CNS stimulants are drugs that increase muscular (motor) and mental activities. These effects may vary from increased alertness and wakefulness (e.g. caffeine) to the production of convulsions (e.g. strychnine).

CNS stimulants produce most or all of the following signs and symptoms:

1. Increase in heart rate.
2. Increase in respiratory rate.
3. Irritability and restlessness.
4. Muscle twitching and hair erection.
5. Convulsions which may lead to death.

The aim of this practical session is to:

1. Investigate the effect of drugs that can stimulate the central nervous system.
2. Demonstrate the site of action of a CNS stimulant drug.

Classification of CNS stimulants:
CNS stimulants are divided according to their main site of action into 3 main subgroups:

1. **Cerebral Stimulants:** e.g. caffeine.

   This group of drugs acts mainly upon the cerebral cortex. In large doses, these drugs produce epileptiform or mixed convulsion.

   Effect of caffeine on the CNS:

   Caffeine increases the motor activity, induces tremors, stimulates the medullary respiratory center & stimulates the CVS by acting on the vagal & vasomotor centers in the brain stem.
When caffeine is administered to a mouse, it produces the following signs:

a- Protrusion of the eye ball.
b- Erection of the tail and hair.
c- Increase in HR and RR.

Mechanism of action of caffeine:

Caffeine is a competitive antagonist of adenosine receptors located on cell membranes of CNS & PNS. Adenosine is an autacoid that primarily produces sedation, regulates delivery of oxygen to cells, dilates cerebral & coronary blood vessels & produces bronchospasm.

2. Medullary Stimulants: e.g. cardiazol and picrotoxin.

These drugs act mainly upon the medulla oblongata. In excessive doses these drugs produce clonic convulsions, which are characterized by being:

a- Asymmetric i.e. the left side of the body convulses at a different time from the right one.
b- Coordinated i.e. when the flexors contract the extensors are relaxed.
c- Spontaneous in origin i.e. the convulsions develop of their own and not in response to external stimuli.
d- Intermittent i.e. not continuous.

3. Spinal Stimulants: e.g. strychnine.

These drugs act mainly upon the spinal cord. In large doses these drugs produce tonic convulsions, which are characterized by being:

a- Symmetric i.e. the two sides of the body convulse simultaneously.
b- Reflex in origin i.e. the convulsions developed only in response to external stimuli as touch, pain or light.
c- Uncoordinated i.e. both flexor and extensor muscles contract at the same time. The body becomes rigidly arched backwards into a posture known as "opisthotonous".
d- Sustained (continuous).
Mechanism of action of strychnine:

Strychnine acts as a selective, competitive antagonist to block the inhibitory effects of glycine at all glycine receptors. It enhances the level of neuronal excitability by selectively blocking postsynaptic inhibition mediated by glycine.

<table>
<thead>
<tr>
<th>Tonic Convulsions</th>
<th>Clonic Convulsions</th>
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<tbody>
<tr>
<td>Symmetric</td>
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<td>Coordinated</td>
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Note:
When large doses are used, the site of action of the mentioned above CNS stimulants is not strictly localized and may become more diffuse. Thus medullary stimulants (e.g. cardiazol) in large doses may spread in the CNS and give signs of spinal cord stimulant (e.g. strychnine).

Practical procedure:

Experiment I:

Inject the calculated dose of strychnine into the dorsal lymph sac (d.l.s.) of the frog (passing through the thigh muscle). Determine the onset of action of strychnine and the type of signs, which will appear.

Onset of action: the time between the administration of the drug and the appearance of symptoms.

Calculation of the administered dose:

The dose of the drug to be administered to an experimental animal is usually given as mg/kg body weight; since the drug cannot be injected in a solid form, a solution of suitable concentration is prepared, and the volume of the solution that should be administered to the animal is determined.
**Example**
- The dose of drug X is 100 mg/kg body weight
- The concentration of the provided drug solution is 1% w/v
- The weight of the frog is 20 gm

100 mg of the drug are injected in 1000 gm frog
X mg of the drug are injected in 20 gm frog
X = 20*100/1000
X = 2 mg

Solution concentration is 1% w/v
i.e. 1g is present in 100 ml
1000 mg are present in 100 ml
2 mg are present in X ml of the solution

X = 2*100/1000 = 0.2 ml

*This means that 0.2 ml of drug X (1% w/v) will be administered to the 20 gm frog.*

**Experiment II: Determination of the site of action of strychnine**

1- Decapitate the frog (decapitation means the removal of the upper jaw which contains the brain, leaving the spinal cord which is supposed to be the site of action of strychnine).

2- Fix the frog on its abdomen.

3- Open the skin in one thigh muscle region and expose the sciatic nerve.

4- Inject strychnine solution to the dorsal lymph sac through the other thigh muscle; convulsions occur after strychnine is absorbed, distributed and reached its target organ, the spinal cord. Note that convulsions appear in the whole body including both lower limbs.

5- Cut the sciatic nerve; the whole frog is in convulsion except the lower limb where the sciatic nerve is cut, indicating that the sciatic nerve is involved in this convulsion.

6- Destroy the spinal cord by introducing a needle in the spinal canal; the whole body becomes relaxed. This indicates that strychnine acts specifically on the spinal cord.
Inject 30 mg/Kg of the provided strychnine solution (0.2 % w/v) into the dorsal lymph sac of the frog.

Fill in the recording sheet below.

**Recording Sheet**

Weight of the frog: ........................................
Dose of the drug: ..............................
Injected volume: ..............................

**Calculations:**

Onset of drug action: .........................

**Observations:**

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