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# Effect of Insulin Administration on Water Drinking in Children

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The effect of insulin administration on water intake, was studied in children submitted to standard protocols for stimulation of secretion of hypophyseal hormones by i.v. treatment with several different drugs: insulin, insulin plus TRH and LH-RH; and propranolol, clonidine or LH-RH. Drinking was measured from 0 to 90 min after drug administration; from blood samples taken at 60 min for hypophyseal hormones analysis, microhaematocrit values were measured, as well as plasma renin activity (PRA) and glycaemia. Water intake was significantly higher in both groups of patients receiving insulin than in the control group (no insulin). Haematocrit values did not change after 60 min. There was a significant correlation of glycaemia of individuals from all three groups and water intake at 60 min. PRA was significantly higher in insulin treated individuals.

Key words: Drinking, Insulin, Thirst.

Insulin has been observed to enhance water intake in the rat, independently of its effects on food intake (2, 5, 9, 11, 15, 18). The mechanisms of insulin induced drinking (IID) are not very well understood. In diabetic humans, the intravenous administration of insulin causes loss of intravascular water (7) as well as in normal rats (18), hypovolemia being probably a dipsogenic factor involved in IID. Insulin has also been reported to be a trigger for the renin release in different species including humans (4, 10), so that angiotensin II, a known dipsogenic factor (6), could be a mediator of IID. The aim of the present study was to investigate if insulin had the same dipsogenic effect in humans as in rats, and its possible relation to some hydrational variables and the renin angiotensin system.

## Materials and Methods

Children patients (22 males and 2 females, in the 3-14 year old range) from the

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«Materno-Infantil Hospital de Nuestra Señora de Covadonga, Oviedo (Spain)», suspicious of hypophyseal disorder (deficient secretion of one or more hypophysary hormones), were subjected to routine study by the «Endocrine Unit». In order to investigate their hypophyseal secretory capacity of GH, FSH, TSH, they were stimulated —as usual— by standard treatment with some of the following substances, given i.v. solely or in combination, depending on the type of disorder to be investigated: insulin 0.1 U/kg b.w. - Actrapid (Novo) or propranolol 0.75 mg/kg b.w. - Sumial (Ici) or clonidine 8 μg - Catapresan (Boehringer Sohn), for GH response; RH-LH 100 μg - Luforan (UCB), for FSH response, and TRH 5 μg - Trh-Prem (Frumtost-Prem), for TSH response. During the time of the trials, water intake was studied. Informed consent was obtained from the parents before the subjects were included in the protocol and parallel study on ingestive behaviour.

Three groups were established according to the treatment they received: a) patients (6 males) from 3 to 12 years of age, treated solely with insulin; b) patients (8 males and 1 female) from 4 to 14 years of age, treated with insulin plus TRH plus LH-RH (combined treatment); and c) patients (8 males and 1 female) from 4 to 13 years of age, treated with propranolol, clonidine or LH-RH; no insulin was administered to this group which from that moment was considered as the control. All of them were fasted from the night previous to the experiment. The basilica vein was cannulated for injection and blood sample collection. Prior to starting the experiment a glass of water was offered and the amount of water drunk recorded. From this moment till the end of the experiment water was available *ad libitum*. Time of the first drinking and total water intake was recorded at 30, 60 and 90 min after drug administration. At 30 min glycaemia was measured by labstix-test as a safety measure but data were not used for statistics. Blood samples were taken 60 min after drug administration via the intravenous cannula. Microhaematocrit was determined immediately from blood samples; these were then centrifuged and plasma samples stored at −20° C. Plasma renin activity (PRA) was measured by RIA, using the Phadebas Angiotensin I test, from Pharmacia Diagnostics AB, Sweden. Results of PRA are expressed as ng of AI generated/ml of plasma/h. Two groups were established for statistical analysis of PRA data: One including all individuals treated with only insulin and individuals treated with insulin plus other drugs; the second included all individuals treated with any drug or combination of drugs excluding insulin. Glycaemia was determined by the glucose-oxidase method (Boehringer Mannhein, GmbH). The Mann-Whitney test, linear regression and coefficient of correlation were used for statistical analysis.

## Results

Individuals receiving insulin, solely or in combination with other drugs, intake significatively more water than others receiving treatment without insulin (fig. 1). After 30 min from the beginning of the ex-

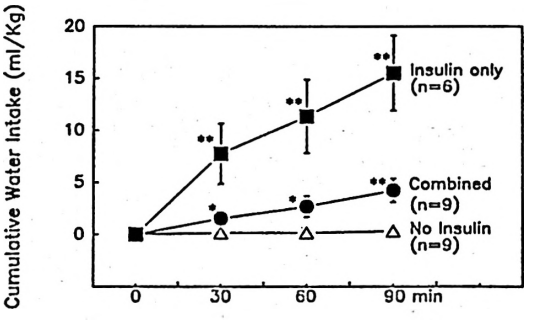


Fig. 1. *Cumulative water intake of children.* Insulin group received i.v. 0.1 U/kg b.w. Combined group received insulin i.v. 0.1 U/kg b.w. + TRH + LH-RH. Control group did not receive insulin (Mean ± SEM); Statistical analysis by Mann Whitney test. *$p < 0.05$; **$p < 0.01$.

