Pastis and hypertension—what is the molecular basis?

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Glycyrrhiza glabra

The therapeutic properties of *Glycyrrhiza glabra* were already known by Egyptians, Greeks, and Romans in antiquity [1]. They used extracts from this plant for a diversity of ailments and as a sweetener. In the modern society it is found in drinks such as Belgian beers, Ouzo, Pernod or Pastis brands. Many chewing gums contain glycyrrhetinic acid. The rationale for adding glycyrrhetinic acid, the active ingredient of liquorice, to chewing gums is the observation that, contrary to glucose, liquorice does not promote bacterial growth and adherence of cariogenic bacteria [2]. In addition liquorice is often added to confectionery. The discovery of the value of liquorice — previously marketed as carbenoxolone, an oleanand derivative of glycyrrhetic acid — in the treatment of peptic ulcer allowed researchers to establish its adverse effect on salt and water metabolism.

Clinical features and erroneous interpretation

Patients with excessive ingestion of liquorice present with hypokalaemic hypertension from a renal artery stenosis. The urinary sediment is normal [3]. A metabolic alcalosis is commonly observed. The renin–aldosterone system is suppressed. Serum cortisol and 24-h urinary cortisol levels are within the normal range. When liquorice is prescribed to normal volunteers under experimental conditions a positive sodium balance with an increase in body weight of about 2–3 kg is observed during the initial 10 days. Thereafter sodium intake equals urinary sodium excretion, suggesting escape from the mechanism causing renal sodium retention. A normal urinary potassium excretion in the presence of low potassium concentrations in serum indicates abnormal renal loss of potassium. Mineralocorticosteroid receptors. Elegant experiments performed by Funder et al. [10] revealed that a lower activity of the 11β-hydroxysteroid-dehydrogenase (11βHSD) results in increased cortisol concentrations in cells expressing mineralocorticoid receptors (Figure 2).

Mechanism of renal sodium retention and potassium loss induced by liquorice

Werder et al. [7] and later the group of Maria New [8] observed a patient with low renin, low aldosterone and hypertension. The pattern of cortisol metabolites excreted in urine was abnormal [7,8]. In the late 1980s, Stewart et al. showed that the changes in the pathways of adrenal steroid metabolism after liquorice ingestion are similar to those observed in children who exhibit a similar low-renin and low-aldosterone hypertension syndrome [9]. The abnormal pattern of cortisol metabolites, i.e. an increase in the urinary ratio of (tetrahydrocortisol plus 5-allo-tetrahydrocortisol)/tetrahydrocortisone ((THF + 5αTHF)/THE) (Table 1) was compatible with an inhibition of the enzyme shuttling biologically active cortisol into cortisone, a steroid without affinity for glucocorticoid or mineralocorticoid receptors. Elegant experiments performed by Funder et al. [10] revealed that a lower activity of the 11β-hydroxysteroid-dehydrogenase (11βHSD) results in increased cortisol concentrations in cells expressing mineralocorticoid receptors (Figure 2).

Of greater potential relevance than the mechanism of liquorice action in the kidney was the discovery of the biological principle that it is an enzyme which is coexpressed with a receptor, and not the receptor itself, that accounts for the specificity of ligand binding to the receptor [10]. *In vitro* studies with mineralocorticoid receptors had previously shown that the affinity through the binding of its active component to mineralocorticoid receptors.

Although the structural similarities between aldosterone and glycyrrhetinic acid suggested a direct mineralocorticoid effect due to glycyrrhetinic acid, several observations were not in line with this concept [4–6]. First, the affinity of glycyrrhetinic acid for mineralocorticoid receptors is negligibly low. Secondly, liquorice has no mineralocorticoid effect in adrenalectomized rats or in patients with Addison’s disease. Thirdly, the mineralocorticoid effect of glycyrrhetinic acid was restored when liquorice was given together with 11β-hydroxy-glucocorticosteroids to animals or humans without adrenal function, suggesting an interaction between glycyrrhetinic acid and glucocorticoids, rather than a direct effect of glycyrrhetinic acid on renal sodium retention and potassium excretion.
Table 1. Differential diagnosis of low-renin, low-aldosterone hypertension of known aetiology

