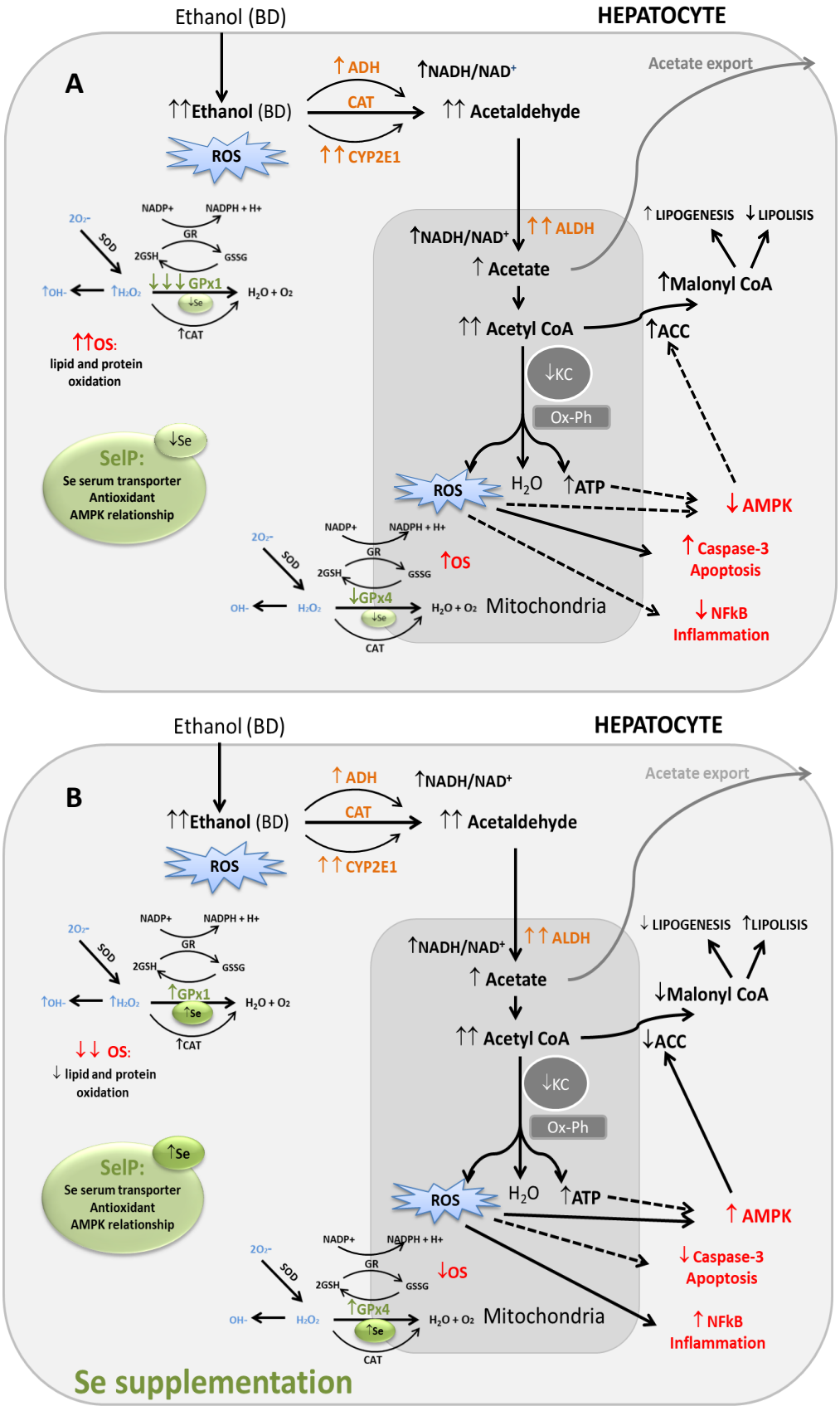
A
Ethanol (BD)
HEPATOCYTE
↑↑Ethanol (BD)
ROS
↑ ADH
CAT
↑↑ CYP2E1
↑NADH/NAD+
↑↑ Acetaldehyde
Acetate export
↑NADH/NAD+
↑↑ ALDH
↑ Acetate
↑↑ Acetyl CoA
↑ LIPOGENESIS
↓ LIPOLISIS
↑Malonyl CoA
↑ACC
↓KC
Ox-Ph
ROS
H2O
↑ATP
↓ AMPK
↑ Caspase-3
Apoptosis
↓ NFkB
Inflammation
Mitochondria
NADP+
NADPH + H+
GR
GSSG
2GSH
SOD
↓↓↓ GPx1
↓Se
↑CAT
H2O + O2
↑↑OS:
lipid and protein
oxidation
SelP:
Se serum transporter
Antioxidant
AMPK relationship
↓Se
↑OS
↓GPx4
B
↑ ADH
CAT
↑↑ CYP2E1
↑NADH/NAD+
↑↑ Acetaldehyde
↓ LIPOGENESIS
↑LIPOLISIS
↓Malonyl CoA
↓ACC
↑ AMPK
↓ Caspase-3
Apoptosis
↑ NFkB
Inflammation
↑GPx1
↑Se
↓↓ OS:
↓ lipid and protein
oxidation
↑Se
↓OS
↑GPx4
Se supplementation

