UNIVERSITY OF GOTHENBURG

SAHLGRENSKA ACADEMY

The effect of the dopaminergic stabilizer OSU6162 on impulsivity induced by dopaminergic receptor agonists

Degree Project in Medicine

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Gothenburg, Sweden 2019

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Abstract

Background: Pramipexole is a dopaminergic receptor agonist with high selectivity for the D2-receptor family. It is used in the treatment of neurological disorders such as Parkinson's disease. It is effective to improve motor symtoms in this condition. It has however behavioural side effects related to impulsivity, such as pathologic gambling and excessive shopping. Animal studies using different models for impulsivity, such as the delay discounting task, have seen an increase in impulsive behaviour in rats treated with Pramipexole.

OSU6162 is a dopaminergic stabilizer which has been shown to improve impulsive behaviour in rats.

Aim: To investigate if rats treated with Pramipexole would show increased impulsive behaviour in the delay discounting task. And if so, whether this increase in impulsivity can be attenuated by OSU6162.

Methods: 10 male Wistar rats were trained in the delay discounting task. When training was complete, they were given subcutaneous injections of Pramipexole (1 mg/kg and 0.1 mg/kg) 20 minutes before starting the delay discounting task.

Results: Treatment of Pramipexole resulted in drowsy behaviour and the data was not further analysed. Because of time limitations, the project was not continued beyond these experiments.

Conclusion: While some other studies have seen an increase in impulsive behaviour in rats treated with Pramipexole, using the delay discounting task, this effect seems slightly elusive. Further tests with different doses of Pramipexole should be performed. The sedating effect of Pramipexole complicates the testing of the compound in this model.

Background

How to define impulsivity

Impulsivity is a broad term that can encompass many different behaviors. Daruna&Barnes (1993) provides a definition that is also useful outside of academic research:

"*... impulsivity encompasses actions that appear poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often results in undesirable consequences.*" (1)

Others, such as Barratt (1994) have recognized that the term impulsivity seem to include a number of different dimensions, such as motor impulsivity (acting without thinking), and non-planning impulsivity (lack of concern for the future). These are factors that are included in the Barratts impulsivity scale (BIS) (2).

Impulsivity in psychiatric disorders

Impulsivity, as defined above, seems to play a part in several psychiatric diseases.
For personality disorders, such as borderline personality disorder, the diagnostic criteria include "impulsive and reckless behaviour". For antisocial personality disorder, one of several diagnostic criteria that can be related to impulsivity is "reckless disregard for safety of self and others" (3).
Other important diagnoses in this regard is ADHD (attention deficit/hyperactivity disorder) and impulse control disorders, including drug and alcohol abuse as well as pathologic gambling and kleptomania (3).

Biological background to impulsivity

Both serotonergic and dopaminergic transmission has been seen to affect impulsive behavior in animal studies. Different receptor subtypes for these transmitters seem to affect impulsive behavior in different ways. For example, pre-clinical studies have shown opposite effect of 5-HT2c-antagonism and 5-HT2a-antagonism in the same model of impulsivity (4).

There also seem to be a paradox regarding the influence of dopamine on impulsivity where ADHD-medication that stimulates dopamine release improves symptoms but dopaminergic agonists and L-dopa used in the treatment of Parkinson can result in side effects such as pathologic gambling, increased libido and excessive shopping (4, 5).

How to measure impulsivity

Reflecting the above mentioned definition of impulsivity as having several aspects, the models for studying impulsivity is generally divided in a two main groups: models that study impulsive action (or so called motor impulsivity) and those that study impulsive choice (6).

Impulsive action can be studied in models that require the subject to withhold a response. Common models used for the study of animals such as rat are Go/-no go and SSRT (stop signal reaction time). In the Go-/no-go for example, the rat can earn a reward by pressing a lever when the "go-signal" shows (which can be a stimuli-light) and when the "no-go signal" shows it must refrain from pressing the lever to earn the reward (7).

Impulsive choice can be studied in models such as the delay discounting task (6).