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<tbody>
<tr>
<td>Mutated gene</td>
<td>Dominant Aldosterone synthase</td>
<td>Recessive 11βHSD2</td>
<td>Dominant Epithelial sodium channel</td>
</tr>
<tr>
<td>Urine</td>
<td>No</td>
<td>†</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(THF + 5αTHF)/THE</td>
<td>No</td>
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<tr>
<td></td>
<td>18-oxo-, 18OH-cortisol</td>
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<tr>
<td>Response to</td>
<td>Dexamethasone</td>
<td>+</td>
<td>–</td>
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<td></td>
<td>Spironolactone</td>
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<td>Spironolactone</td>
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<tr>
<td>Exogenous form</td>
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<td></td>
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11βHSD2, 11β-hydroxysteroid dehydrogenase type 2; GA, glycyrrhetinic acid; THF, tetrahydrocortisol; 5αTHF, 5-allotetrahydrocortisol; THE, tetrahydrocortisone.

Fig. 1. Chemical structures of aldosterone and glycyrrhetinic acid.

of the mineralocorticoid receptor for cortisol and aldosterone was of the same magnitude. Since cortisol concentrations are about 100–1000-fold higher than those of aldosterone, cortisol would quantitatively be the most abundant ligand for the mineralocorticoid receptor. By shuttling cortisol to cortisone in aldosterone receptor-expressing tissues, the 11βHSD removes cortisol from the receptor and guarantees its selectivity for aldosterone. In the presence of liquorice the 11βHSD is inhibited and cortisol has free access to the mineralocorticoid receptor, thereby inducing sodium retention, potassium loss, and low-renin, low-aldosterone hypertension (Figure 2).

11β-HSD isoenzymes

Currently two isozymes of 11β-HSD have been cloned. The enzymes share only 14% homology and have different physiological roles, regulation, and tissue distribution. 11βHSD1 acts predominantly as a reduc-

tase in vivo, is localized in the endoplasmic reticulum membrane with a luminal orientation of the catalytic domain, is NADP-dependent, has a K_m in the micromolar range, and is expressed in most tissues. Its biological relevance is thought to be the catalysis of the
reactivation of cortisone to cortisol, and by that mechanism might regulate access to glucocorticosteroid receptors [3,11–13]. 11βHSD2 on the other hand displays 11β-oxidase activity, is localized in the endoplasmic reticulum membrane with a cytoplasmic orientation of the catalytic domain, is NAD-dependent, has a nanomolar \( K_m \) and is preferentially found in tissues expressing mineralocorticoid receptors, including the cortical collecting duct of the kidney [3,12,14]. The pivotal role of 11βHSD2 in excluding endogenous glucocorticoids from the mineralocorticoid receptor is now widely accepted. This assumption is based first, on the observations of the effect of glycyrrhetic acid on this enzyme, and second, on the studies of the syndrome of apparent mineralocorticoid excess, a disease state that results from a loss of function mutation in 11βHSD2 [3,15]. Phenotypically, the administration of high doses of glycyrrhetic acid and mutations in 11βHSD2 are identical (Table 1).

### Health hazards of liquorice

There is probably a great interindividual and possibly intraindividual variation in the susceptibility to glycyrrhetic acid. In the most sensitive individuals, regular daily intake of no more than about 100 mg glycyrrhetic acid, corresponding to 50 g liquorice sweets (assuming a content of 0.2% glycyrrhetic acid), seems to be enough to produce adverse effects [18]. Most individuals who consume 400 mg glycyrrhetic acid daily experience adverse effects. Provided glycyrrhetic acid has no other effects at lower doses the following consideration with respect to health hazards can be made: 100 mg glycyrrhetic acid per day is the lowest observed adverse effect level. If a safety factor of 10 is considered, a daily intake of cortisol shuttle.

References


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