Fig 1.

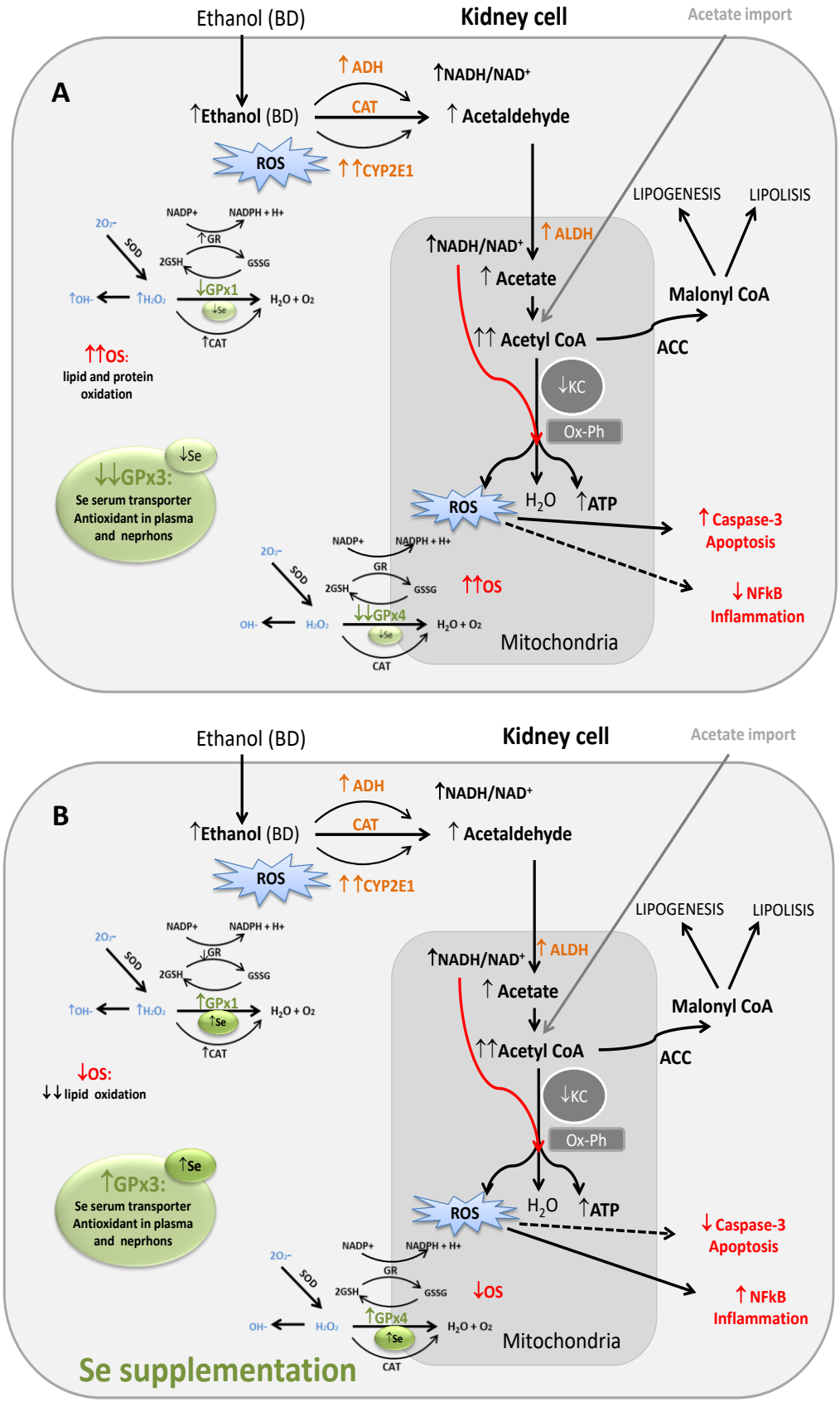
A
Ethanol (BD)
Kidney cell
Acetate import
↑ADH
CAT
↑CYP2E1
↑NADH/NAD+
↑ Acetaldehyde
↑Ethanol (BD)
ROS
LIPOGENESIS
LIPOLISIS
↑ALDH
↑NADH/NAD+
↑ Acetate
↑↑ Acetyl CoA
Malonyl CoA
ACC
↓KC
Ox-Ph
ROS
H2O
↑ATP
↑ Caspase-3
Apoptosis
↓ NFkB
Inflammation
↑↑OS:
lipid and protein
oxidation
↓Se
↓↓GPx3:
Se serum transporter
Antioxidant in plasma
and neprhons
NADP+
NADPH + H+
GR
GSSG
2GSH
SOD
↓GPx1
↓Se
↑CAT
H2O + O2
↓↓GPx4
↑↑OS
Mitochondria
B
Ethanol (BD)
Kidney cell
Acetate import
↑ADH
CAT
↑CYP2E1
↑NADH/NAD+
↑ Acetaldehyde
↑Ethanol (BD)
ROS
LIPOGENESIS
LIPOLISIS
↑ALDH
↑NADH/NAD+
↑ Acetate
↑↑Acetyl CoA
Malonyl CoA
ACC
↓KC
Ox-Ph
ROS
H2O
↑ATP
↓ Caspase-3
Apoptosis
↑ NFkB
Inflammation
↓OS:
↓↓ lipid oxidation
↑Se
↑GPx3:
Se serum transporter
Antioxidant in plasma
and neprhons
NADP+
NADPH + H+
GR
GSSG
2GSH
SOD
↑GPx1
↑Se
↑CAT
H2O + O2
↑GPx4
↓OS
Mitochondria
Se supplementation

Fig 2.

