Open Field Behaviour and Reaction to Novelty in Göttingen Minipigs: Effects of Amphetamine and Haloperidol

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Abstract

The purpose of the study was to quantify behavioural changes of healthy Göttingen minipigs in response to experimentally altered dopamine neurotransmission. Since dopamine function is important in the pathogenesis of several human neuropsychiatric diseases, it is important for future evaluation of minipig models of diseases involving dopamine that the changes in behaviour in response to changed neurotransmitter function can be quantified. We recorded the behaviour of eight Göttingen minipigs in a ten-minute open field and a five-minute novelty test, and investigated the effects of *d*-amphetamine (0.7 mg/kg) and haloperidol (0.2 mg/kg) in this setting.

D-amphetamine as well as haloperidol produced appreciable changes in motor behaviour and decreased explorative behaviour in line with the elsewhere reported effect of these drugs. It was possible to make a clear distinction between the behavioural profiles of these compounds.

In conclusion, we have demonstrated the usefulness of a ten-minute open field and a five-minute novelty test for quantifying behavioural changes of Göttingen minipigs in response to experimentally altered dopamine neurotransmission. This provides the basis for using these behavioural tests in future evaluations of minipig models of diseases characterised by dopaminergic disturbances.

Keywords: Pig, Behaviour, Amphetamine, Haloperidol, Open field, Novelty

Introduction

Behaviour is an important parameter in several disciplines within neuroscience, and it is a keystone in studies of animal welfare, neurobehavioural genetics and of brain function. Pig behaviour is most often studied in relation to animal welfare but has gained increased interest in neuroscience (*Arnfred et al., 2003a; Arnfred et al., 2003b; Arnfred et al., 2004; Cumming et al., 2001; Danielsen et al., 2000; Lind et al., 2004; Mikkelsen et al., 1999; Moustgaard et al., 2002; Parrott et al., 2000*). The large brain of pigs has promoted their use, and of minipigs, in PET scanning studies of brain dopamine function (*Danielsen et al., 2000; Danielsen et al., 1999*) and the pig has also been established as useful for PET studies of the serotonergic system (*Brust et al., 2003; Cumming et al., 2001*). Chronic toxic brain effects, such as foetal alcohol effects (*Riley & Meyer, 1984*), and Parkinson's disease (*Mikkelsen et al., 1999*) have also been studied in pigs.

The purpose of this study was to quantify behavioural changes of healthy Göttingen minipigs in

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response to experimentally altered dopamine neurotransmission. Since dopamine function is important in the pathogenesis of several diseases, like schizophrenia, Tourette's syndrome, Attention Deficit Hyperactive Disorder (ADHD), and Parkinson's disease, it is important to be able to detect changes in this neurotransmitter profile in the behaviour of Göttingen minipigs. A few studies on the behavioural effects of dopamine agonists, including amphetamine (*Terlouw et al., 1992b; Terlouw et al., 1992a; Sharman et al., 1982; Fry et al., 1981; Laferrière et al., 1995; Bolhuis et al., 2000*) and the dopamine antagonist haloperidol (*von Borell & Hurnik, 1991*) have been conducted on Landrace pigs. Several of these studies, however, have focused on the relation to stereotypic behaviour, or to the temporal distribution of the drug-effects. The effect of these compounds on behaviour has not been studied in healthy minipigs so far.

For several reasons, purpose-bred laboratory pigs, such as the Göttingen minipig, can be advantageous to use in experimental research as opposed to use of conventional pigs, bred for meat-production. In particular, the standardisation of the breed, the adult weight and precise definition of the microbiological status can be of importance.

Here, we introduce the use of a ten-minute open field and a five-minute novelty test for quantification of behaviour of Göttingen minipigs and investigate the effects of two test substances amphetamine (AMPH) and haloperidol (HAL), in this setting. It is essential for future evaluation of minipig models of diseases involving dopamine that the changes in behaviour in response to changed neurotransmitter function can be quantified.