Delay discounting as a way of studying impulsivity in animals

Delay discounting has been used extensively to study impulsive behaviour in both animals and humans (4). The general principle of the method is that the subject is given a choice

between two rewards, one of them is larger and delivered after a delay and the other is smaller and delivered immediately. Impulsive behavior is then defined as choosing the smaller (but immediate) reward more often (3).

In practice this can be achieved in many ways, earlier methods, such as Thiébot (1985), did for example use a maze where the longer path led to the larger reward (8). Nowadays this is usually achieved by using levers and systems to automatically deliver the reward after a delay (3).

A way to use the delay discount procedure is to stepwise increase the delay to the large reward. Introduced by Evenden (1996) this is a common method for studying rats. The result of this method is a delay-discount curve that sees the decreased choice of the larger reward as the delay increase (9).

The list of drugs tested in rat using the delay discount task is quite extensive. Among the most studied is amphetamine which is usually seen to increase impulsive choice (that is, choice of the smaller reward) (3).

Dopaminergic receptor agonists

Pramipexole is a dopaminergic receptor agonist used in the treatment of neurological diseases such as Parkinson's disease where it is used alone or in combination with L-dopa (10). It has high selectivity for dopamine D2-receptors and does not interfere much with serotonergic and adrenergic receptors (11).

In Parkinson patients, Pramipexole improves control of motor symtoms. Side effects however includes behavioral problems such as impulse control disorders (12).

OSU6162 - a dopaminergic stabilizer

OSU6162 was developed during the 1980's by researchers in Gothenburg (13). Among them Arvid Carlsson who in 2000 was awarded the Nobel price in Medicine or Physiology for the discovery of dopamine as a neurotransmitter in the CNS (14).

OSU6162 is known as a dopamine stabilizer and has affinity for dopaminergic D2 and D3-receptors where it seems to function as an antagonist(15). It also seems to have antagonistic effect on 5-HT1- and 5-HT2-receptors (16).

The term "dopamine stabilizer" comes from the ability to stabilize behaviour related to dopaminergic functions. It has for example been shown to attenuate the hyperlocomotion induced by amphetamine in rats (17) as well as increase the locomotion in rats who has less baseline activity as a result of habituation (18).

OSU6162 has also been tested in humans, as a potential treatment against alcohol dependence (19), fatigue induced by brain damage (20) and Huntingtons disease (21).

A study by Fredriksson (2019) saw improved motor impulsivity in rats treated with OSU6162. It was suggested that the improved impulsive control can contribute to the ability of OSU6162 to attenuate alcohol-mediated behaviour (22).

Aim

The aim of this project is to investigate if rats treated with the dopaminergic agonist Pramipexole will show increased impulsive behaviour in the delay discounting task. And if so, whether this increase in impulsivity can be attenuated by the dopaminergic stabilizer OSU6162.

Materials and methods

Materials and equipment

Training and testing were done using 10 operant conditioning chambers (see figure 1 and 2).

The chambers were equipped with two retractable levers, left and right of a pellet dispenser.

Above each lever was a stimulus light and on the opposite wall was a house light.

4 infrared photodiodes register movement in the chamber and one photodiode registered movement in the pellet receptacle.

The pellet dispenser delivered 45 mg sucrose pellets.

The software controlling the chambers was written in-house by the author of this thesis.

