A new perspective on appetite control: protein tyrosine phosphatase 1b (ptp1b) inactivation by oxidative phytochemicals

Obesity and leptin

Obesity and overweight are resulted from poor control on appetite. A major part of appetite control relies on leptin and its receptor signal pathway (Figure 1). One obvious evidence supporting this idea can be observed from the mutation on leptin (ob gene in obese mice) or leptin receptor (db gene in diabetic mice). C57Bl mice with ob/ob gene will develop obesity while mice with-db/db gene will develop obesity and diabetes. The recessive ob gene mutation is due to an early termination on the leptin gene transcript. A replacement therapy on ob/ob mice with full length leptin resulted in reduced appetite and reduction in body weight.

Leptin signal pathway and PTP1B

The leptin signal pathway relies on Janus kinase (JAK) and signal transducer/activator of transcription (STAT) proteins to propagate its signal. When leptin binds to its receptor, JAK2 is activated to phosphorylate leptin receptor and STAT3. The phosphorylated STAT3 dimerize and become capable of modulating gene expression in the nucleus. The JAK/STAT signal is modulated by a negative regulator, protein tyrosine phosphatase 1b (PTP1B), which dephosphorylates STAT3 and thus renders STAT3 back to its ground state.

Insulin signal pathway and H$_2$O$_2$ formation

Activated insulin receptor can provoke several different pathways. One interesting but still poorly understood pathway is the activation of NADPH oxidase (NOX) which results in an increase in oxygen superoxide. Oxygen superoxide is then converted to hydrogen peroxide (H$_2$O$_2$) by superoxide dismutase (SOD). It has been shown that endogenous H$_2$O$_2$, arisen from insulin stimulation, can inactivate PTP1B, which in turns potentiates insulin signal transiently, as illustrated in Figure 2.

Reversible inactivation of PTP1B by H$_2$O$_2$

PTP1B is a phosphoryl hydrolase catalyzed by a cysteine residue. During the catalysis, the catalytic cysteine is deprotonated to thiolate anion which becomes a nucleophile. The cysteine thiolate anion is susceptible to H$_2$O$_2$ oxidation to sulphenic acid (-SOH) which renders PTP1B inactive. The sulphenic group on cysteine will condense with its adjacent amine group of n+1 peptide residue to become a sulphenylamide, resulting in an isothiazolidine ring on the peptide.
backbone. At the sulphenylamide stage, PTPIB enzyme activity can be restored by thiol reducing agents, e.g., glutathione or diithiothreitol, to its active thiolate anion stage. Thus, a mild oxidation on the catalytic cysteine of PTPIB is considered reversible, although the oxidation itself involves formation of covalent bonds. If the sulphenic group on PTPIB is further oxidized to sulphinic acid (─SO₂H) or sulphonic acid (─SO₃H), PTPIB enzyme activity is lost irreversibly, as illustrated in Figure 3.

**Figure 3** Reversible and irreversible oxidation of cysteine thiol on PTPIB. The thiol or thiolate anion of catalytic cysteine on PTPIB can be oxidized to a sulphinic acid form which can condense with an amine group to form a sulphenylamide resulting in an isothiazolidine ring on the peptide backbone. The sulphenylamide can be reduced by thiol reducing agents like diithiothreitol (DTT) or glutathione (GSH). If the sulphinic acid is further oxidized to sulphonic acid or sulphonic acid, they cannot be reduced back to the thiol form in vivo.

**Difficulty on PTPIB inhibitors**

Since the PTPIB gene knocked out mice was published in 1999, many scientists have been seeking a potent PTPIB inhibitor, which in theory can treat diabetes, overweight or even certain form of breast cancer (her2 oncogene is also regulated by PTPIB). The difficult part of finding a satisfactory PTPIB inhibitor is because T cell PTP (TCPTP) isoform bears a very similar active site contour. So PTPIB inhibitors are not able to distinguish these two PTP isozymes apart. As TCPTP is important for maintaining immune system function, mice lack TCPTP will suffer immune deficiency or even lethality. It is paramount to inhibit PTPIB but not TCPTP. For example, a recent PTPIB inhibitor with a selectivity of 30-fold over TCPTP is not good enough for pharmaceutical purpose, because pharmaceutical reagents require an isozyme selectivity of 1000 fold or greater (>3-order difference in IC₅₀) to be considered safe.

**Oxidative phytochemicals to augment \( \text{H}_₂\text{O}_₂ \) inactivation on PTPIB**

Since PTPIB can be inactivated transiently by endogenous \( \text{H}_₂\text{O}_₂ \), while PTPIB specific inhibitors are not ready for medical use, an alternative approach of inhibiting PTPIB may be using phytochemicals to mimic the action of \( \text{H}_₂\text{O}_₂ \). What compounds possess such oxidative power as \( \text{H}_₂\text{O}_₂ \)? Isothiocyanate compounds found in cruciales are capable of inactivating PTPIB. More recently, guava leaf extract from our laboratory suggest that polar phytochemicals in the guava leaf extract are also capable of inactivating PTPIB enzyme with stronger reactivity (20-80 folds higher pseudo-first reaction rates than those of isothiocyanates). While the identities of these compounds have not been identified, they do show a hypoglycemic efficacy when fed to healthy mice as well as a supplementary effect to insulin stimulated glucose uptake in adipocytes (presumably through an inactivation on PTPIB but elucidated on the insulin pathway). These results would suggest guava leaf extract, i.e., guava leaf tea, may have an appetite suppressing effect because of its oxidative potential on PTPIB.

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**Conflicts of interest**

The author declares no conflict of interest.

**References**