2. Materials and methods

2.1. Animals

The study comprised eight Göttingen minipigs (Göttingen minipigs ™, Dalmose, Denmark), three females and five vasectomised males, aged three to eight months, and weighing 7-32 kg. To minimise abnormal behaviour all minipigs were kept in an enriched environment with shavings and straw bedding with free access to peat moss and apple tree branches. The pens were illuminated by natural daylight and the room temperature varied between 18 and 24 ºC. Animals were fed according to the recommendations of the breeder with a commercial pelleted diet for minipigs (Altromin (Brogaarden, Denmark)) supplemented daily with 1 kg of vegetables. Water was provided *ad libitum*.

2.2. Treatments

In a blind latin-square procedure, the minipigs were subjected to one of the following treatments: AMPH 0.7 mg/kg (*d*-amphetamine sulphate BP93 prepared in a 1% solution), HAL 0.2 mg/kg (Serenase® 0.5%, Janssen-Cilag) or the vehicle, NaCl 1.5 ml (0.9%). The animals were tested twice a week with the same compound (in the two different tests) and the treatment changed every week. All injections were given s.c. and doses were chosen on the basis of studies on Landrace pigs (*Terlouw et al., 1992b; Terlouw et al., 1992a; Hjarvad & Jensen , 2003*), aimed at being able to observe a notable, but non-sedative, effect of the drug. The time of testing was based on serum concentration curves of AMPH following i.m. injection in monkeys (*Castner & Goldman-Rakic, 1999*). The time of maximal concentration in monkeys was extrapolated by the addition of 5 minutes to account for the s.c. route we used. All procedures were in accordance with the Danish Animal Experimentation Act (based on the Council of Europe Convention ETS 123) on a licence granted by the Ministry of Justice.

2.3. Behavioural tests

Thirty-five minutes after injection, the behavioural response was tested in an arena (2.30 x 3.20 m) – in the Novelty test (NT) (day1) or the Open field test (OF) (day 2) – placed within the housing premises. The floor was covered with shavings to facilitate cleaning between tests, and to reduce the odour from stools of the preceding subject. The minipigs had been habituated to the test arena in the preceding four weeks in eight sessions of 40 min. The

duration of the NT was five min following a habituation period of five min. The test was initiated as the object was presented in the centre of the arena using a cord drive. The object was a ½ litre plastic bottle, which changed colours between tests.
On the basis of pilot studies, the duration of the OF was set to 10 min without any prior intra-test habituation period. This was concluded from a comparison between a five-minute and a ten-minute recording period showing that the largest difference in behavioural responses between drug treatments was obtained when recording 10 min, furthermore some of the behaviours preferentially occurred in the last five minutes of the test (unpublished results).

2.4. Behaviour

The behavioural sampling took place by one-zero sampling in 10-second intervals and was made by direct observation, except for measures of ambulation (OF), which were calculated from video recordings. The arena was divided into 12 equal sections, and ambulation was calculated as the number of sections entered with the middle chest (behind the shoulder blades). Recorded behaviours are listed in Table 1. The behavioural variables are showed in italics throughout the text.

2.5. Inter-observer reliability

For this purpose we studied six, two-year-old Göttingen minipig boars and three 18-month-old minipig castrates, fed and kept according to the recommendations for feeding of minipigs.
Selected items were chosen for an investigation of the consistency and reliability of different observers. The qualitative behavioural pattern *motor slowness* and the behaviours *posturing* and distant look were chosen, as these behaviours are likely to be scored more subjectively. An inexperienced observer was instructed in the scoring criteria by an experienced observer and nine minipigs were scored in a five-minute OF before, and 30 min after, administration of 0.15-0.18 mg/kg haloperidol i.m.. A kappa value was calculated (*Altman, 1991*) for the qualitative behavioural pattern; the inter-observer agreement for the quantitative items is given as the mean and standard deviation for the differences in ratings of these items between the two observers.