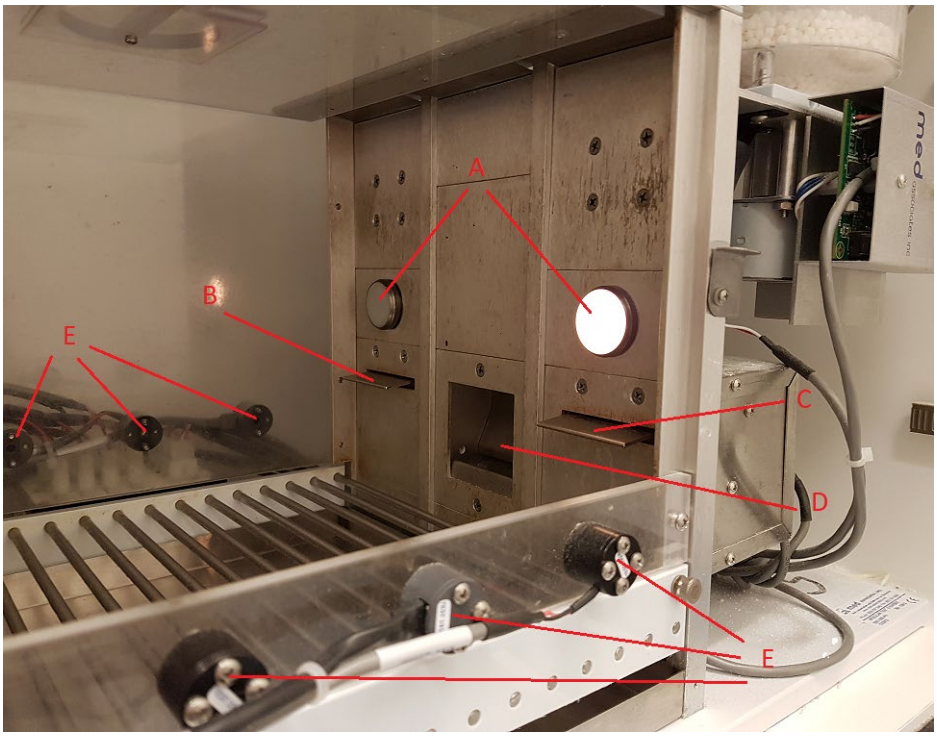

Figure 1. The operant conditioning chamber used for the delay discounting task. **(A)** two stimuli lights. **(B)** Left lever. **(C)** Right lever. **(D)** Pellet dispenser. **(E)** infrared photodiodes that detect movement inside the chamber.

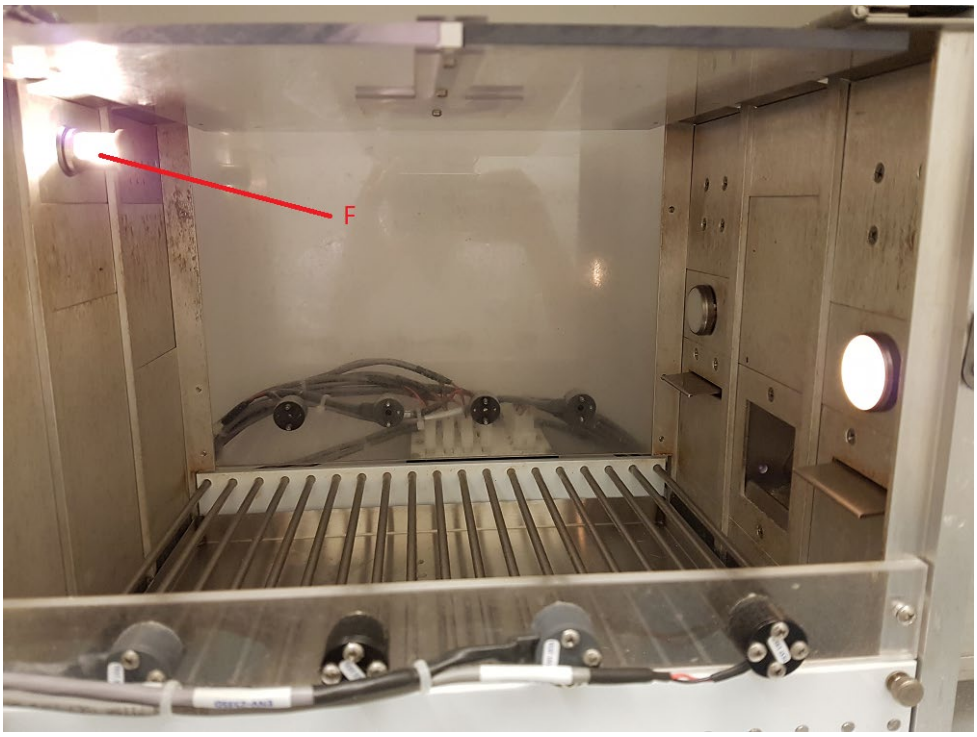

Figure 2. The operant conditioning chamber. **(F)** The house light.