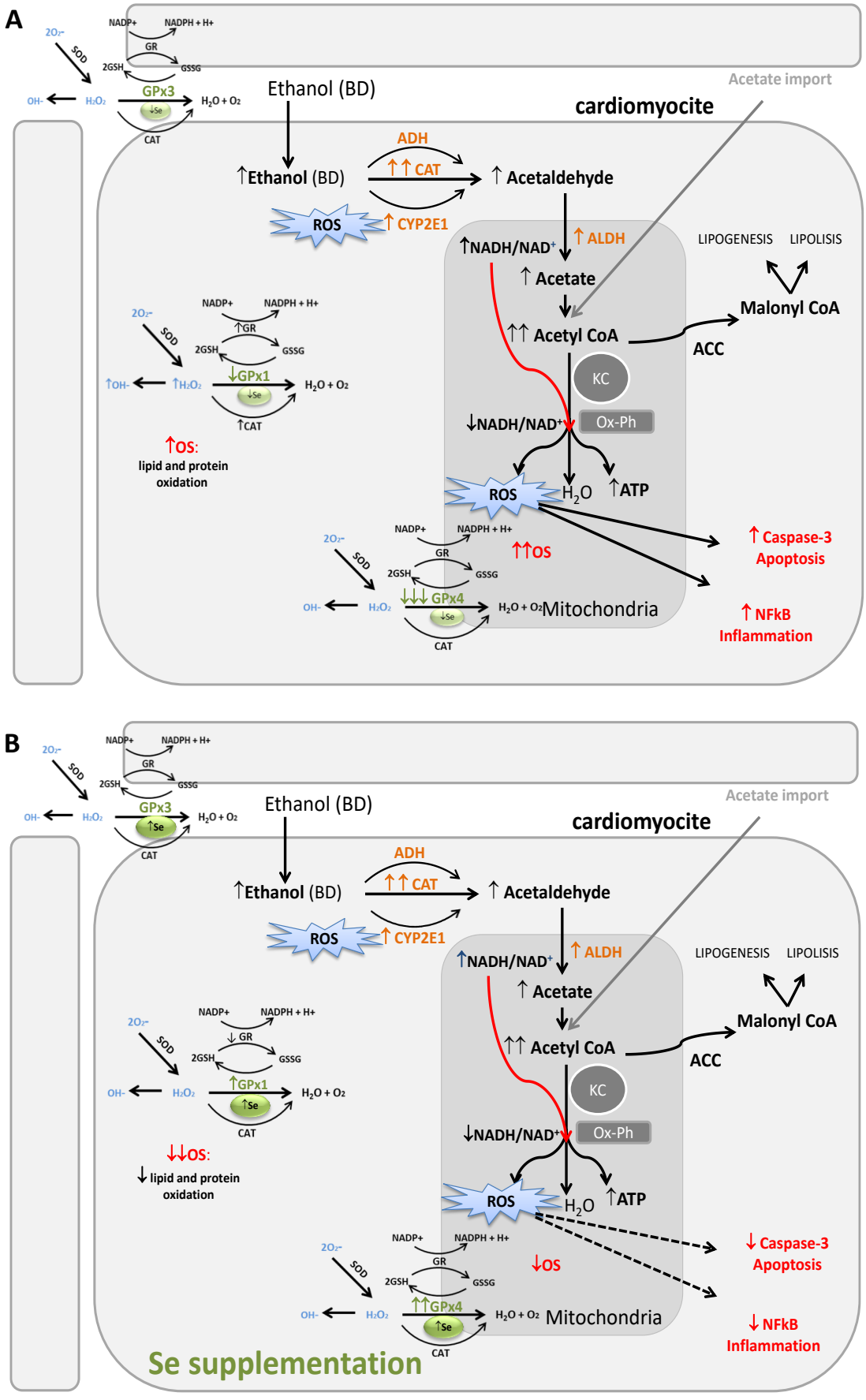
A
Ethanol (BD)
Acetate import
cardiomyocite
ADH
↑↑ CAT
↑ Acetaldehyde
↑Ethanol (BD)
ROS
↑ CYP2E1
↑NADH/NAD+
↑ ALDH
LIPOGENESIS
LIPOLISIS
↑ Acetate
Malonyl CoA
↑↑ Acetyl CoA
ACC
KC
↓NADH/NAD+
Ox-Ph
ROS
H2O
↑ATP
↑OS:
lipid and protein oxidation
↑↑OS
↑ Caspase-3 Apoptosis
↑ NFkB Inflammation
Mitochondria
GPx3
GPx1
GPx4
SOD
GR
CAT
B
Ethanol (BD)
Acetate import
cardiomyocite
ADH
↑↑ CAT
↑ Acetaldehyde
↑Ethanol (BD)
ROS
↑ CYP2E1
↑NADH/NAD+
↑ ALDH
LIPOGENESIS
LIPOLISIS
↑ Acetate
Malonyl CoA
↑↑ Acetyl CoA
ACC
KC
↓NADH/NAD+
Ox-Ph
ROS
H2O
↑ATP
↓↓OS:
↓ lipid and protein oxidation
↓OS
↓ Caspase-3 Apoptosis
↓ NFkB Inflammation
Mitochondria
Se supplementation
GPx3
GPx1
GPx4
SOD
GR
CAT

Fig 3.