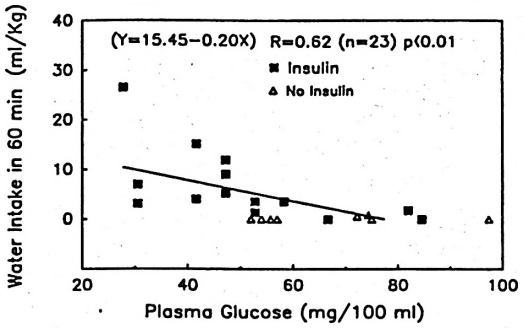


Fig. 2. *Regression and correlation of plasma glucose and water intake of children treated and not treated with insulin.*

periment, all individuals receiving only insulin had drunk, and 6 out of 9 from the group receiving combined treatment. On the contrary, by that time only 2 out of 9 from the control group had drunk. By 90 min, 14 out of 15 individuals receiving insulin or combined treatment had drunk, but only 3 out of 9 from the control group. Haematocrit values of the three groups after 60 min did not differ (43.17 ± 1.74 %, insulin only group, n = 6; 44.67 ± 2.62 %, combined treatment group, n = 9; 42.71 ± 3.38 %, control group, n = 7). At that time, blood glucose was significantly reduced ($p < 0.01$) in insulin (40.28 ± 3.91 mg/100 ml, n = 6) vs. control group (69.23 ± 5.18 mg/100 ml, n = 9); no significant difference of glycaemia values of control group vs. combined treatment (58.68 ± 6.51 mg/100 ml, n = 8) was observed. There was a significant correlation of glycaemia in individuals from all three groups and water intake at 60 min (fig. 2). PRA was significantly higher in the insulin (solely or in combination) treated individuals (5.46 ± 1.20 ng AI/ml · min, n = 10) than in the control —no insulin— group (2.27 ± 0.44 ng AI/ml · min, n = 7). Nevertheless no significant correlation was found with water intake (R = 0.36).

## Discussion

Insulin induced a significant increase in water intake in our patients. These results indicate a generalization of the effects already reported by others in the rat (2, 5, 9, 11, 15, 18), demonstrating that this phenomenon is more than a rat specific behavior. Although IID is a clear effect, its physiological meaning —if there is any— remains unknown. The most obvious effect of insulin is a decrease in blood glucose. This appears to be a main factor in induction of thirst, as both factors correlate significantly in our study. This interpretation in humans is consistent with findings by others (3), who demonstrate the inhibition of both eating and drinking of rats in response to insulin by gastric load of glucose, which prevents hypoglycaemia. The differences of response between insulin and insulin plus TRH plus LH-RH groups (minus drinking in the combined treatment) were totally unexpected. Without taking a position on the causes of this attenuating effect on thirst, the inverse effect observed on blood glucose should be noted. This, again, seems to demonstrate a direct relation of the drinking effect to glycaemia, corresponding to the maximum response of thirst in animals with the maximum drop in blood glucose levels. Insulin has been reported to cause loss of intravascular water in diabetic humans (7) as well as in the normal rat (18). However, hypovolemia was not a factor for induction of thirst in our experiment, as changes in haematocrit values were not found after insulin administration.

Another possible factor involved in IID could be the activation of the adrenergic system which takes place after insulin administration (7, 13, 14). Catecholamines and the adrenergic nervous system activity are both closely related to renin release by the kydneys (8), which, in turn, provoke the generation of Angiotensin II, which is dipsogenic in several species (6), including

man (12), where the peptide has a moderate power to produce thirst. Although in accordance with results from others (8) we found higher PRA in insulin treated patients than in controls, PRA values did not correlate significantly with water intake. Nevertheless there is some evidence from experiments run in our laboratory that this mechanism is related to IID, at least in rats, where propranolol, which inhibits renin release, abolishes intake after insulin administration (submitted for publication). On the contrary, it has been demonstrated that nephrectomy does not block IID (19). Naturally all this does not exclude other factors different from those depending on changes in plasma volume and/or the renin-angiotensin system and adrenergic activation. Other mechanisms, depending on the histaminergic system have been demonstrated to participate in IID in rats (9). Other different possibilities are the effect of insulin on brain sodium levels (1) as well as the direct effect of the hormone on circumventricular organs (16, 17). None of these hypotheses can be excluded beforehand in humans.

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## Resumen

Se estudian 24 niños sometidos a protocolos estándar para la estimulación de secreción de hormonas hipofisarias por tratamiento con varios fármacos: insulina; insulina más TRH y LH-RH; propanolol; clonidina; y LH-RH. Se mide la ingesta de agua, durante 90 min, después de la administración de los fármacos. A los 60 min se miden el microhematocrito, la actividad de renina plasmática y la glucemia. La ingesta de agua es significativamente mayor en los individuos tratados con insulina sola e insulina más TRH y LH-RH que en los del grupo control que no recibe insulina. El hematocrito no se modifica. La actividad de renina plasmática es significativamente más alta en los individuos tratados con insulina.

Palabras clave: Ingesta agua, Insulina, Sed.

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