2.6. Data analysis

The dependent variables were subjected to analysis of variance by mixed model methods with multiple error terms using the MIXED procedure in the statistical package, SAS (version 8.2, SAS Institute Inc., 1999-2001). For infrequently occurring type of behaviour, the Poisson distributed GLIMMIX macro (glmm800.sas) was added to the analysis. The model included HAL, AMPH and sex as fixed effects. The day of testing was used as the repeated effect with identity of the minipig nested with age as the subject. The variance structure of the residuals of the repeated measurements was modelled by compound symmetry of heterogeneous variance. To obtain homogenous variance, data was transformed to either logarithmic or square-root values.
Individual test scores were used as experimental units. All analyses were performed as two-tailed tests. The Differences of Least Squares Means were used for comparison of the individual treatments.
The comparison between treatments of the behaviour *non-forward locomotion* was based on the Wilcoxon matched-pairs signed rank test due to the lack of variability in the control group (mean ~ zero). The analysis was performed as one-tailed tests, because the *a priori* hypothesis was that this behaviour could only increase with drug treatment.
The qualitative behavioural pattern, *motor slowness*, was analysed using McNemar's test, where paired proportions of the individual drug treatments were compared with respect to the presence of symptoms (score > 0). The analyses were performed as two-tailed tests and the level of significance was set to 0.05.

3. Results

3.1. Inter-observer reliability

The inter-observer reliability for *motor slowness* was κ=0.68 (good) (*Altman, 1991*). Out of 270 ten-

Table 1. Definitions of the recorded behaviors.

Behaviour	Definition
Motor behaviour	
Standing [1, 2]	Standing still > 2 s. without exploring the surroundings and not performing the behaviour posturing.
Walking [1, 2]	Walking at least one forward step.
Ambulation [1]	Number of squares entered in 10 min.
Bouts of locomotion [1]	*Calculation*: Number of intervals containing standing as well as walking.
Motor slowness [1]	Qualitative assessment on a scale 0-5 (0= no slowness and 5= immobility)
Explorative behaviour	
Exploration [1, 2]	Sniffing or manipulating (> 2 sec) the surroundings in a non-stereotypic manner.
Scans [1, 2]	Turning of head while looking around.
Looking at novel object [2]	Standing and looking on object.
Physical contact with object (frequency and duration) [2]	Recording of frequency of sniffing, *manipulating* or biting in the object. *Calculation* of mean duration: number of intervals with object contact divided with number of contacts.
Potential conflict behaviours	
Head dipping [1, 2]	Momentary (< 2 sec.) lowering and lifting of the head to the floor.
Intentional behaviour [1, 2]	Initiation of a behaviour without completion of the pattern
Comfort behaviour [1, 2]	Scratching of body with hoofs or by means of surroundings, stretching of body.
Elimination [1, 2]	Deposition of urine or faeces.
Escaping [1, 2, ¤]	Attempting to get out of the arena by jumping toward the wall.
Behavioural shifts [1]	*Calculation:* Number of shifts between the behaviours: standing, walking, exploration, conflict behaviours, posturing, backward locomotion, rotation around hind legs (>180º).
Potentially abnormal behaviour	
Non-forward locomotion [1]	Non-locomotory leg movements, backward locomotion and rotation around hind legs (>180º).
Posturing [1]	Standing in an awkward, odd or un-physiological position > 2 sec.
Head/facial/oral activity [1]	Head shaking, jerking head movements, facial dyskinesias and chewing that is not associated with exploration, licking or yawning.
Distant look [1]	Standing without focusing and with a distant look > 2 sec
Stereotypie behaviour [1, ¤]	Any behaviour having a stereotyped appearance (repetitive and with little variation and no obvious function).
Other behaviour	

1. Recorded in the OF 2. Recorded in the NT ¤ Omitted from the statistical analysis due to infrequent occurrence

second intervals from the scoring of nine HAL-treated minipigs in the inter-observer reliability test, observer no. 1 identified the behaviour *posturing* in 22 intervals (8.2% of the time) and *distant look* in 108 intervals (40.0 % of the time), while observer no. 2 identified *posturing* in 24 intervals (8.9% of the time) and *distant look* in 97 intervals (35.9% of the time). The mean difference in scoring of individual minipigs was 0.22 intervals (0.95%) and SD 1.48 intervals (6.4%) for *posturing* and a mean of 1.22 interval (1.22%) and a SD of 1.20 intervals (1.2%) for *distant look*.

3.2. Open field

Both treatments clearly affected the behaviour of the minipigs (Fig. 1). Administration of AMPH significantly increased motor behaviour, except for *ambulation*, which was not significantly affected. In addition, AMPH increased *behavioural shifts* ($F(1,13.7)=5.75$, $p=0.03$). This compliments the global impression of AMPH treated minipigs having a fragmented and rigid behavioural pattern with short bouts of walking, followed by standing alert with numerous quick turnings of the head (*scans*).