Training in the operant conditioning boxes

The protocol for the delay discount task was based on the one used by Mar & Robbins (2007) (23).

Preparation

Before start of training, the animals were handled by the researcher in order to accommodate them to human interaction. This was done by lifting up and gently petting the animals for around one minute.

Each animal were weighed and marked using a permanent marker pen (each assigned a number 1-10) on the tail.

The animals were assigned one operant box each, so that they would use the same box throughout the entire project (that is, both training and experimental procedures).

Fixed ratio

The aim of the very first training in the operant chambers was to teach the animals to use the levers to gain sucrose pellets.This was done using a *fixed ratio 1* schedule, that is, one lever press results in one pellet.

This was done once daily and each session lasted 30 min.

During the session, both levers were extended and so could be pressed but only one was active and pressing this resulted in a sugar pellet being delivered.

The animals were counterbalanced for which lever were learned first, so half of the rats started with the left lever active and the other half started with the right lever active.

The animals were regarded as having learned to use a lever when 30 lever presses, resulting in a sugar pellet each, were made during a session. It took between 9-25 sessions for all animals to learn this.

When the animal had learned to use both levers it would, the next session, start training on the delay discounting task.

Delay discounting task

One session per day, 5-7 days/week was conducted. Each session consisted of 4 blocks with different delays (0 sec, 10, 20, 40), the blocks were in this order of increasing delay. In turn, each block consisted of 10 trials, 8 of which were free-choice trials when the animal could chose between the two levers. 2 of the trials were forced-choice, in which only one lever was extended and available to press. For a schematic representation of the task se figure 3.

Each trial lasted 100 seconds. When a trial started, the house light turned on and the levers were extended (only one lever if it was a forced choice trial). If no lever were pushed within 10 seconds, the levers were again retracted and the house light turned off, this would be registered as an omission. The animal would then spend the rest of the trial in the dark until the next trial started.

If the animal pushed one lever within the 10 second time limit it would result in a sugar pellet immediately being delivered via the pellet dispenser or it would have 3 pellets delivered after a delay depending on which lever was pushed. The delay would depend on which block the trial was in.

So for example, if the rat chose the lever assigned as the “delay-lever” during the second block, 3 pellets would drop after a delay of 10 seconds.

The aim of the training in the delay discount task was to achieve stable choice between sessions as well as an effect of delay on the choice. Ideally, the choice of the delay lever should be high in the first block, when the delay is 0 seconds. When this was achieved, experiments with pharmacological compounds could be started using the delay discounting task.

After around 2 weeks of training, while the session to session choice of the delayed lever was stable, the animals chose the delayed lever only around 40% of the time in the first block and there was no effect of delay. It was therefore decided to make changes to the protocol.