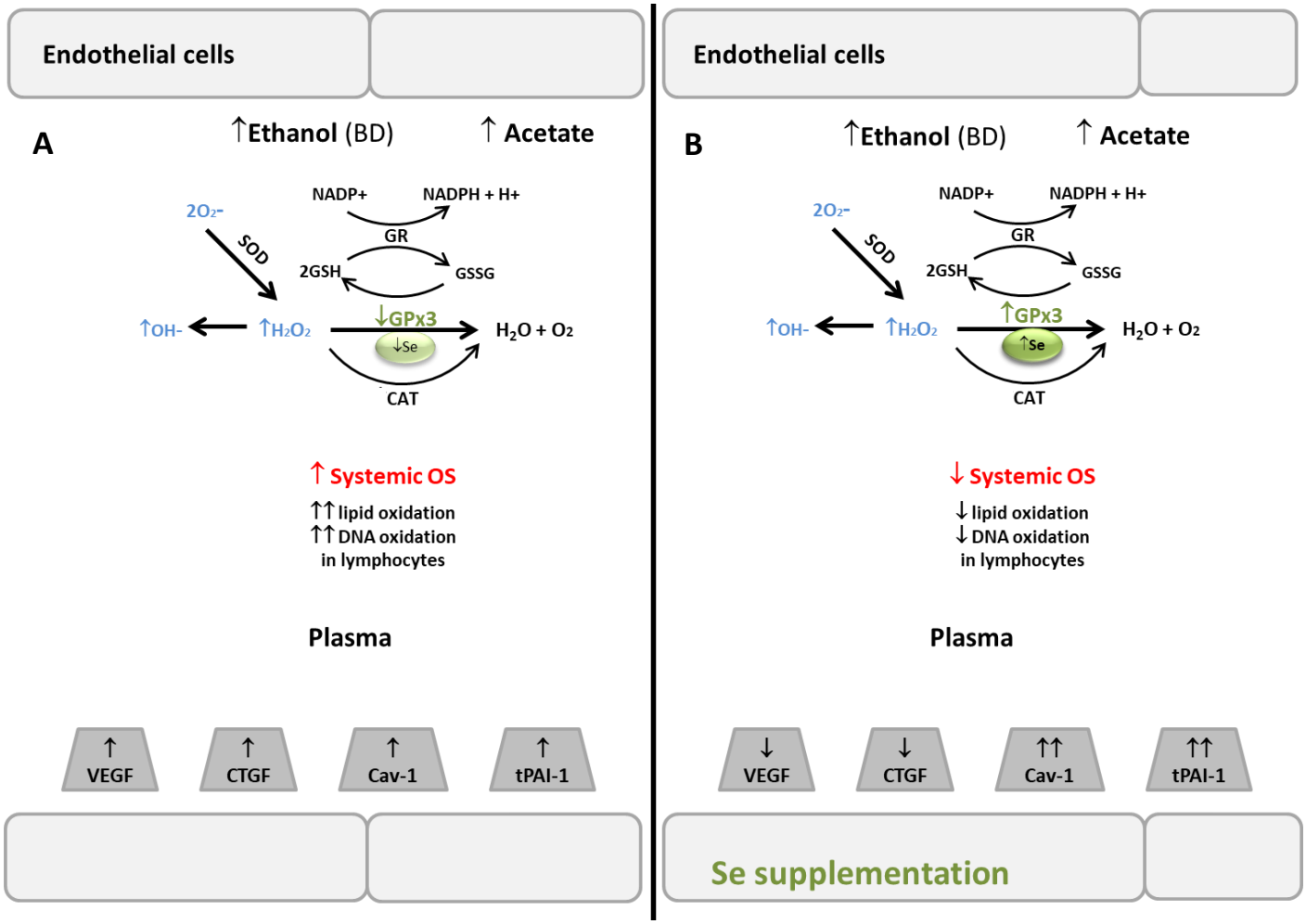
Endothelial cells
A
↑Ethanol (BD)
↑ Acetate
2O2-
SOD
NADP+
NADPH + H+
GR
2GSH
GSSG
↑OH-
↑H2O2
↓GPx3
↓Se
H2O + O2
CAT
↑ Systemic OS
↑↑ lipid oxidation
↑↑ DNA oxidation
in lymphocytes
Plasma
↑ VEGF
↑ CTGF
↑ Cav-1
↑ tPAI-1
Endothelial cells
B
↑Ethanol (BD)
↑ Acetate
2O2-
SOD
NADP+
NADPH + H+
GR
2GSH
GSSG
↑OH-
↑H2O2
↑GPx3
↑Se
H2O + O2
CAT
↓ Systemic OS
↓ lipid oxidation
↓ DNA oxidation
in lymphocytes
Plasma
↓ VEGF
↓ CTGF
↑↑ Cav-1
↑↑ tPAI-1
Se supplementation

