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L-carnitine attenuates antipsychotic-induced hyperprolactinemia by stimulating pituitary GABA receptors

Antipsychotic-induced hyperprolactinaemia occurs overall in up to 70% of patients with schizophrenia, depending on the medications used. Hyperprolactinemia may cause sexual dysfunction, amenorrhea, infertility, galactorrhea, and osteoporosis, which in general relates to the degree of prolactin elevation. When antipsychotic-induced hyperprolactinemia warrants treatment, several approaches can be attempted, such as dose reduction of the offending antipsychotic, switch to a prolactin-sparing antipsychotic (i.e. aripiprazole, olanzapine, quetiapine or clozapine), addition of a dopamine partial agonist (aripiprazole) to the current regimen, and addition of a dopamine agonist (i.e. bromocriptine or cabergoline). There is limited evidence for the management of antipsychotic-induced hyperprolactinemia, and these strategies, however, carry the risk of precipitating an exacerbation or relapse of psychotic symptoms, which may put the patient at a greater risk for adverse consequences, possibly worse than experiencing hyperprolactinemia itself.

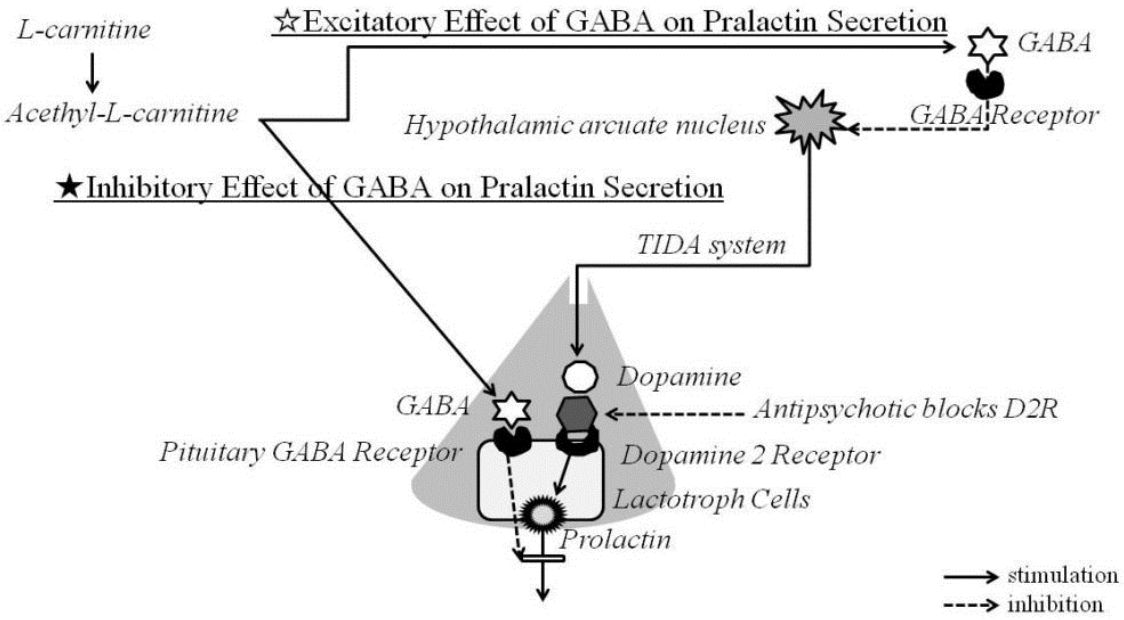

Fig. 1. The mechanism by which L-carnitine attenuates antipsychotic-induced hyperprolactinemia
L-carnitine is used for GABA biosynthesis in the brain. GABA exerts a dual control on prolactin secretion, one excitatory mediated by the impairment of TIDA system, the other inhibitory occurring at the level of the anterior pituitary. The former excitatory effect of GABA on prolactin secretion may not influence prolactin levels in patients with antipsychotic-induced hyperprolactinemia because TIDA system has already been blocked by antipsychotics. Thus, L-carnitie attenuates antipsychotic-induced hyperprolactinemia by stimulating pituitary GABA receptors.

We found that L-carnitine tended to decrease antipsychotic-induced high prolactin levels in clinical psychiatric settings. L-carnitine was coadministrated over a period of three months in seventeen psychiatric

inpatients treated with antipsychotics and valproate. As serum carnitine levels increased from 66.1±4.7μmol/L to 89.2±7.8μmol/L, the prolactin levels decreased from 52.2±8.4ng/ml to 33.7±6.6ng/ml. The ratio of prolactin levels at one month against baseline was significantly negatively correlated with the ratio of acylcarnitine/free carnitine levels at one month against baseline by using Spearman's correlation coefficient (r=-0.537, p=0.0319). L-carnitine attenuates antipsychotic-induced hyperprolactinemia in a concentration-dependent manner. L-carnitine turns into acety-L-carnitine in the body, which is an acetylated form of L-carnitine and most abundant naturally occurring derivative. According to the ^{13}C NMR study, acetyl-L-carnitine is incorporated into the carbon skeleton of the neurotransmitter gamma-aminobutyric acid (GABA). L-carnitine is used for GABA biosynthesis in the brain. GABA exerts a dual control on prolactin secretion, one excitatory mediated in part by the impairment of the tubero-infundibular dopaminergic (TIDA) system function, the other inhibitory occurring at the level of the anterior pituitary (Fig. 1). The two sites of action may be responsible for the excitatory and inhibitory effects of GABA on prolactin secretion. However, the former excitatory effect of GABA on prolactin secretion may not affect prolactin levels in patients with antipsychotic-induced hyperprolactinemia because TIDA system has been blocked by antipsychotics. Thus, the latter inhibitory effect of GABA on prolactin secretion may influence on prolactin levels, resulting in a mild prolactin sparing effect. Anterior pituitary GABA receptors have been shown to play a functional role in the inhibitory control of prolactin secretion. The inhibitory action of GABA seems to be mediated mainly by the activation of the high affinity receptor, which may appear in high proractin levels by suckling. Proactin lowering effect of GABA is a receptor-mediated event, where the high affinity receptor population is present. Scince antipsychotic-induced hyperprolactinemia may induce high affinity receptors like suckling, GABA reduces prolactin levels through pituitary GABA receptors (Fig. 1).

Although the main physiological control of prolactin secretion is exerted by the inhibiting action of dopamine, anterior pituitary GABA receptors have been shown to play a functional role in the inhibitory control of prolactin secretion in schizophrenia patients with antipsychotic-induced hyperprolactinemia. L-carnitine attenuates antipsychotic-induced hyperprolactinemia by stimulating pituitary GABA receptors. This mechanism is irrelevant to the dopaminergic system, therefore psychotic symptoms may not be aggravated. Pituitary GABA receptor stimulation by L-carnitine may be a new strategy for antipsychotic-induced hyperprolactinemia.

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