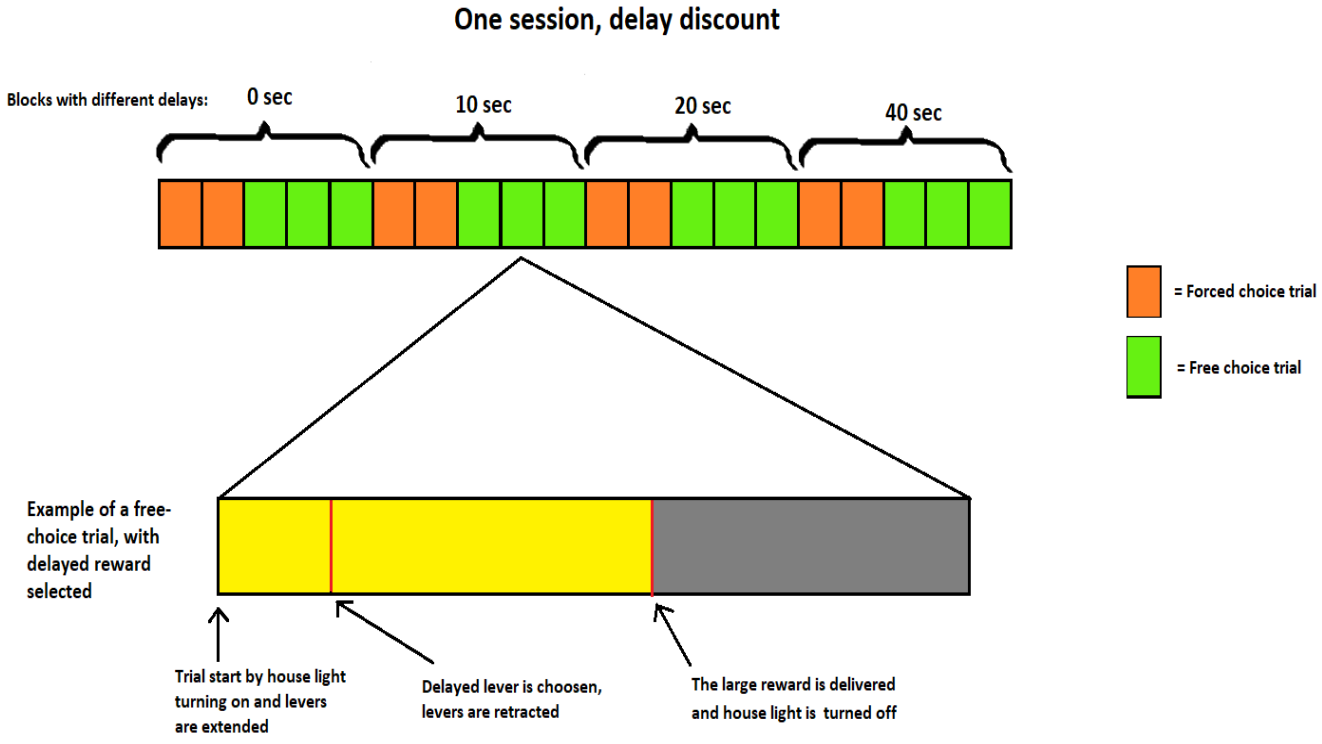

Figure 3. A schematic representation of the delay discounting task. In this example, each block consists of 2 forced choice trials and 3 free choice trials.

Change of protocol for delay discounting

In order to achieve a higher choice of the delayed lever in the first block as well as to see an effect on choice depending on delay, it was decided to make changes to the protocol.

The reward for choosing the delayed-lever was increased to 4 sugar pellets and the stimuli light would signal the delay-time to make it more clear to the animal that pushing the lever would result in a reward being delivered.

An additional moment was also added to the very start of the trial, where the animal now had to nose poke into the pellet receptacle for the levers to be extended. This was to ensure the animal would be centered between the two levers when they were extended.

The number of free choice trials in respective block was reduced from 8 to 6, while the number of forced-choice was kept at 2 per block.

The length of each trial was also reduced, depending on the delay time, so that the entire session lasted for 30 minutes instead of 65 minutes. This would make it likely that the plasma levels of the pharmacological compounds to be tested would stay more even over the course of the test.

Experimental procedures

After 9 sessions of training on the delay discount task after a new protocol was adopted, the rats showed an effect of delay as well as a choice of the delayed lever at around 80% at the first block (0 seconds delay to large reward).They were thus ready for testing of the drug.

The experiment was designed as a cross-over study. The 10 animals were randomized into two groups, 5 animals in each. For each dose of the drug tested, there were two test days.

On testing day 1, one of the groups received injections with the drug and the other group received vehicle injection. 20 minutes after injection, the animals were placed in the boxes and the session started.

