaemia, in a way like performing repeated blood sampling for monitoring responses of adrenaline. However, it has the disadvantage of measuring only a single function and clearly does not test global cortical function. Other groups have combined a number of tests in a battery in an attempt to measure more aspects of brain function during acute hypoglycaemia [27, 28, 42]. This has the obvious advantage of testing more brain functions but does lose discriminatory power, as the battery takes a long time to administer, during which the brain's exposure to hypoglycaemia is changing, if only in duration. It also loses sensitivity if the various test results are summed into a single value, as favoured by some.

In fact these differences in approach have been useful for increasing our understanding of brain function and dysfunction in hypoglycaemia. Using a limited number of tests, there is good evidence that some, including the four-choice reaction time, do not adapt to antecedent exposure to hypoglycaemia in diabetes [20, 24, 30, 43–46]. This means that these aspects of cognition will deteriorate well before symptom generation as hypoglycaemia develops in hypoglycaemia unaware or hypoglycaemia aware subjects. This is compatible with the clinical picture of confusion preceding symptom generation, the failure of the patient to detect his/her own hypoglycaemia and the increased risk of accidents during hypoglycaemia and severe hypoglycaemia occurring without warning, as it provides for an inability to respond to potentially symptomatic responses even when they eventually occur. In contrast, using summed scores from multiple tests [27], or tests of other cognitive functions [37, 45], other groups have shown a degree of adaptability of cortical function in hypoglycaemia unawareness. These data are not necessarily incompatible with the clinical situation, as the change in glucose thresholds for cognitive impairment is less than those for initiation of neurohumoral responses or generation of symptoms. In other words, these workers suggest a smaller window of opportunity for symptom recognition and the taking of appropriate action to arrest the hypoglycaemia, while our data suggest the window may be completely closed (and shuttered!). The apparently discrepant data also indicate that different brain functions (and therefore different brain regions) behave differently in response to hypoglycaemia adaptation. This is entirely consistent with the evidence that different brain functions (and regions) behave differently during hypoglycaemia per se, as evidenced by their different sensitivities to hypoglycaemia. There is good evidence in man for regional differences in brain glucose metabolism [47] and these discrepancies in functional studies are an exciting opportunity to examine the mechanisms by which different brain regions can adapt to hypoglycaemia. The eventual goal will be to devise therapies to limit all cognitive dysfunctions during hypoglycaemia in intensively treated diabetes.

### **Clinical management of hypoglycaemia unawareness syndromes**

Defective counterregulation and hypoglycaemia unawareness can be induced by antecedent hypoglycaemia and is reversed in diabetic subjects by hypoglycaemia avoidance. It follows that the appropriate management of hypoglycaemia unawareness is the manipulation of diabetes therapy to avoid all plasma glucose concentrations of less than 3 mmol/l. The British Diabetic Association has introduced a slogan "make 4 the floor", creating a safety net for patients. It is important to realise that it is conceptually very different from the traditional approach to the management of problematic hypoglycaemia, which has been to "relax" glycaemic control – avoidance of hypoglycaemia is entirely compatible with a near-normal glycated haemoglobin. Indeed successful strategies often reduce HbA1c, as the rebound hyperglycaemia and the swinging from hypo- to hyperglycaemia and back again is avoided. This is not to diminish the difficulties of achieving truly good diabetes control, which should be defined as near-normal HbA1c with no problematic hypoglycaemia.

While a patient is hypoglycaemia unaware, they must be warned not to drive a car or put themselves (or others) in a position where damage could be done. The psychological aspects of hypoglycaemia unawareness must also be addressed. Sudden swings in mood, irrational behaviour, even aggression, can be associated with asymptomatic hypoglycaemia, at the very least the inability to recognise the situation leads to aggressive rejection of attempts to help and this is an extremely frustrating as well as frightening condition for the spouses, partners and families of the affected patient. In clinical practice the syndrome must be actively sought, by interviewing the patient and the partner, by examination of the home glucose records for recordings of 3 mmol/l or less and by direct questioning, not for hypoglycaemia, which people define in different ways, but for all episodes of needing to eat quickly, night sweats, restless nights etc.

Having identified a problem, what action is available? At least in type 1 diabetes, most individual episodes of severe hypoglycaemia are explicable, the most common associations being inadequate food intake, unusual exercise, over-estimation of insulin requirement and alcohol [48]. All conventional insulin regimens use insulin administered in the wrong place and with the wrong time course of action. Taking enough soluble (regular) insulin to cover a meal with the expectation of post-prandial normoglycaemia inevitably creates relative hyperinsulinaemia 2 to 5 h later, as the action profile of conventional insulin is flatter and longer than that of the prandial burst of endogenous insulin from a healthy pancreas. This mandates the use of between meal and bedtime snacking, if tight control is desired [49]. The new short-acting insulin analogues may diminish this need [50] and may be considered for a patient with difficult control. The associated tendency for the insulin effect to run out between meals may be best compensated by using an insulin pump [51], although such therapy is expensive.

Nocturnal hypoglycaemia may be a particular problem [52]. Recent studies in children have confirmed early studies [52] showing how common – and how asymptomatic – nocturnal hypoglycaemia is during insulin therapy [52] and it is possible that unrecognised nocturnal hypoglycaemia may be enough to maintain a condition of hypoglycaemia unresponsiveness the following day [54]. This is likely to be a vicious circle, with recent demonstrations of diminished hormonal responses to asymptomatic but not symptomatic nocturnal hypoglycaemia in adolescents [55]. Strategies such as moving the evening intermediate acting insulin to the latest possible opportunity (and reducing the dose) to achieve more stable control of waking glycaemia with less risk of nocturnal hypoglycaemia may help [56]. Another alternative is the use of an infusion of soluble insulin overnight in a simplified pump regimen [57, 58]. In susceptible patients, the use of rapid acting insulin analogues for the evening meal is associated with reduced frequency of nocturnal hypoglycaemia [59, 60], adding to the earlier suggestions that the pre-evening meal soluble insulin is a major contributor to hypoglycaemia in the early hours of the morning. Other strategies include establishing a higher range for pre-bedtime glucose targets (>7 mmol/l) [61] and attention to the composition of the bedtime snack. Including a protein source with alanine [62] as a gluconeogenic substrate or a “slow-release” carbohydrate such as uncooked cornstarch [63] may help. A recent acute study suggesting a beneficial effect of terbutaline at bedtime [62] was not supported by a recently published clinical trial [64].

Finally, exercise is an extremely important issue. Many patients do not appreciate that the hypoglycaemic effects of exercise are very prolonged – if the exercise is vigorous and/or prolonged, especially if the exercise is unusual for that subject. Sustained low grade or very vigorous short-term exercise lowers blood glucose for 12 to 18 h, as depleted muscle and liver glycogen stores are replenished [65]. A recognition of the need for significantly (20–60%) less overnight insulin after such exertion is as important as the increased carbohydrate intake and reduced insulin at the time of the exercise. Mixing exercise with alcohol, which suppresses gluconeogenesis with a similar time course [66] such as at all-night dancing parties, can be lethal and care must be taken for appropriate manipulation of insulin.

Most of all hypoglycaemia avoidance is a matter of education – of diabetes health care professionals as well as of patients. It is not easy and requires diligence and thought from the patient – often with a high demand for monitoring and planning. For these reasons, the search for simpler strategies to protect against cortical dysfunction during hypoglycaemia continues.

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