The most prominent behavioural changes in response to treatment with HAL include significantly increased levels of *standing* and decreased levels of *ambulation* ($F(1, 8.1)=142.86$, $p<0.001$), *exploration* ($F(1,5.89)=840.65$, $p<0.0001$) and *behavioural shifts* ($F(1, 13.8)=5.90$, $p=0.03$). Also, the treatment with HAL significantly increased *posturing* ($F(1,10.2)=126.64$, $p<0.0001$) and *distant look* ($F(1,7.63)=234.74$, $p<0.0001$).

Noteworthy is that *distant look* in the OF increased considerably in the last part of the test (Fig. 2).

The qualitatively assessed behavioural pattern, *motor slowness*, was significantly affected by HAL ($p<0.05$). The average score for pigs receiving HAL was 2.71, whereas it was 0 for pigs receiving the vehicle or AMPH.

Head/facial/oral activity and *non-forward locomotion* occurred rarely and were not affected by AMPH and HAL in this study.

We found a significant gender effect on the behaviour *distant look* ($F(1, 6.4)=106.8$, $p<0.0001$) with female pigs expressing more of this behaviour than male pigs. All other behaviours were not affected by gender, except for *ambulation*, where the data did not permit analysis of a gender effect.

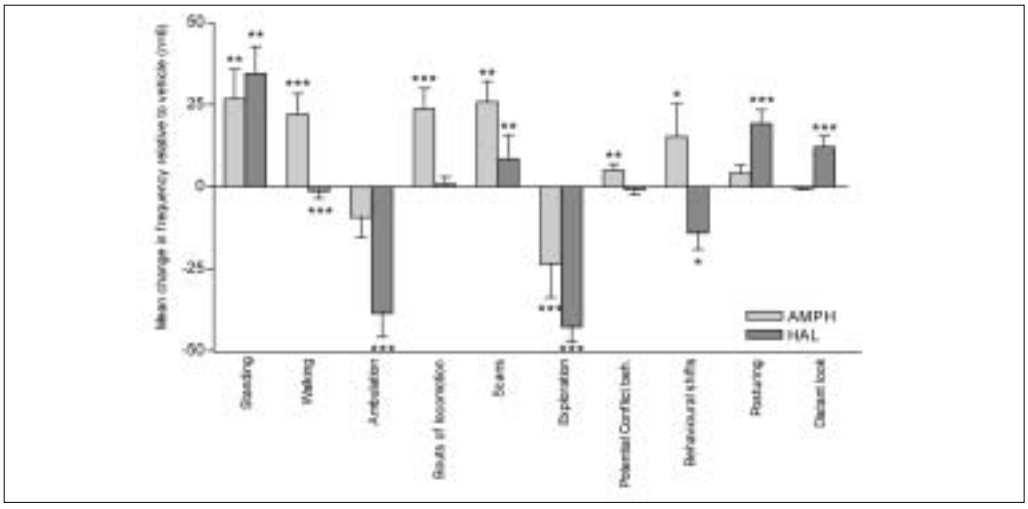

Fig. 1. Effects of AMPH and HAL on behaviour of minipigs in the Open field test. The drug-induced behaviour is significantly different from control behaviour: * $p<0.05$, ** $p<0.01$, *** $p<0.0001$