On testing day 2, the treatment was reversed so that the group that received drug injection now received vehicle injection, and vice versa.

Between the two test-days were 2 days of rest and 1 day of normal training without injections.

Drugs

Pramipexole was dissolved in saline (0.9%) and was given in subcutaneous injection, with an injection volume of 2 ml/kg.

Two different doses of Pramipexole were tested, 1 mg/kg and 0.1 mg/kg.

Animals

10 male, Wistar rats from Charles River, Germany. 3 months of age at arrival and around 6 months of age at the start of the experimental procedures.

Housed 2-3 per cage at a 12 hour light cycle (7 am – 7 pm).

Food and water were available *ad libitum*.

Ethics

The ethical number for the animal research conducted in this project is 137-2015. The research was approved by the regional ethics committee in Gothenburg (Göteborgs djurförsöksetiska nämnd).

Data analysis

The primary variable analyzed were the choice of the delayed lever during free choice trials, as a percentage of the total lever presses during respective block.

Other variables analyzed were movement in the box, head pokes during delay period, omissions and latency to press lever.

A limit of at least 3 lever presses per block were used to include that block in the analysis.

Results

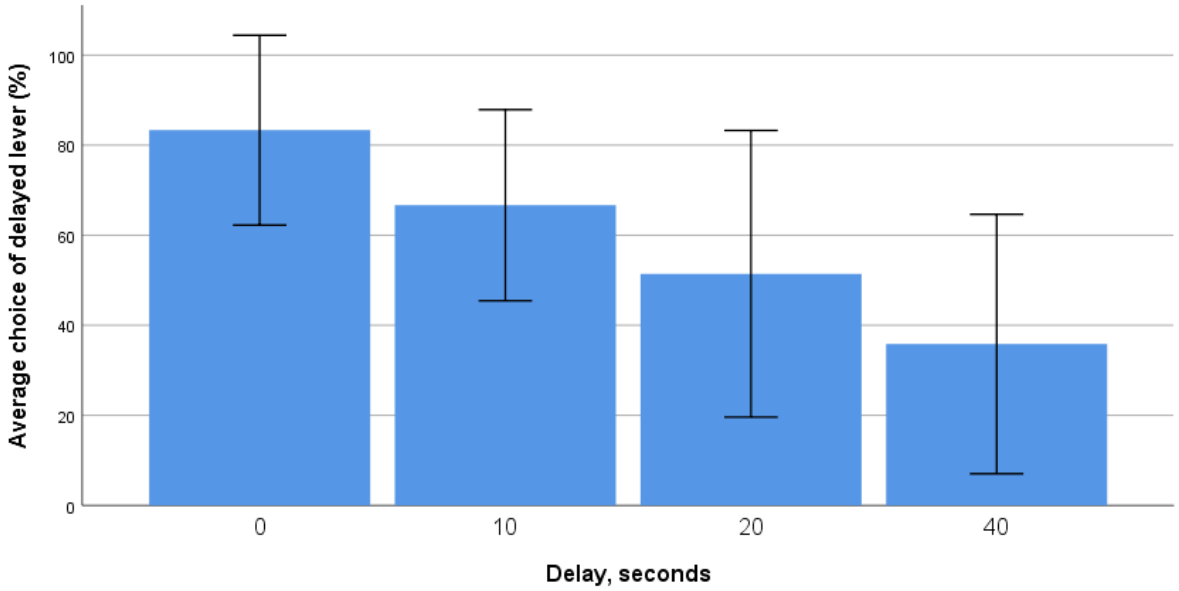

Figure 4. Average choice of the delayed lever at the end of training in the delayed discounting task (n = 10). This was after 9 sessions using the new protocol. Error bars: +/- 2 SE.

Training was completed after 9 sessions in the delay discounting task. As can be seen in figure 4, there was considerable variation in choice of lever. A repeated measure, within subject ANOVA showed no significant effect of delay ($F = 6.538$, $p = 0.136$).