Fig 4.

LEGENDS:

Fig. 1 EtOH metabolism in liver: oxidative implications. **Effects of sodium selenite supplementation**. (**A**) EtOH is oxidised in hepatocytes, mostly through the alcohol dehydrogenase (ADH) enzyme, which in turn produces an increase in cytoplasmic NADH/NAD^+ ratio. In BD exposure, ADH is saturated (KM < 5 mM) and CYP2E1 increases its activity, generating a large amount of ROS, that together with an imbalance of the antioxidant enzymes Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase 1 (GPx1) and Glutathione Reductase (GR), leads to cytosolic lipid and protein oxidation (OS). This large amount of ADH- and CYP2E1-generated acetaldehyde enters the mitochondria and is oxidised into acetate by acetaldehyde dehydrogenase (ALDH), increasing intramitochondrial NADH/NAD^+ ratio. The acetate formed is converted into Acetyl CoA which enters the Krebs cycle (KC) and via oxidative phosphorylation (Ox-Phos) produces ATP and ROS. At blood alcohol levels greater than 0.01 g/dL, hepatic KC is markedly suppressed, and the remaining acetate is exported into the blood. The increase in ATP and ROS production in mitochondria decreases AMP-dependent protein kinase (AMPK) activity. This decrease leads to higher Acetyl CoA carboxylase (ACC) activity and higher Malonyl CoA levels which increase lipogenesis and prevents lipolysis. High mitochondrial ROS production, together with lower GPx4 expression, leads to mitochondrial OS. This, in turn, is related to higher caspase-3 activation and apoptosis, as well as to a lower NFkB activation. Despite the lower Se deposits in liver caused by BD, expression of the main hepatic selenoprotein SelP is not affected by BD exposure, and therefore its action delivering Se to serum and other tissues seems to be unaffected; (**B**) Sodium selenite supplementation in adolescent BD rats by increasing hepatic Se deposits, increases GPx1 expression and activity, preventing cytosolic lipid and protein oxidation. It also increases GPx4 expression and decreases mitochondrial OS. This latter reduces apoptosis, increases NFkB activation and increases AMPK activity, while also improving hepatic lipid profile. Solid lines and hatched lines indicate stimulatory and inhibitory actions, respectively.