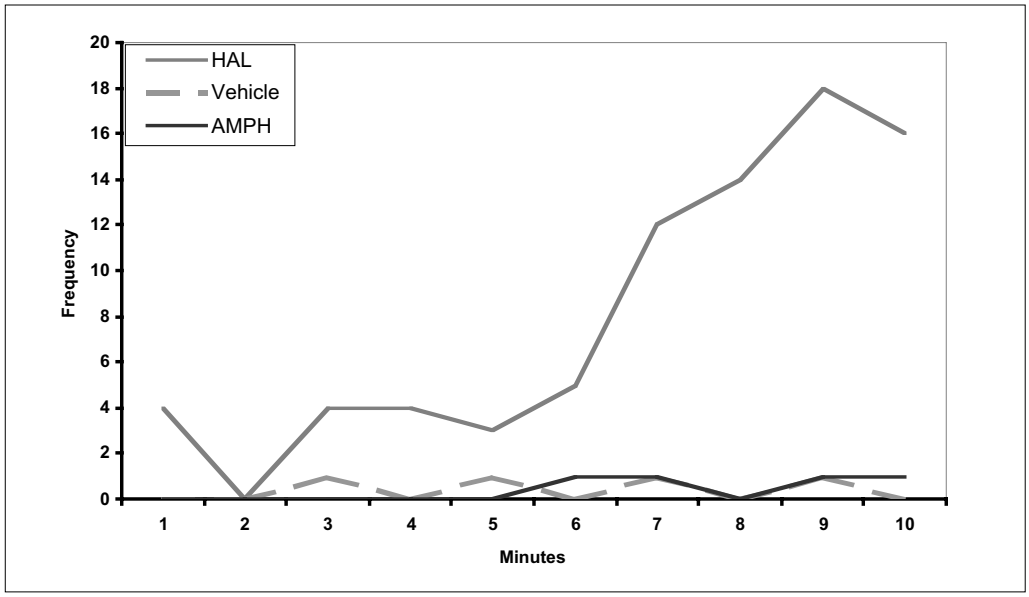

Fig. 2. The time-course of occurrence of the behaviour *Distant look* in the Open Field test (n=8).

3.3. Novelty test

In the NT, both AMPH and HAL significantly decreased explorative behaviour as shown by the decreased number of *physical contacts* ($F_{AMPH}(1, 5.18)=239.58$, $p<0.0001$) ($F_{HAL}(1,5.18)=120.15$, $p<0.001$) and mean *duration of contact with object* ($F_{AMPH}(1, 6.45)=1082.01$, $p<0.0001$) ($F_{HAL}(1, 6.54)=1455.78$, $p<0.0001$) (Fig. 3). *Looking at object*, however, was increased ($F_{AMPH}(1, 5.94)=1983,54$, $p<0.001$) ($F_{HAL}(1,5.97)=368.54$, $p<0.0001$). Since *looking at object* could be related to the time *standing* (still) and therefore could be confounded, *standing* was included in the analysis as a covariate. This, however, did not change the result. There were significant gender effects on all the recorded behaviours in the novelty test. Females had increased levels of *looking at object* ($F(1, 5.87)=2006.78$, $p<0.0001$), while males had more *physical contacts* ($F(1,6.82)=34.25$, $p=0.0007$) and longer *duration of contact with object* ($F(1,6.12)=1442.95$, $p<0.0001$).

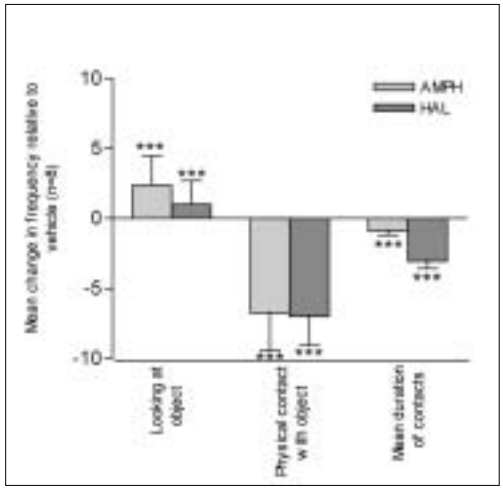

Fig. 3. Effects of AMPH and HAL on behaviour of minipigs in the Novelty test. The drug-induced behaviour is significantly different from control behaviour: * $p<0.05$, ** $p<0.01$, *** $p<0.0001$

4. Discussion

The results show that experimentally induced changes in dopaminergic neurotransmission cause distinct and quantifiable behavioural responses in Göttingen minipigs subjected to an Open field test (OF) and a Novelty test (NT).