Two doses of Pramipexole were tested, first 1 mg/kg and then 0.1 mg/kg. Unfortunately both doses resulted in the animals appearing somnolent and very few lever presses were registered. The animals that received treatment were mostly sleeping while in the box. Therefore the data was not further analyzed.

Using the first dose of 1 mg/kg Pramipexole, only one animal completed all 4 blocks (in other words, it achieved the designated threshold of 3 lever presses per block), whereas all other

animals made no lever presses at all.

In the vehicle group on the other hand, only one animal failed to complete all 4 trials.

When administered the second dose of 0.1 mg/kg, more lever presses were made. However, the treated animals completed in total only 17 blocks out of a possible 40 (10 animals, 4 blocks each).

When given the vehicle solution the animals completed 33 out of 40 blocks.

Discussion

The aim of this project was to first asses if the dopaminergic agonist Pramipexole could have an effect on impulsive choice in the delay discounting task, and if so, if the dopamine stabilizer OSU6162 could attenuate this effect.

One earlier study with rats treated with Pramipexole have seen an increase of impulsive behavior in the delay discounting task at doses ranging between 0.1-0.3 mg/kg, and a tendency towards impulsive behavior at 0.03 mg/kg (24). However the effect could be elusive, as Koffarnus (2011) did not see a significant effect at those doses (25).

In one other study, using a different model of impulsivity, Pramipexole was shown to increase impulsivity at 0.3 mg/kg and 1 mg/kg (26).

Due to time limitations only two doses of Pramipexole were tested during the project. Unfortunately, both doses resulted in such a large number of omissions, and the animals being visibly tired, that the results were not further analyzed.

Earlier studies have seen a dose-dependent increase of omissions in the delay discounting task with doses ranging from 0.10 – 0.30 mg/kg (24) and other studies indicates that Pramipexole

has an effect on locomotion and sleep in rats (27).

Doses between 0.1-0.3 mg/kg are generally used in behavioral models when studying Pramipexole (28). It seems strange therefore that 0.1 mg/kg, when tested in this experiment would make the animals so sleepy. This could be due to a too short wash out period after the larger dose or experimental errors when handling the drugs for example. It seems warranted to try doses in this range again.

What took the most time during the project was the training of the animals in the delay discounting task. Because the response was not satisfactory using the first protocol a change of protocol was made, which meant that more time for training was needed.

The change of protocol that was made was due to the low choice of the delayed-lever at 0 seconds and little effect of the increasing delay on choice.

This meant that there was little room for more “impulsive” choice to be seen, as the animals often choose the immediate reward at baseline.

The addition of a cue light to signal the delay was added to the procedure in order to speed up the learning process and increase the choice of the delayed lever, as has been observed in an earlier study (29).

The reward for the delayed reward was also increased from 3 to 4 sugar pellets. Krebs (2016) saw an increase in the choice of the delayed reward by increasing its size, as well as a larger effect when amphetamine was tested (30).

The animals were not put on a restricted diet for this pilot. This is often the case in models that use conditioned training. Experience within the research group indicates that the learning is greatly sped up by restricting the diet.

Studies indicate that a restricted diet decrease the number of omissions but do not affect the choice of lever (29, 31).

While the principle of the delay discount task is simple, that the subject is to choose between two rewards, there are a number of methodological questions that must be considered. What affects the choice of one reward (or lever) over the other?

Evenden & Ryan (1996) identified three factors that might influence the choice of lever during the delay discount task, at baseline: 1) the programmed delay, 2) the habit to respond on one of the levers as the session progresses and 3) a conditioned association of the delay-lever with delay (9).

Ideally, the first factor would dominate in the rat's choice of lever. The second and third factors would make the result of the task harder to interpret and if their influence of choice is large, one could question the use of the method as a way to measure impulsivity.

Earlier studies suggest that the second factor play a lesser part (9, 31) which can be tested by using a mock delay-discount task where the delay on each block is 0 seconds.