Fig. 2. **EtOH metabolism in kidney: oxidative implications**. **Effects of sodium selenite supplementation**. (**A**) EtOH is mostly oxidised in hepatocytes, but when EtOH arrives in large amounts to blood, as occurs in BD exposure, other tissues collaborate with liver. This is the case of kidney; kidney cells contain the enzyme alcohol dehydrogenase (ADH), which in turn produces an increase in cytoplasmic NADH/NAD^+ ratio. If this is not sufficient, it could increase CYP2E1 activity generating large amount of ROS, which together with antioxidant enzyme imbalance leads to cytosolic lipids and protein oxidation. The amount of acetaldehyde generated by ADH and CYP2E1 enters the mitochondria and is oxidised to acetate by acetaldehyde dehydrogenase (ALDH), this acetate production, together with the acetate taken up from blood increases intramitochondrial NADH/NAD^+ ratio. Acetate is converted to Acetyl CoA which enters the Krebs cycle (KC) and via oxidative phosphorylation (Ox-Phos) produces ATP and ROS. Mitochondrial ROS production, together with a lower GPx4 expression, leads to mitochondrial OS. This, in turn, is related to higher caspase-3 activation and apoptosis, and to a lower NFkB activation. The lower Se deposits in kidney caused by BD also affects expression of the main kidney selenoprotein, GPx3, which decreases. Therefore its action delivering Se to serum decreases; **(B)** Sodium selenite supplementation in adolescent BD rats by increasing renal Se deposits increases GPx1 expression and activity, preventing cytosolic lipid oxidation. Supplementation also increases GPx4 expression and decreases mitochondrial OS, decreasing apoptosis and increasing NFkB activation. It also increases GPx3 expression which probably will shunt Se to serum. Solid lines and hatched lines indicate stimulatory and inhibitory actions, respectively.

Fig. 3 EtOH metabolism in heart: oxidative implications. **Effects of sodium selenite supplementation**. (**A**) Heart, due to the lack of ADH, may oxidize some ethanol mainly through CAT and/or CYP2E1, but these rates are low, however it could generate ROS that joint to an imbalanced antioxidant system leads to cytosolic oxidation of lipids and proteins. The acetaldehyde generated by CAT and CYP2E1 enters the mitochondria and is oxidised to acetate by acetaldehyde dehydrogenase (ALDH). This acetate, together with the acetate taken up from blood in an uncontrolled manner, increases the intramitochondrial NADH/NAD^+ ratio. Acetate is converted to Acetyl CoA which then enters the Krebs cycle (KC) and via oxidative phosphorylation (Ox-Phos) produces ATP and ROS. Mitochondrial ROS production, together with the extremely low GPx4 expression, leads to mitochondrial OS. This, in turn, is related to higher caspase-3 activation and apoptosis, and to a higher NFkB activation (fibrosis). The lower heart Se deposits caused by BD do not affect the extracellular expression of GPx3 in heart, a protein is related to serum glucose alteration; **(B)** Sodium selenite supplementation in adolescent BD rats increases Se heart deposits; increases GPx1 expression and activity preventing cytosolic lipid and protein oxidation. It also increases GPx4 expression and decreases mitochondrial OS, thus decreasing apoptosis and NFkB activation. Solid lines and hatched lines indicate stimulatory and inhibitory actions, respectively.

Fig. 4 EtOH metabolism in plasma. Effects of sodium selenite supplementation. High EtOH consumption leads to large amount of acetate and ROS in plasma, but it also provokes an unbalanced antioxidant system in which serum GPx (GPx3) decreases, generating lipid and protein oxidation in serum. BD exposure also generates profound oxidation in lymphocytes DNA, therefore systemic OS appears. This OS could be related to the increase in serum endothelial markers such as Vascular Endothelial Growth Factor (VEGF), Connective Tissue Growth Factor (CTGF), Caveolin 1 (Cav-1) and Plasminogen Activator Inhibitor-1 (tPAI-1). By increasing serum Se levels, sodium selenite

supplementation in adolescent BD rats increases GPx3 activity preventing serum lipid oxidation and lymphocyte DNA oxidation, leading to lower systemic OS. This supplementation also decreases the levels of proangiogenic growth factors VEGF and CTGF, something that is considered beneficial; however the increase in serum Cav-1 and tPAI-1 was even greater.