AMPH produced appreciable changes in the behaviour. The most conspicuous effect on motor behaviour was the frequent occurrence of short *bouts of locomotion*. The fragmented, repetitive, and low variability in this behaviour indicated a stereotypic nature. This variable was calculated from recording the behaviours *walking* and *standing*, and hence, the subjectivity in rating this behaviour is low. Landrace pigs also displayed short bouts of locomotion after administration of AMPH (*Terlouw et al., 1992b; Terlouw et al., 1992a*). Explorative behaviour, including the object-directed exploration, decreased when challenged with AMPH, as also seen in rats (*Kumar, 1969; Robbins & Iversen, 1973*).

Administration of HAL induced marked changes in behaviour, which were well reflected in the recorded behavioural effects. Administration of HAL decreased motor activity in accordance with results obtained from rodents (*Cabib et al., 1991; Simón et al., 2000*). In addition, all measures of explorative drive, including novelty-related, were decreased – also in accordance with findings in rats (*Marriott & Spencer, 1965*). The decreased exploratory drive is thought to be a manifestation of decreased "motivational arousal" (*Salamone, 1988*) and motor deficits (*Salamone et al., 1994*).

Regarding the category of potential abnormal behaviour, HAL increased *distant look* both in the OF and in relation to novelty. This probably corresponds to findings in monkeys where HAL elicited staring (*Palit et al., 1997*). *Distant look* increased considerably in the last part of the OF (Fig. 2). While it could be that this behaviour only emerges at this particular time-point (40 min) after injection, it may also be that this behaviour does not occur until the animal has habituated to the test-situation. This is an important argument for not shortening the recording period in the OF.

The odd postural positions (*posturing*) were very conspicuous during HAL administration, which is in accordance with the side-effects of classical antipsychotics and probably also corresponds to the "marked cataleptic posture" observed in monkeys (*Palit et al., 1997*).

The behavioural response of HAL, as observed in the quantitative observation, was also reflected in the qualitative assessment, in which *motor slowness* was noted as being far more conspicuous than in saline- and AMPH-treated minipigs. Furthermore, this parameter is often reported as a side-effect of treatment with typical antipsychotics, as the bradykinesia is an extra-pyramidal side-effect arising from blocking of the dopamine system in the motor part of the basal ganglia (*Glenthøj, 1995*).

The inter-observer reliability for the qualitative assessed behavioural pattern, *motor slowness*, as well as for the scoring of the behaviours *posturing* and *distant look* was high. Thus, it seems possible to score these behaviours objectively. Including a qualitative assessment of *motor slowness* in the behavioural assessment of a future animal model of neuropsychiatric disturbances could assist in providing information about the cause of a decrease in motor activity. For example, fear and decreased explorative motivation can also decrease locomotor activity in an open field test, but these would not be accompanied by pathophysiological motor symptoms. Recording of *posturing* and *distant look* could provide relevant information, which is not obtainable with a quantitative method, although the underlying condition for these phenomena should be interpreted with care. These symptoms can originate from a variety of disturbances (neurological, medical, psychomotoric etc.).

We found significant gender effects in the behaviour of Göttingen minipigs. Whereas only a gender difference in *distant look* was present in the OF, all behaviours in the NT were influenced by gender. Since the female group differed from the male group in the same direction as the effects of the test substances in the NT, there is a risk of a floor effect for

females in such a model. For instance, several of the female pigs had very few, if any, physical contacts with the novel object, leaving little room for a decrease in this behaviour being caused of the test substances. Further studies are needed for an evaluation of gender differences in the susceptibility to the their effects since the statistical analysis of the data did not permit this in the present study.

In the present study, we have demonstrated that the behaviour of Göttingen minipigs can be quantified in an OF and a NT, and that behavioural changes evoked by experimentally altered dopamine neurotransmission can be assessed using these tests. However, due to the cross-sectional nature of the tests, they are not suitable for producing a thorough description of the two drugs used. (*Rebec & Bashore, 1984*). Further characterisation of these effects, including their temporal distribution, should be examined by other behavioural methods, as for example done in Landrace pigs (*Bolhuis et al., 2000; Terlouw et al., 1992a*). Rather, we focus on characterisation of the behaviour of the individual animal, and the ten-minute OF and the five-minute NT appear suitable for this purpose.

In conclusion, we have demonstrated the usefulness of a ten-minute open field and a five-minute novelty test for quantifying behavioural changes of Göttingen minipigs in response to experimentally altered dopamine neurotransmission.

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