Several studies see a choice of the delayed lever at 0 seconds below 100% (23). This could be explained by the third factor identified above.

It was also noted during this project, that some rats chose the immediate lever almost always and independent of delay. It can be compared to Madden (2010) that saw that some rats could only be made to press the delayed lever at a very short delay (around 3 seconds) and only after a very high number of training sessions (24).

This problem was also identified by Evenden & Ryan (1996) and interestingly enough, they found that this behavior could be counteracted by assigning the rats that only chose one lever to a program where they could only choose the other lever (9).

More animals should be used in a more full scale experiment to achieve a statistical significant effect of delay, both in training and when comparing different treatment groups in experimental procedures. As can be seen in figure 4, there was a considerable variance in the choice of the levers, which is known to be the case from other studies (23).

One could also consider using younger rats and potentially rats of a different breed.

In this project, Wistar rats were used. Both Wistar rats and several other breeds have been used in other studies and they have been able to learn the model (24, 26). There could however be a difference in how fast different breeds learn and adapt in the model. The author of this thesis has found no such studies comparing different breeds in the delay discount task.

While no useful result in regard to the effect of Pramipexole in this model could be found, there have been valuable lessons learned about the model itself.

The research group will continue to use the model for further studies of both Pramipexole and other compounds, taking advantage of the changes to the protocol that was listed above.

One future project will be to study the combination of reserpine, which is a monoamine depleting drug, and Pramipexole. This combination has been seen to increase impulsive behavior in rats (32).

Acknowledgements

I would like to thank my supervisor, Professor Elias Eriksson for his support and encouragement during this project as well as the last couple of years that I have spent at the department of pharmacology.

I also want to thank Daniela Atanasovski and Christopher Pettersson for their help with my

experiments. I am also grateful to all the people at the department of pharmacology, Gothenburg University for their help in my project.

Populärvetenskaplig sammanfattning

Vi har alla en tendens att bete oss mer eller mindre impulsivt. Det kan handla om impulsiva köp på internet eller andra dålig beslut som vi senare ångrar.
Vid vissa psykiatriska sjukdomar utgör det impulsiva beteendet ett stort problem som får svåra konsekvenser, som till exempel vid spelberoende och alkoholberoende. Även vissa läkemedel kan ge biverkningar som innebär dålig kontroll av impulser.
Ett sådant läkemedel är Pramipexol, som är en så kallad dopaminagonist. Pramipexol används vid behandlingen av Parkinssons sjukdom och behandlar effektivt motoriska problem som uppstår vid denna sjukdom. En del patienter som tar detta läkemedel får dock problem att kontrollera impulser, vilket kan resultera i spelberoende eller skadligt sexuellt beteende.

Ett annat läkemedel, OSU6162, har i en tidigare studie setts minska impulsivt beteende hos råttor. Det är ett läkemedel som utvecklats i Sverige men som idag inte används kliniskt.

Det finns flera olika sätt att inom forskningen mäta impulsivt beteende. En metod är den så kallade *delay discounting*. Denna metod går ut på att försöksobjektet får välja mellan två olika belöningar: en liten belöning som man direkt får tillgång till och en större belöning som man först efter en stund får tillgång till. Om försöksobjektet väljer den mindre belöningen skulle detta kunna tolkas som impulsivt beteende.

I detta projekt har råttor studerats i en *delay discounting* modell där de har kunnat välja mellan de två olika belöningarna (en mindre som kommer omedelbart och en större som

kommer efter en fördröjning) genom att trycka på spakar.

Syftet har varit att studera om impulsivt beteende kan framkallas genom att behandla råttorna med Pramipexol och, om så är fallet, huruvida OSU6162 kan motverka detta beteende.

Tyvärr kunde inget resultat fås från försöken då behandling med Pramipexol resulterade i att råttorna blev trötta och inte tryckte på spakarna.

Trots detta har projektet gett viktiga lärdomar om hur denna modell fungerar och planen är att fortsätta använda den till att studera olika läkemedel.

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